SYNTHETIC STUDIES TOWARD BIOLOGICALLY ACTIVE QUINONES AND ALKALOIDS

by

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Synthetic Studies toward Biologically Active Quinones and Alkaloids

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ABSTRACT: Part 1 describes the synthesis and biological evaluation of small-molecule phosphatase inhibitors. The targets for the synthesized compounds are mainly Cdc25 phosphatases, which play a key role in regulating cell cycle and are often over-expressed in cancers. Highlights of the synthesis are the amide bond formation, the synthesis of secondary amines via *o*-Ns chemistry, the ring opening of the lactam by the amine, the preparation of various (iso)quinolinediones and the substitution reactions of (iso)quinolinediones with amines and thiols. The synthesis and reaction of isoquinonlinediones are particularly highlighted in the total synthesis of caulibugulones A-E. Biological assays established the (iso)quinolinediones as new phosphatase inhibitors with considerable selectivity against the Cdc25 family of DSPases.

Part 2 describes the synthetic studies toward the total synthesis of parvistemonine, which represents one of the most challenging synthetic targets among Stemona alkaloids. The studies are mainly focused on the development of a fragmentation strategy aimed at the total synthesis of parvistemonine. Highlights of these studies are the synthesis of vinyl azides, the fragmentation reaction of tertiary alcohols and the use of the trimethylsilyl-methylene group as a directing group in the fragmentation reaction. These studies demonstrate a novel vinylogous azido alcohol fragmentation reaction in simple model systems and a regioselective fragmentation reaction of hydroxy indolines.

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ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
ADP	Adenosine-5'-diphosphate
Arg	Arginine
Asp	Aspartic acid
ATP	Adenosine-5'-triphosphate
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bz	Benzoyl
Cbz	Carbobenzoxy
Cdc	Cell-division cycle
CDK	Cyclin dependent kinase
Cys	Cysteine
Dba	Dibenzylideneacetone
DBB	4,4'-Di-*t*-butylbiphenylide
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DEAD	Diethylazodicarboxylate
DEPC	Diethylcyano phosphonate
DHP	Dihydropyran
DIB	(Diacetoxyiodo)benzene
DIEA	Diisopropylethyl amine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DNA	Deoxyribonucleic acid
DSPases	Dual specificity phosphatase
EDCI	1-Ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride
EI	Electron ionization

ERK	Extracellular regulated kinase
ESI	Electron-spray ionization
FDPP	Pentafluorophenyl diphenylphosphinate
Glu	Glutamic acid
GST	Glutathion-S-transferase
HPLC	High performance liquid chromatography
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HOBT	Hydroxybenzotriazole
IC_{50}	Median inhibition concentration
Im	Imidazole
KHMDS	Potasium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
L-Selectride	Lithium tri-*sec*-butylborohydride
MAPK	Mitogen-activated protein kinase
MCPBA	m-Chloroperoxybenzoic acid
MOM	Methoxymethyl
MS	Molecular sieves
Ms	Methanesulfonyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NOESY	Nuclear Overhauser enhancement and exchange spectroscopy
Ns	Nitrobenzenesulfonyl
PIFA	[Bis(trifluoroacetoxy)iodo] benzene
PP	Protein phosphatase
PPTs	Pyridinium p-toluenesulfonate
PSTPaes	Protein serine threonine phosphatase
PTP	Protein tyrosine phosphatase
PTPases	Protein tyrosine phosphatases

PyBrop	Bromotrispyrrolidinophosphonium Hexafluorophosphate
Pyr	Pyridine
RC	Recognition complex
SAR	Structure activity relationship
SEM	Standard error of the mean
Ser	Serine
TBDPS	*t*-Butyldiphenylsilyl
TBS (= TBDMS)	*t*-Butyldimethylsilyl
TEA	Triethylamine
Tf	Trifluorosulfonyl
THF	Tetrahydrofuran
THP	2-Tetrahydropyran
Thr	Threonine
TIPS	Triisopropylsilyl
TMS	Trimethylsilane
TPAP	Tetrapropylammonium perruthenate
Ts	p-Toluenesulfonyl
Tyr	Tyrosine
VHR	Vaccina human-related

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1.1. Introduction

1.1.1. Biological Background

Covalent modification is one of the methods that can regulate enzyme activity.[1] For example, simple covalent attachments of a functional group, such as a phosphoryl moiety can convert a fully active enzyme into an inactive form (Figure 1)[1], although in many cases phosphorylation can activate an enzyme.

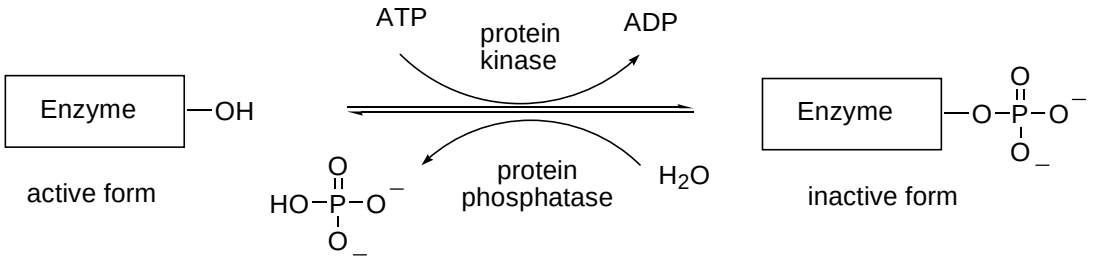


Figure 1. Regulation of enzymes by covalent modification[1]

This protein phosphorylation is a key process in cell signaling, metabolism, growth and differentiation and is controlled through kinases and phosphatases.[2] Protein kinases catalyze phosphorylation of hydroxy groups on serine, threonine and/or tyrosine residues in target enzymes, whereas phosphatases catalyze dephosphorylation.[2] Protein phosphorylation fulfills a major role in signal transduction pathways, highly controlled processes by which cells convey information from the cell surface to their nucleus or other remote subcellular sites.[2] This information then regulates cell growth and differentiation, metabolism, cell cycle and cytoskeletal function.[2] Phosphatases are generally classified in three families: Ser/Thr protein

phosphatases (PSTPases), Tyr protein phosphatases (PTPases) and dual-specificity protein phosphatases (DSPases).

Dual-specificity protein phosphatases (DSPases) are sub-classes of PTPases (Figure 2).[3] PSTPases have been classified according to their substrate specificity, metal ion dependence and sensitivity to inhibition. cDNA cloning has revealed at least 40 different enzymes of this type, including PP1, PP2A, PP2B, PP2C and PP3. PTPases have diverse biochemical and cellular roles. For example, PTP1B regulates both epidermal growth factor and insulin signaling pathways. The DSPase VHR (vaccina human-related) regulates mitogenic signaling by specifically dephosphorylating members of the MAPK (mitogen-activated protein kinase) family, namely the extracellular regulated kinases ERK1 and ERK2. The Cdc25 (cell-division cycle 25) family of DSPases regulates cell-cycle progression by dephosphorylating and activating cyclin-dependent kinases (CDKs). CDKs are inactivated by phosphorylation at adjacent threonine and tyrosine residues near their amino termini, and dephosphorylation at both sites by Cdc25 phosphatases catalyses their activation and allows the CDKs to propagate cell-cycle signal transduction.[2,3,4]

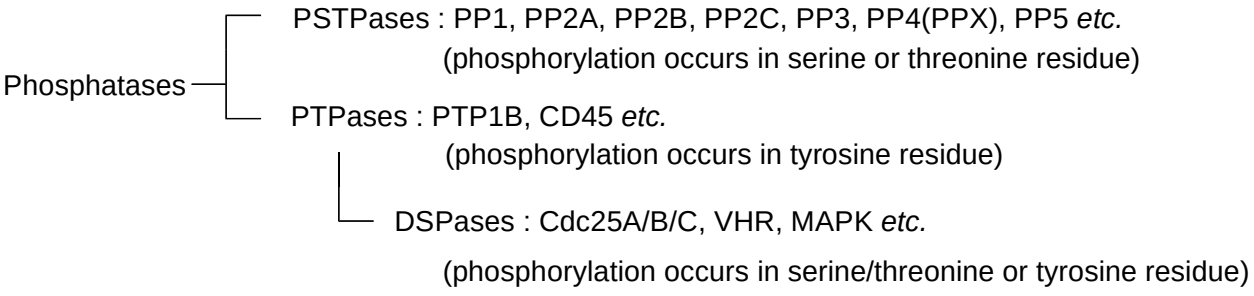


Figure 2. Classification of phosphatases

Cell duplication events associated with cell growth and division in eukaryotic cells fall into a four distinct phases, M, G1, S and G2 (Figure 3).[5]

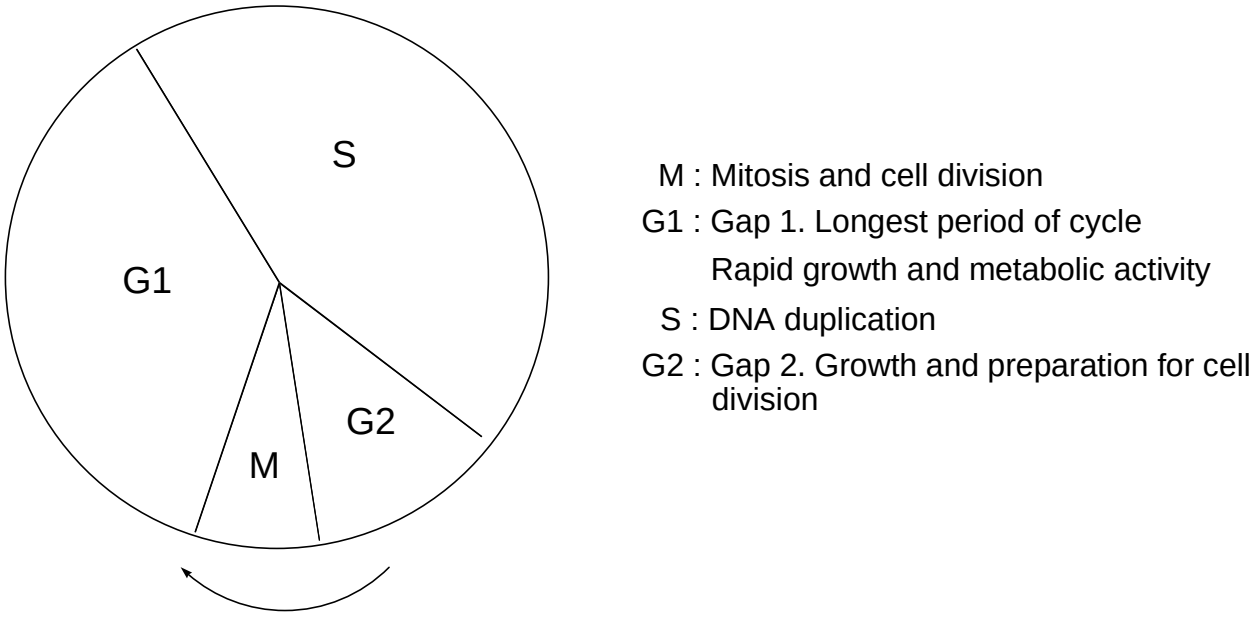


Figure 3. Cell cycle[5]

In this cell cycle, phosphorylation acts as a replication switch since the post-RC (Recognition Complex) state comes after phosphorylation of proteins in the pre-RC. Since the post-RC state is incapable of re-initiating DNA replication, phosphorylation ensures that eukaryotic DNA replication happens only once per cell cycle.[5] In this context, the Cdc25 phosphatase family plays an important role in controlling cell cycle progression by activating cyclin-dependent kinases (Cdk).[6] There are three homologues of Cdc25 in humans: Cdc25A, Cdc25B and Cdc25C.[6] Cdc25B and C regulate the G2/M transition by dephosphorylating and activating the Cdk1/cyclinB mitotic kinase complex, whereas Cdc25A is involved in the G1/S phase transition. Over-expression of Cdc25A and B is often found in human tumors, so they are considered to be potential target for anti-tumor drugs.[6] So far, two crystal structures of the Cdc25

catalytic domain were disclosed (Figure 4 and Figure 5),[4(a),7] however none exposes the nature of interactions with small-molecule phosphatase inhibitors. Therefore, it has been difficult to define rational parameters for potent inhibitors.

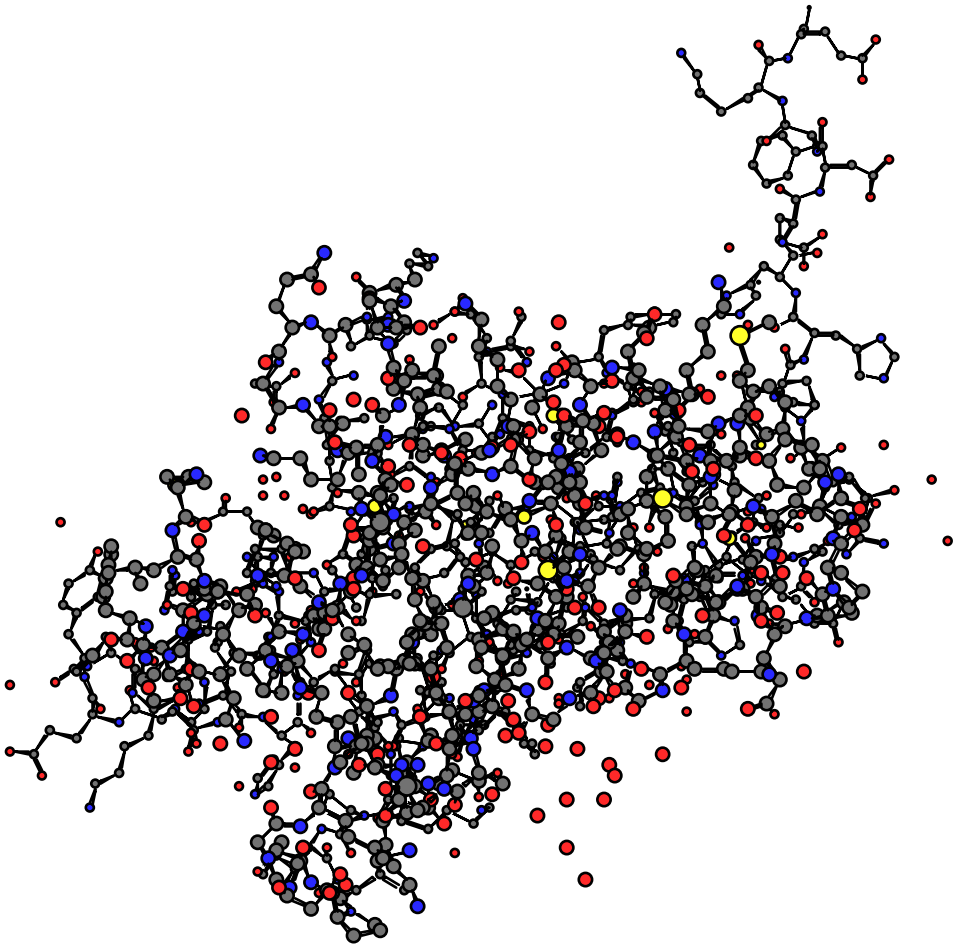


Figure 4. X-ray crystal structure of the Cdc25A catalytic domain[4(a)]

Both Cdc25A and Cdc25B have the canonical His-Cys-Xaa5-Arg PTPase catalytic-site motif, which is a characteristic of all tyrosine phosphatases.[4(a),6,7] Although the two Cdc25s are similar in overall structure of the catalytic domain, Cdc25B readily binds tungstate and sulfate in its catalytic site whereas Cdc25A fails to bind oxyanions in its catalytic site.[7] This difference might result from the shallow nature of the Cdc25A active site compared with the active site of

Cdc25B. Thus, Cdc25B is structurally more similar to other DSPases. Interestingly, Cdc25A has an identical topology to the bacterial sulfur-transferase protein rhodanese, however the significance of this homology is unclear.[6] The differences in their active site crystal structures suggested that designing specific inhibitors for Cdc25 isoforms should be possible.[6]

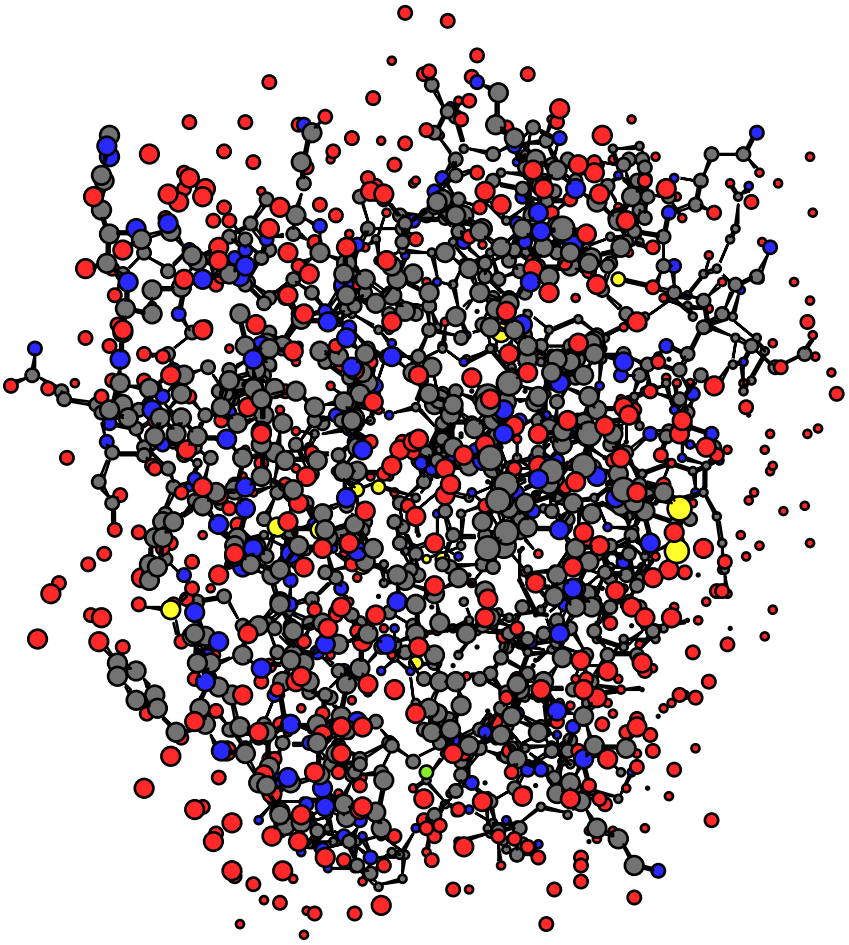


Figure 5. X-ray crystal structure of the Cdc25B catalytic domain[7]

The mechanism of dephosphorylation of PTPases is considered to be a two-step sequence via phosphoenzyme intermediates.[1(b),4(a),8] In the first step, the Cys residue of the phosphatase acts as a nucleophile to attack the phosphoryl group of substrates and forms a cysteinyl

phosphate intermediate.[8] The Arg residue of the enzyme makes bidentate hydrogen bonds with the phosphoryl group in the substrate through the guanidinium group.[8] The Asp residue of the PTPases acts as a general acid by protonating the ester oxygen of the leaving group.[8] In the second step, the attack of a water molecule to the phosphoenzyme intermediate occurs with the help of the same Asp residue, now functioning as a general base, to release the free enzyme and inorganic phosphate (Figure 6).[8]

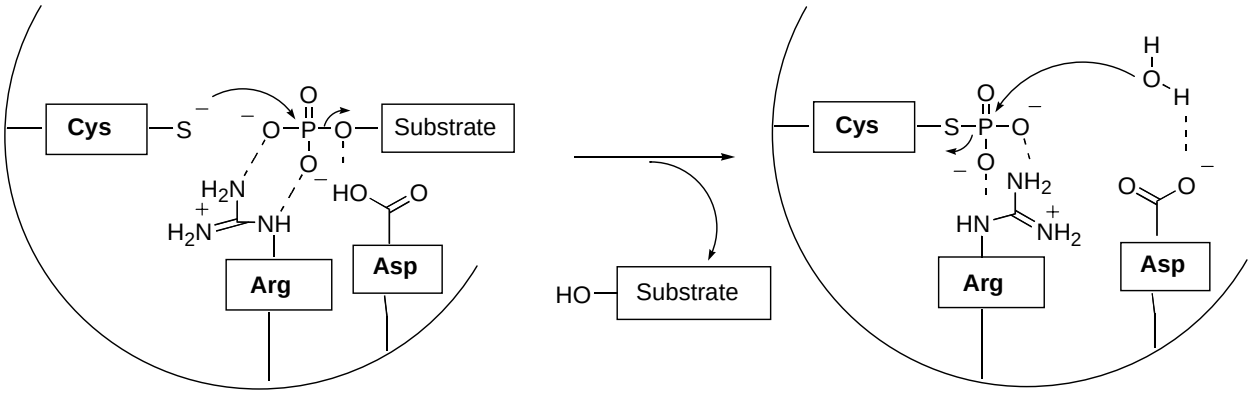


Figure 6. Mechanism of dephosphorylation of PTPases[8]

More specifically, Rudolph proposed two possible mechanisms for Cdc25 shown in Figure 7.[9] In the top reaction pathway, he proposed the classical mechanism using a bisanionic substrate leading to a meta-phosphate-like transition state. In this case, a leaving group is protonated by the Asp residue of the enzyme. In the bottom reaction pathway, he proposed a novel mechanism using a monoprotonated substrate, leading to the same meta-phosphate-like transition state. In this case, the leaving group is protonated by the substrate.

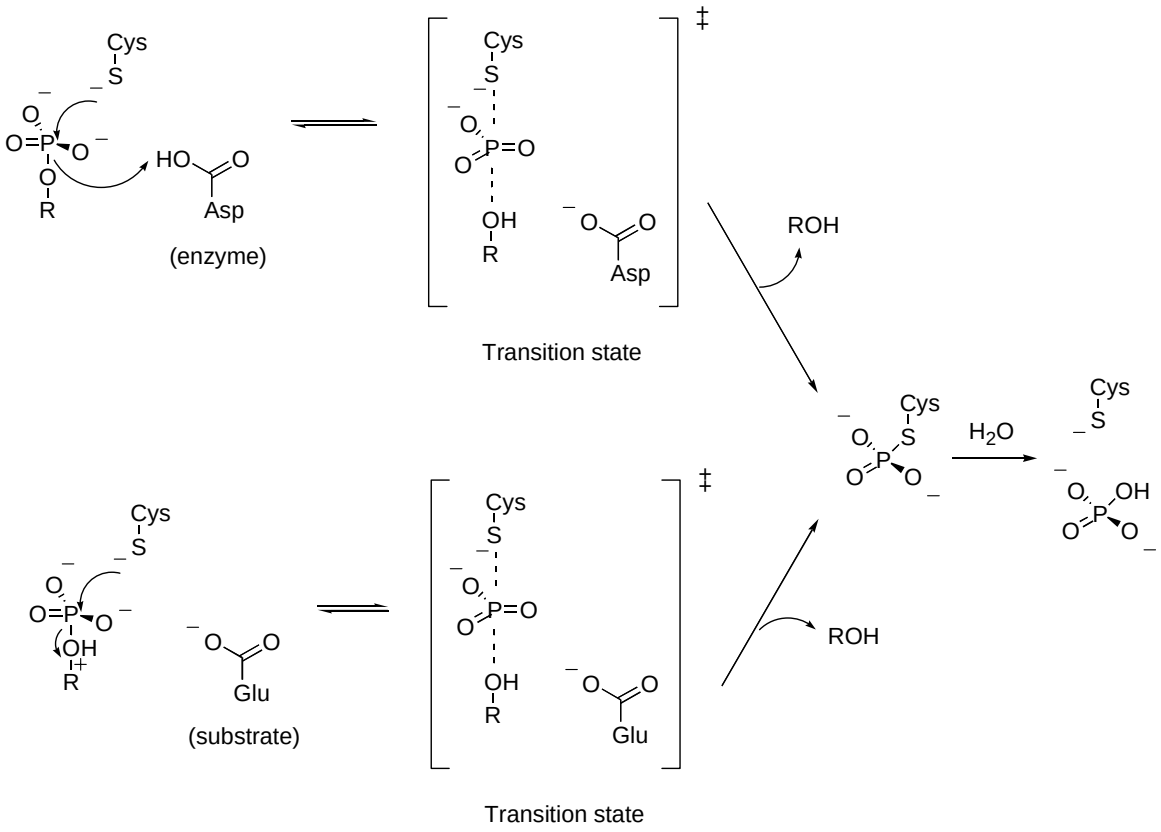


Figure 7. Reaction mechanisms for Cdc25 proposed by Rudolph[9]

On the basis of the structure of the catalytic domain and the mechanism of dephosphorylation of Cdc25, two special characteristics of Cdc25 phosphatases are thought to be responsible for the lack of success in finding reversible active site directed inhibitors.[10] The first characteristic is that Cdc25 is highly susceptible to inactivation by covalent modification and oxidation of the active site motif HCX_5R. In this motif, H is a histidine residue, C is the catalytic cysteine, the five X residues form the loop, and R is an arginine residue. The catalytic cysteine exists as a thiolate anion in the free enzyme. This active site thiolate is considered to be the source of susceptibility of Cdc25s to covalent modification and oxidation.[11] Assays of Cdc25s are likely to demonstrate covalent and irreversible inhibition with reactive compounds. This trait is generally avoided in medicinal chemistry.[12] The second characteristic is the open and

somewhat featureless architecture of the Cdc25 active site as depicted in Figure 4 and Figure 5. These exposed active site regions are not suitable for the structure-based design of compounds with complementary binding surfaces and result in a low and nonspecific activity toward phospho-peptide substrates and peptide mimetics.[13]

According to recent studies, the active site of cysteine of Cdc25s could form a disulfide bond with a neighboring cysteine after H_2O_2 oxidation (Figure 8).[14] It has also been reported that treatment of Cdc25s with H_2O_2 in vitro leads to oxidation of the active site cysteine to cysteine-sulfenic acid (Cys-SOH) and results in inhibition of activity.[15] The disulfide bond likely confers efficiency in the redox regulation of Cdc25s and protects further oxidation. It has also been shown that recovery of enzyme activity depends on the cellular reductant. These reports suggest that redox regulation of Cdc25 phosphatase activity may be important for cell cycle regulation.

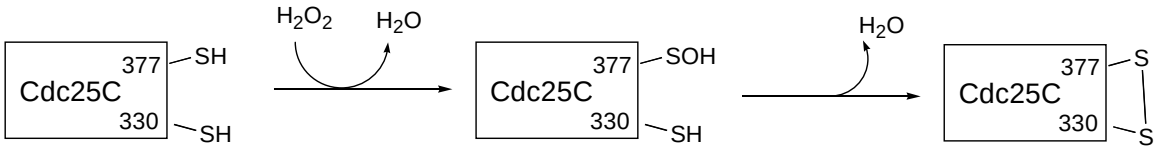


Figure 8. Oxidation of Cdc25C by H_2O_2[14]

1.1.2. Dual Specificity Phosphatase Inhibitors

The over-expression of members of the Cdc25 family and their role in regulating cell-cycle progress and survival make them attractive targets for new, potent and selective small-molecule inhibitors.[6,16] In particular, over-production of Cdc25A and B has often been found in breast cancer tissue.[13] The Cdc25 over-expression has also been detected in other diseases such as gastric carcinomas, colon cancer, non-small cell lung carcinoma and aggressive non-Hogkin's lymphomas.[10,16] Therefore, potent and selective inhibitors of Cdc25 family are highly desirable and significant efforts have been made to identify such molecules.

Natural products have been a major source of Cdc25 inhibitors (Figure 9). Sulfircin, which is produced by a deep-water sponge from the *Ircinia* genus, is a nonspecific phosphatase inhibitor originally identified as an antifungal agent. Due to its relative structural and stereochemical simplicity, sulfircin has been used as a basic pharmacophore for the development of a small analog library.[17] Sulfircin showed an inhibition against Cdc25A with an IC_{50} of 7.8 μM and VHR with an IC_{50} of 4.7 μM. Another extract from a marine sponge, dysidiolide, was initially reported as the first natural product DSPase inhibitor, but a later study claimed that pure dysidolide did not inhibit Cdc25B.[18] Recently, Shirai and co-workers indicated that the natural product was moderately active against Cdc25A with an IC_{50} value of 35μM.[19] Nonetheless, Peng and colleagues synthesized analogs of dysidiolide by modifying another readily available natural product, cholesteryl acetate.[20] Dephostatin, isolated from the *Steptomyces* strain MJ724-NF5, was identified as an active compound against PTPases.[21] The benzoquinone antitumor antibiotics dnacins A and B, extracts form *Nocardia* strain C-14482, were found to be moderate inhibitors of glutathione-S-transferase (GST)-tagged-Cdc25B.[22] RK-682 was isolated from the Penicillium strain NK374186 and showed activity against VHR with an IC_{50} value of 2.0 μM.[23] Cyclic

depsipeptides, stevastelines A and B, were isolated from the Penicillium strain NK374186 and shown to be good inhibitors of VHR, with IC_{50} values of 2.7 and 19.8 μM.[24] Vitamin K_3 (menadione) was found to be an irreversible inhibitor of Cdc25B with an IC_{50} value of 3.6 ± 0.6 μM.[25] Nocardiones A and B were isolated from the Nocardis strain TP-A0248 and shown to inhibit the activity of Cdc25B with an IC_{50} of 17 μM.[26] Coscinosulphate was isolated from the New Caledonian marine sponge *Coscinderma mathewsi* and proven to be a potent deactivator of Cdc25A with IC_{50} of 3.0 μM.[27] Suramin is one of the oldest synthetic therapeutics and has been used for the treatment of sleeping sickness and onchocerciasis.[28] Zhang and coworkers screened sumarin and 45 sumarin analogues against a panel of seven PTPases and found sumarin to be a potent inhibitor of Cdc25A with an IC_{50} of 1.5 μM.[29] In addition, 3 analogues of sumarin were found to be potent (IC_{50} < 5 μM) and specific inhibitors of Cdc25A. Some polyprenyl-hydroquinones and polyprenyl-furans, isolated and identified independently from three sponges (*Spongia officinalis, Ircinia spinulosa, Ircinia muscarum*) were found to be potent Cdc25 phosphatase inhibitors.[30] However, these compounds were found to be inactive against the PSTPase PP2C-α and the three kinases CDK1, CDK2 and CDK3, implying that a potent and selective inhibitor of the Cdc family could be derived from these structures.

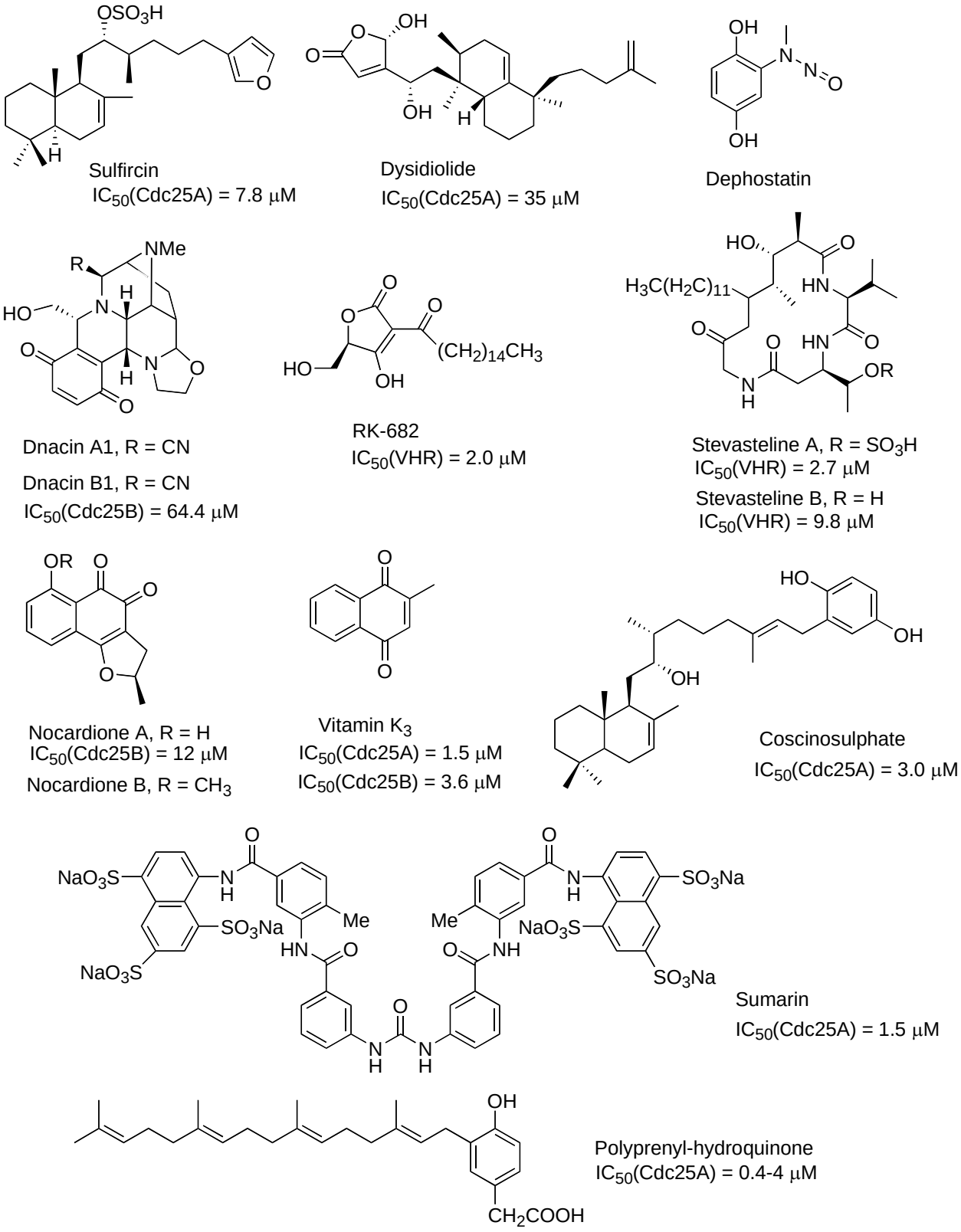
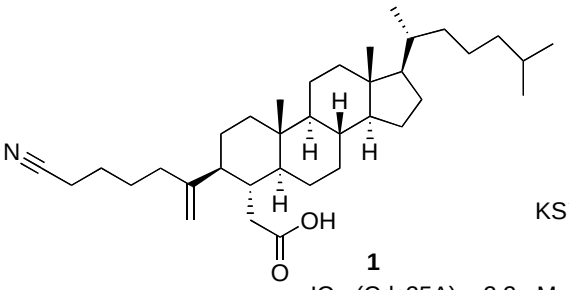


Figure 9. Natural product DSPasese inhibitors

In addition to natural products, a number of synthetic compounds were also tested for inhibitory activity against the Cdc25 family (Figure 10).[6,16] Compound **1**, which was produced by pyrolysis of a cholesteryl derivative, inhibits Cdc25A in the low μM range.[20] Compound **2**, which was developed in an effort to produce a simpler inhibitor structure, showed higher potency than the parent compound.[31] Compound **3**, an analog of vitamin D3, possesses Cdc25A-inhibitory activity in vitro and causes G1 arrest in HL60 cells, as expected of Cdc25A inhibitors.[32] Although, like with almost all of the described compounds, little is known about their selectivity against PTPases or even against other Cdc25 isoforms in vitro or within cells, synthetic quinones have also been found to have activity against Cdc25. Cellular studies with compound **4**, a vitamin K analog, indicate blockage of cell cycle progression at the G1/S checkpoint, an increase in Cdk2 phosphorylation and a concomitant decrease in Cdk2 activity, consistent with inhibition of Cdc25A.[33] Another synthetic vitamin K analog, compound **5**, was independently identified as a partial-competitive inhibitor of Cdc25.[16(b)] Bergnes and colleagues, in an effort to explore the active site of Cdc25, designed a group of mechanism-based inhibitors using a four-component Ugi reaction. One diamide, compound **6**, was the first submicromolar inhibitor of Cdc25 reported to date and had a 7- and 120-fold selectivity for Cdc25A compared with VHR and PTP1B, respectively.[34] Bockovich and coworkers prepared 24 analogues of sulfircin and reported compounds **7**-**10** as the most active analogues[18b)] This study revealed that compounds with the longest side chains were equipotent or more potent than the natural product, indicating the importance of the length of the side chain. The Sodeoka group derivatized RK-682 by manipulating the substituents at C-3 and increasing the hydrophobicity at the C-5 position to produce potent inhibitors **11**-**14** with selectivity for Cdc25B.[35] Two series of analogues of alkylphospholipids were prepared and evaluated for their ability to inhibit Cdc25 phosphatase by

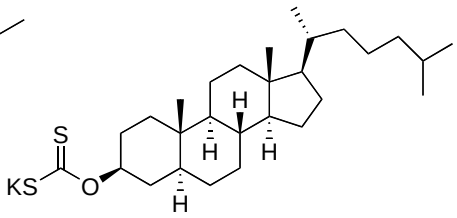
the Koufaki group. The most active compound was the *N*-morpholino derivative **15,** which was shown to cause very weak inhibition of Dspases.[36] Rudolph and coworkers described that indolyldihydroxyquinones such as **16** and **17** bind reversibly to the active site of Cdcs with submicromolecular potency.[10] SAR studies of the 50 derivatives show interesting and consistent trends, revealing features required for inhibition of Cdc25s. The compounds did not exhibit time-dependent inhibition, indicating that they do not form covalent bonds or oxidize the active site thiol. BPR0L075 (**18**), a synthetic compound discovered in the course of identifying new microtubule inhibitors, showed cytotoxic activity in a variety of human tumor cell lines.[37] Additional studies indicate that the effect of this compound on the cell cycle is associated with an increase in cyclin B1 levels and a mobility shift of Cdc2 and Cdc25C. Therefore, BPR0L075 can be considered as an inhibitor of Cdc25C. Ham et al. reported that the fluorinated compound **19**, derived from optimizing the electronic properties of the quinone system using the semi-empirical AM1 method, was 3-fold more potent than the parent compound **5** as an inhibitor of Hep3B cell growth.[38] This compound is also possibly a potent inhibitor of the Cdc family.

Unfortunately, selective and highly potent inhibitors of Cdc25 are still lacking in spite of considerable synthetic and biological studies with natural and synthetic compounds. Therefore, it is worthwhile to find a potent and selective inhibitor of Cdc25 and use it to elucidate the cancer biology of Cdc25 subtypes.



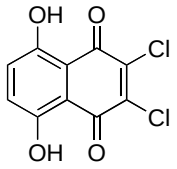
1

IC_{50}(Cdc25A) = 2.2 μM



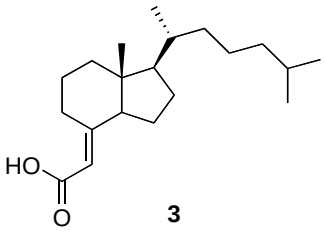
2

IC_{50}(Cdc25A) = 1.1 μM



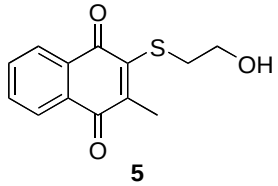
4

IC_{50}(Cdc25A) = <5 μM



3

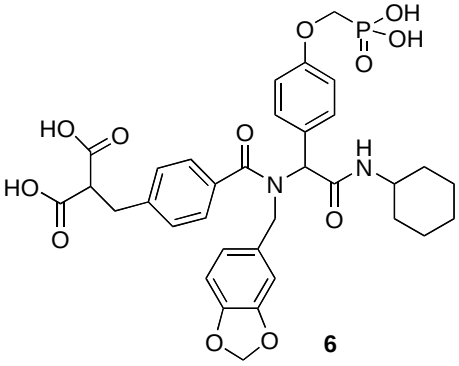
IC_{50}(Cdc25A) = 7.7 μM



5

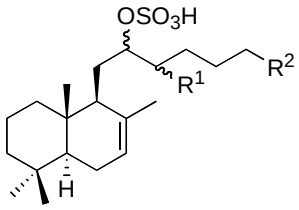
IC_{50}(Cdc25A) = 0.8 μM

IC_{50}(Cdc25B) = 3.8 μM



6

IC_{50}(Cdc25A) = 0.7 μM



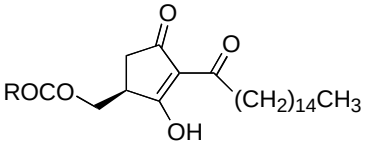
7, R^1 = H; R^2 =3-Furyl

IC_{50}(Cdc25A) = 2.8 μM

8, R^1 = H; R^2 =3-Furyl

9, R^1 = Me; R^2 = 3-Furyl

10, R^1 = H; R^2 = Ph

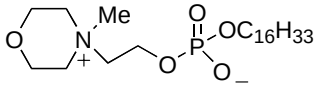


11. R = C_6H_4-3-COC_6H_5

12. R = C_6H_4-4-COC_6H_5

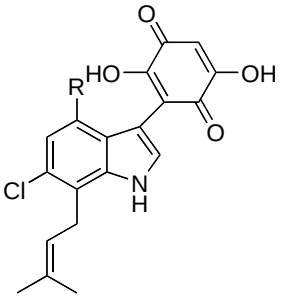
13. R = C_6H_4-3-C(-N=N-)CF_3

14. R = C(=N_2)$CO_2CH_2CH_3$



15

IC_{50}(Cdc25A) = 40 μM



16, R = H

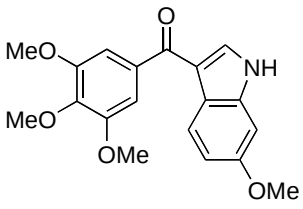
IC_{50}(Cdc25A) = 4.0 μM

IC_{50}(Cdc25B) = 7.2 μM

17, R = Cl

IC_{50}(Cdc25A) = 5.0 μM

IC_{50}(Cdc25B) = 2.3 μM



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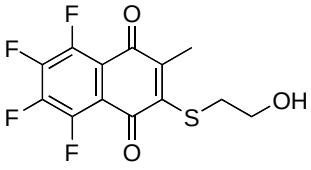


19

Figure 10. Synthetic DSPases inhibitors

1.1.3. Wipf Group Research on Phosphatase Inhibitors

The Wipf group has been involved in the synthesis of several potent phosphatase inhibitors. Initially, a library of small-molecule PSTPase inhibitors was prepared using combinatorial synthetic methods (Figure 11). In this case, a natural product (calyculin A) was used in the design of pharmacophore platforms for combinatorial synthetic approaches.[39] Among the library compounds, SC-ααδ9 was found to be a competitive inhibitor of all human Cdc25 isoforms in vitro with low μM *K*i values. SC-ααδ9 also inhibits cell cycle progression at both the G1 and G2/M phases in synchronized murine mammary carcinoma cells, causes enhanced tyrosine phosphorylation of Cdk1, Cdk2, and Cdk4, and decreases Cdk4 kinases activity.[39] Later, SC-ααδ9 was found to be a phospholiphase inhibitor.[40]

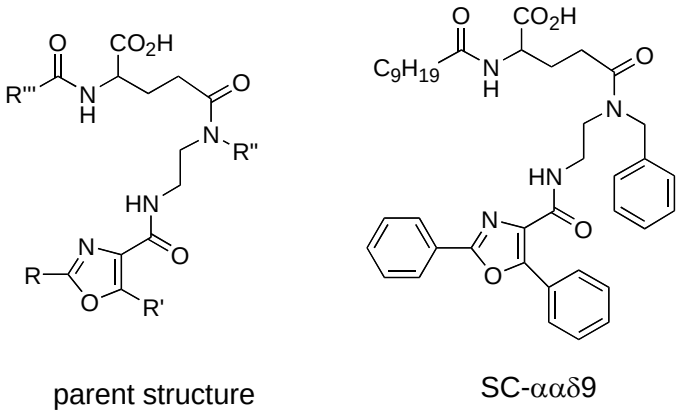
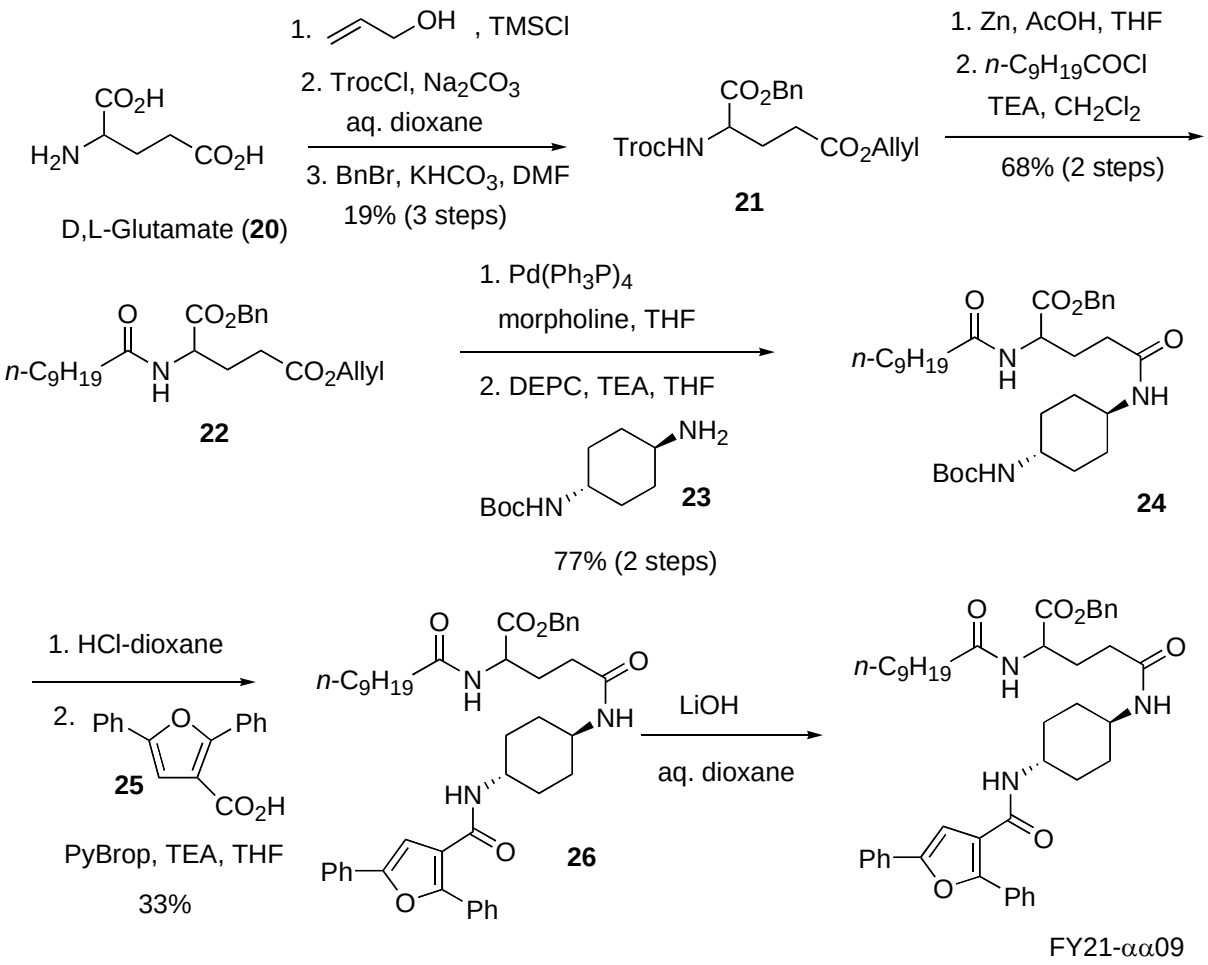


Figure 11. SC-ααδ9 and its parent structure

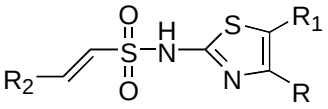
Rigidifying the SC-ααδ9 pharmacophore yielded FY21-αα09, which is slightly more potent as an inhibitor of Cdc25 and has improved selectivity for the Cdc25 class of phosphatases.[2(a)] The synthesis of FY-αα09 is illustrated in Scheme 1. *D,L*-Glutamic acid (**20**)

was selectively esterified with TMSCl in allyl alcohol, N-protected with TrocCl, and benzylated with bezyl bromide to provide **21**. Protected glutamate **21** was acylated after removal of the Troc-group at the *N*-terminus to give **22**, which was deallylated under catalytic Pd conditions, and coupled to mono-Boc-protected diamine **23** to give **24** in 52% yield from **20**. Cleavage of the Boc group in **24** with hydrochloric acid and coupling with oxazole **25** using PyBroP as a coupling reagent gave **26**, which was easily saponified with lithium hydroxide to give the desired FY21-αα09.



Scheme 1. Synthesis of FY21-αα09[2(a)]

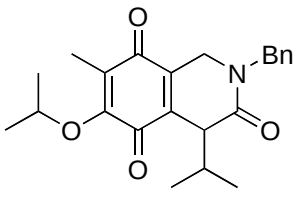
The development of a new heterocyclic scaffold, compound **27**, was inspired by the SAR of substituents at the oxazole moiety of SC-ααδ9 (Figure 12).[41] A library of sulfonated aminothiazoles was prepared and screened for inhibitory activity against Cdc25B, VHR and PTB 1B. Among the best inhibitors, compounds were all substituted with halogenated aromatic rings at positions of R and R_2.



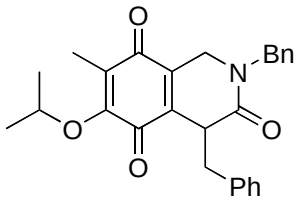
27

Figure 12. Aminothiazole scaffold

Ninety-six synthetic intermediates related to the dnacin group of naphthyridinomycin antibiotics were screened for inhibition of the dual-specificity phosphatase Cdc25 and for DNA cleavage.[42] Biological evaluation led to low-micromolecular inhibitors of DSPases, such as compound **28** and **29** (Figure 13). These results implied that the isoquinoline-5,8-dione functionality of the natural product might be responsible for the inhibition of Cdc25.



28

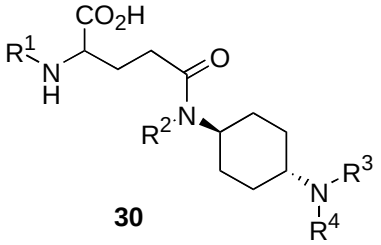


29

Figure 13. Representative structures of dnacin analogues

1.2. Strategy and Goals

As mentioned in Section 1.1.3, FY21-αα09 showed slightly higher potency than SC-ααδ9 as an inhibitor of Cdc25 as well as selectivity for the Cdc25 class of phosphatases.[2(a)] Although the difference in activity between FY21-αα09 and SC-ααδ9 was not significant, we thought that the cyclohexyl-diamine core might serve as a better spacer between the oxazole moiety and the carboxylic acid chain than the ethylene diamine linker. Thus, we selected **30** as a new pharmacophore and decided to synthesize some derivatives of this lead structure (Figure 14).



30

R^2, R^3 = H, Bn

R^1, R^4 = SO_2Ar, COHet, COC_9H_{19}

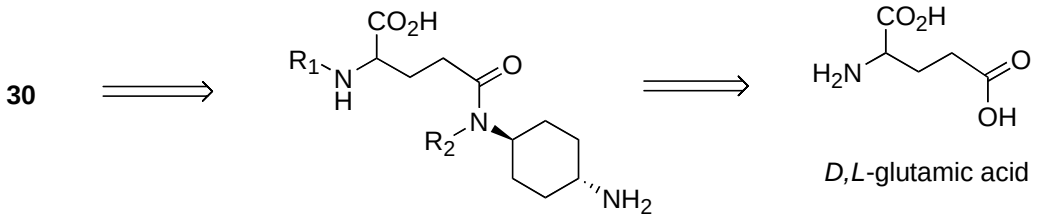
Ar = aromatic

Het = heterocyclic

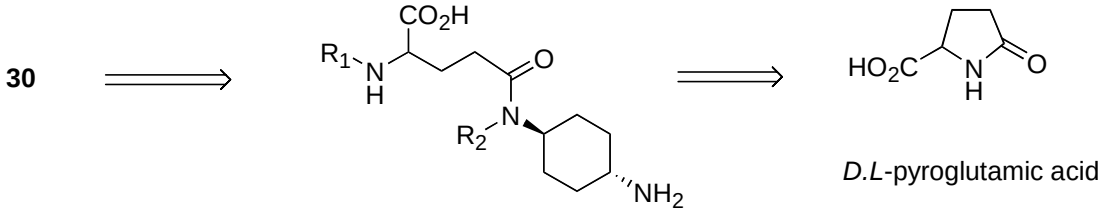
Figure 14. Planned modifications of FY21-αα09

As synthetic methods for compound **30**, two routes were designed as shown in Scheme 2. For the first route, we decided to use a similar sequence as previously in the synthesis of FY21-αα09 and SC-ααδ9, starting with *D,L*-glutamic acid. For the second route, we decided to use *D,L*-pyroglutamic acid as a starting material and a ring opening of the lactam as a key reaction. At that time, we decided to pursue both routes to select the best one for potential further use in scale-up.

1. First route to compound **30**

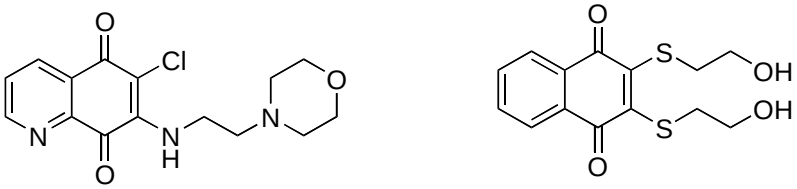


2. Second route to compound **30**



Scheme 2. Two retrosynthetic approaches to **30**

The screening of NSC compounds[43] by the Lazo group (Department of Pharmacology, University of Pittsburgh) identified some new potent phosphatase inhibitors.[44,45] Among them, two compounds, namely NSC 663824 and NSC 95397, showed significant activity against Cdc25 (Figure 15). Therefore, syntheses of analogues of these two compounds were highly desirable.



NSC 663824 NSC 95397

Figure 15. NSC 663284 and 95397

We decided to synthesize analogues of NSC 663824 first with isoquinoline and phthalazine moieties in place of the quinoline in NSC 663824, in order to probe the effect of the location of the nitrogen atom in the aromatic ring (Figure 15). Also, we decided to synthesize a regioisomer of NSC 663824 and analogues with different substituents to see how substitution patterns affected the activity. For another series of analogues of NSC 663824, we planned to synthesize compounds with different substituents at the C-6 position in the (iso)quinoline-dione to explore the possibility to reduce the toxicity of compounds in animal cells.

For the synthesis of analogues of FY21-αα09, some key (iso)quinoline-dione intermediates would be prepared mainly according to known literature procedures. Then, the desired analogues would be obtained from these key intermediates via addition-elimination or addition-oxidation reactions (Figure 16).

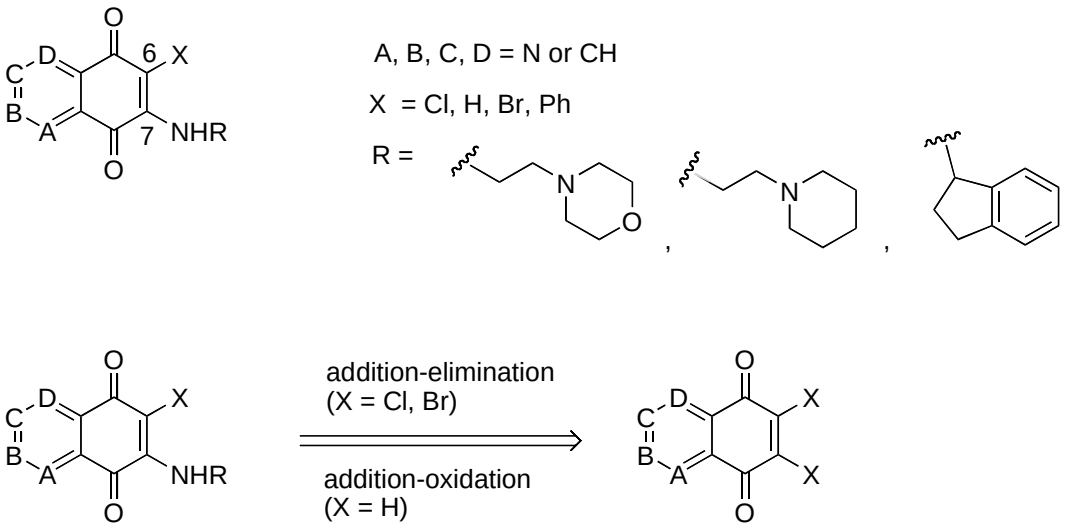
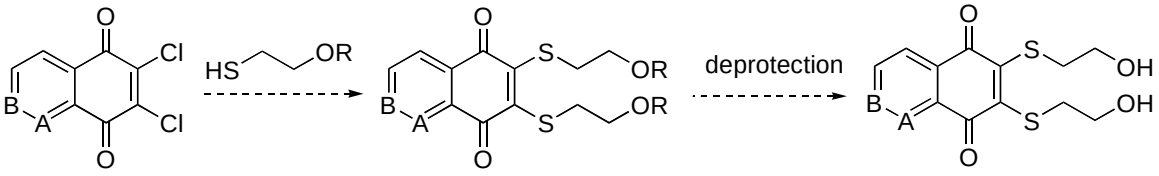


Figure 16. Analogues of NSC 663284

For the synthesis of (iso)-quinoline analogs of NSC 95397, we envisioned that the direct addition of 2-mercaptoethanol to dichloro-(iso)quinoline-dione would lead to a complex mixture, which would be difficult to separate, due to competitive *O*- and *S*-alkylations. Thus, we planned a stepwise sequence, which involved a selective *O*-protection of 2-mercaptoethanol, addition-elimination, and removal of the alcohol protective group (Scheme 3).



A, B = N, CH or CH, N

Scheme 3. Planned synthesis of (iso)-quinoline analogs of NSC 95397

Even though quinone compounds have exhibited good inhibitory activities against Cdc25, they are thought to be irreversible inhibitors presumably due to the covalent adduct formations with active site residues of Cdc25.[46] This trait is generally avoided in medicinal chemistry.[10,12] Thus, we also decided to synthesize some heterocyclic analogues with 2-aminoethanol-morpholine moieties to avoid the possibility of covalent adduct formation between quinones and active site residues of enzymes (Figure 17). The goal of our synthesis was therefore to remove the opportunity for covalent binding between the active site residues and the inhibitor while simultaneously increasing the affinity for this site by establishing new noncovalent interactions.

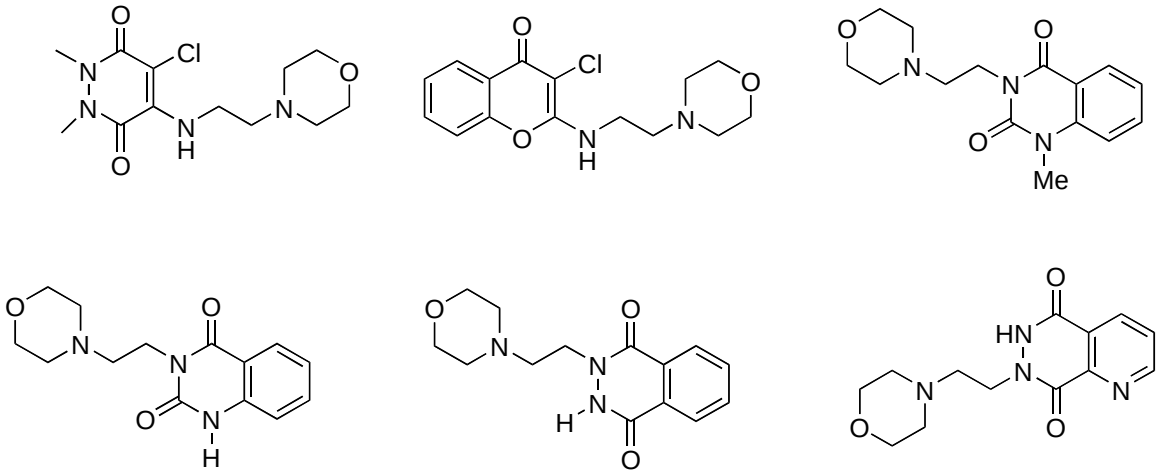


Figure 17. Targets for analogue synthesis

Finally, we decided to synthesize several natural caulibugulones, novel cytotoxic isoquinoline diones and iminoquinones, isolated from an extract of the marine bryozoan *Caulibugula intermis* (Figure 18) and evaluate their biological activities against phosphatases.[47] Caulibugulones attracted our attention because they had isoquinoline moieties, which have been found in potent phosphatase inhibitors. Moreover, we envisioned that their exhibited cytotoxicities might be related to their inhibitory activity against phosphatases.

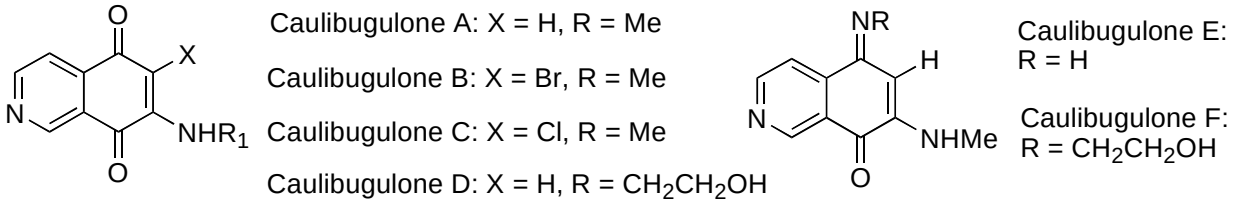


Figure 18. Caulibugulones

1.3. Results and Discussion

1.3.1. Synthesis of Analogues of FY21-αα09

As the first analogues of FY21-αα09, we selected **JUN 1** and **JUN 2**, the hybrid compounds of FY21-αα09 and SC-ααδ9, in the hope that the hybridization of two active compounds would lead to a potent inhibitor against Cdc25 (Figure 19).

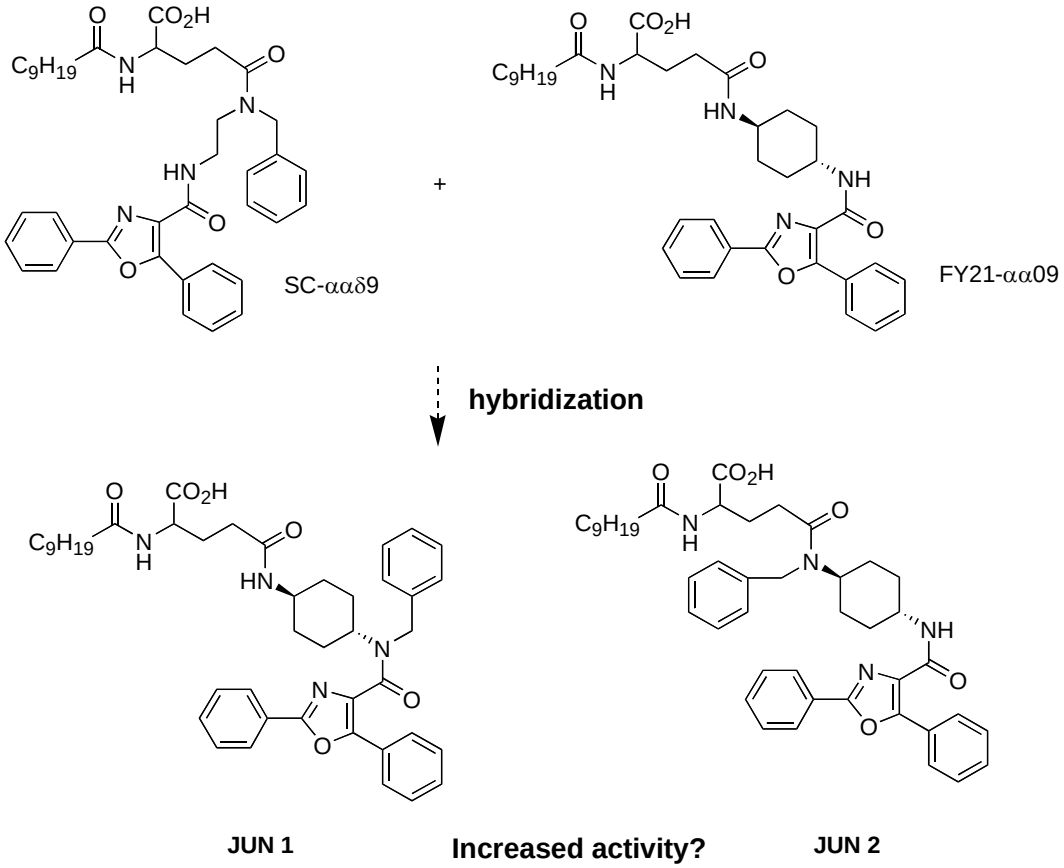
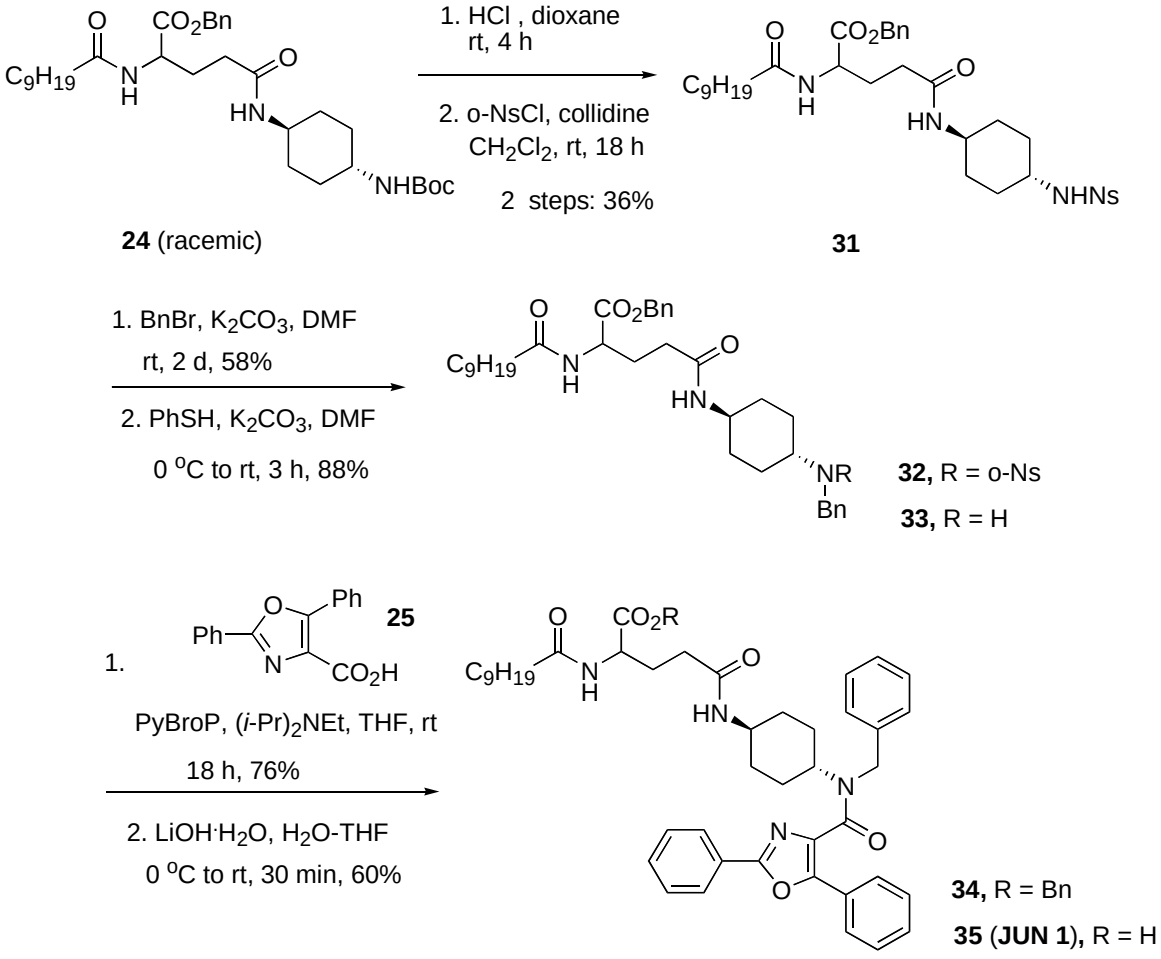


Figure 19. Design of **JUN 1** and **2**

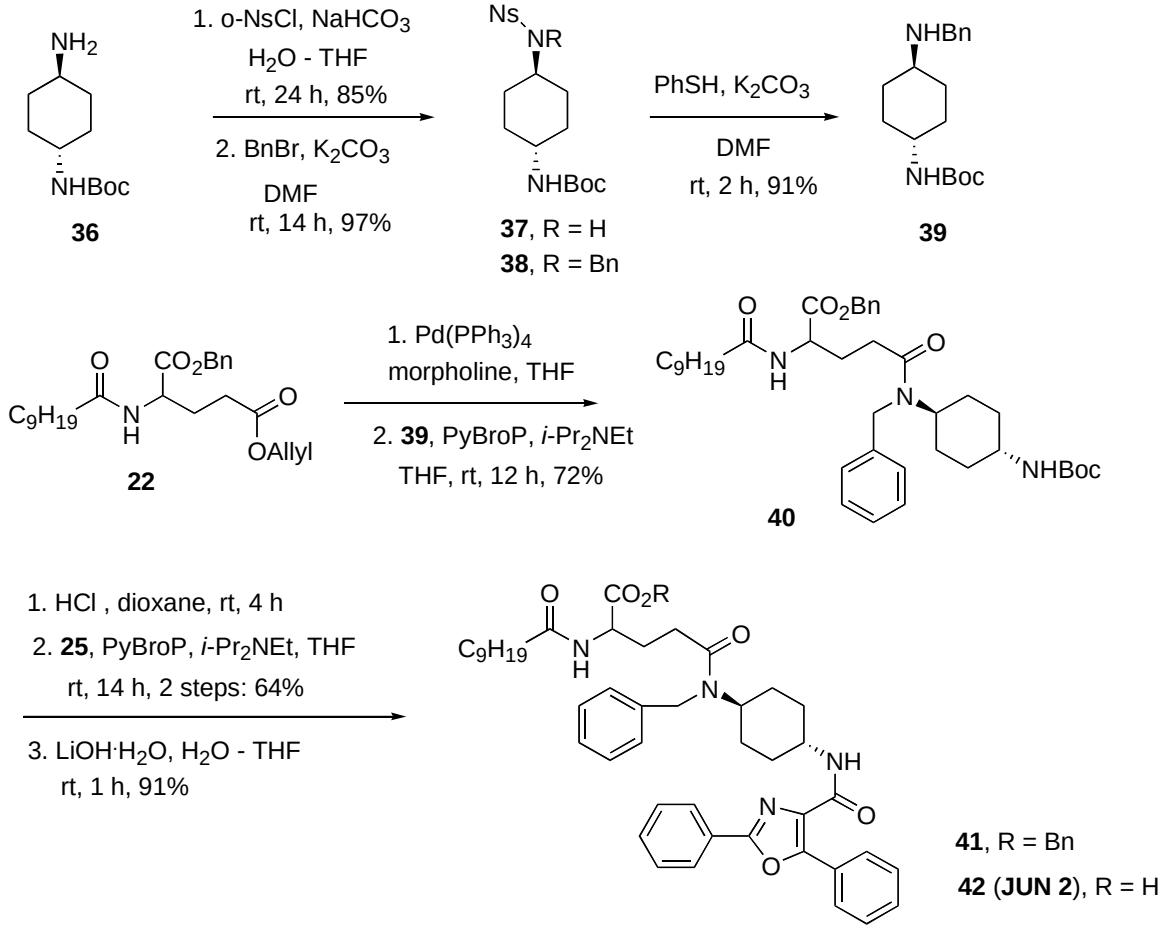
The synthesis of **35** (**JUN 1**)[48] began with the known compound **24**,[2(a)] which was used as a key intermediate for the synthesis of FY21-αα09 (Scheme 4). After deprotection of the Boc group of **24** with HCl in dioxane, several attempts for reductive amination with benzaldehyde

were made, but failed to produce the desired product **33**. Therefore, other protocols for the benzylation of **24** were investigated and we found that an indirect route[49] worked well. Nosylation of the amine derived from **24** gave **31**, and *N*-benzylation followed by removal of the nosyl group gave **33** in good yield. The coupling reaction of **33** with oxazole fragment **25**[50] in the presence of PyBrop as a coupling reagent, followed by saponification of **34**, afforded the target compound **35** (**JUN 1**).



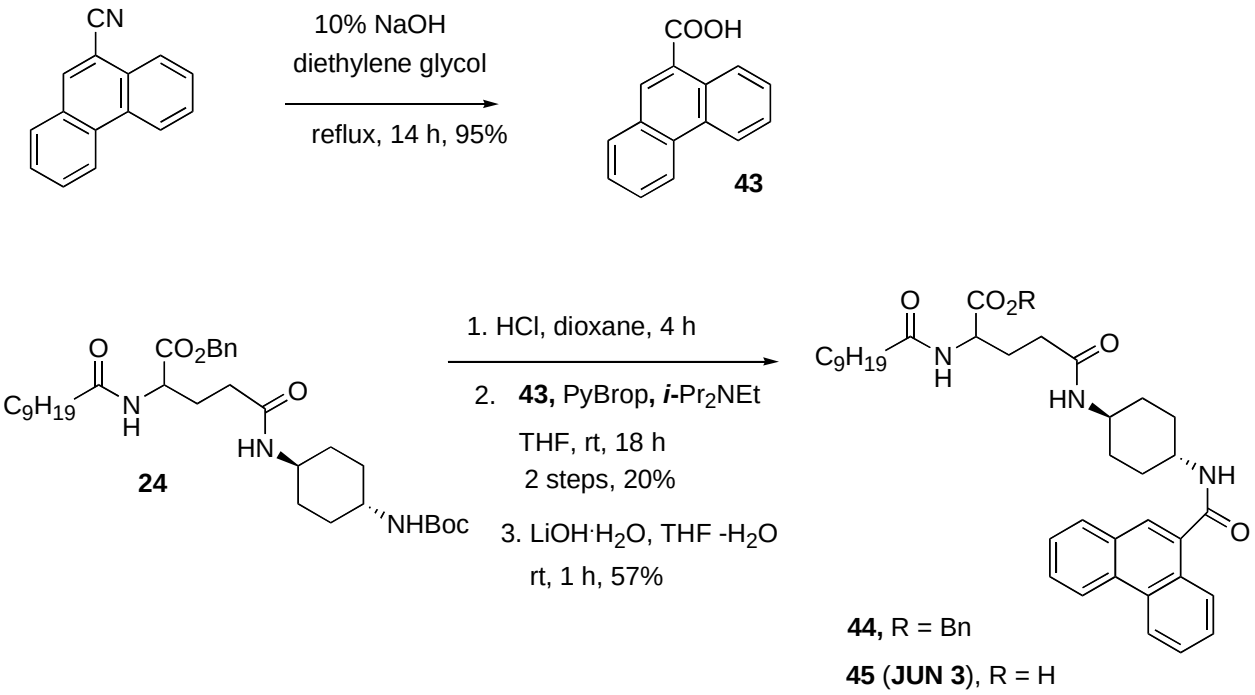
Scheme 4. Synthesis of **JUN 1**

For the synthesis of **JUN 2** (a regioisomer of **JUN 1**), the mono-Boc protected diamine **36** was prepared from 1,4-diaminocyclohexane and the primary amine in **36** was benzylated to give **39** via a 3-step protocol described in the synthesis of **JUN 1** (Scheme 5). The coupling of benzyl amine **39** with the acid derived from **22**[2(a)] in the presence of PyBrop and Hünig's base led to amide **40**. Deprotection of the Boc group in **40**, followed by coupling with oxazole **25** provided **41** in moderate yield. Finally, saponification of **41** provided **42** (**JUN 2**) in 91% yield.



Scheme 5. Synthesis of **JUN 2**

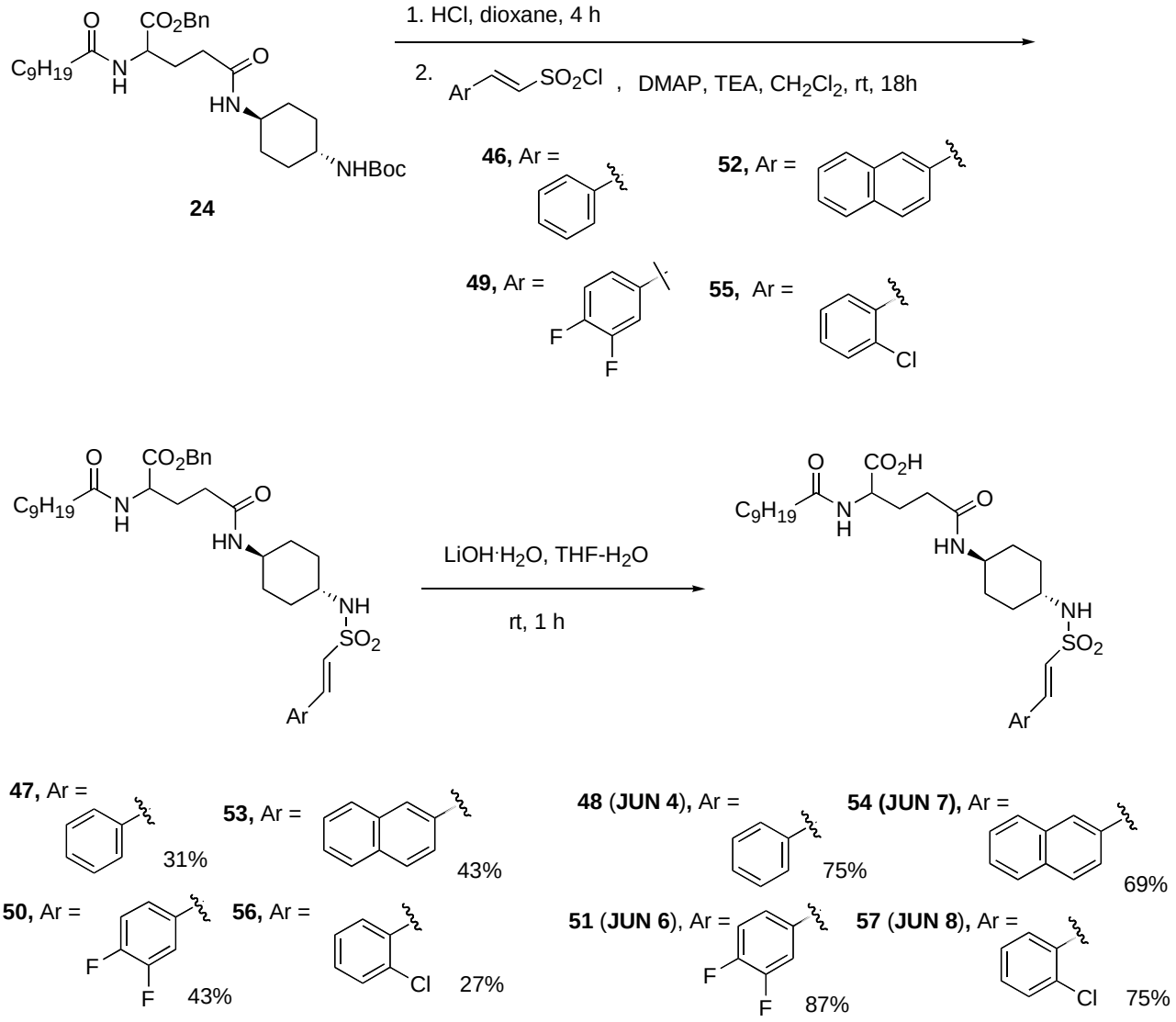
In other analogues of FY21-αα09, we decided to replace the oxazole moiety of FY21-αα09. For the synthesis of **JUN 3**, acid **43**[51] was required (Scheme 6). After several attempts to hydrolyze 9-cyanophenanthrene, we found that heating at reflux in diethylene glycol with 10% NaOH gave the desired product acid **43** in good yield. Under alternative conditions, the reaction often stopped at the amide intermediate, and the use of diethylene glycol as a solvent was critical to accomplish the desired conversion. Subsequently, a reaction sequence analogous to the synthesis of **JUN 1** was used to prepare compound **45** (**JUN 3**). The low yield in the coupling reaction may be due to the low solubility of **43** in THF.



Scheme 6. Synthesis of **JUN 3**

For the synthesis of **JUN 4**, the α,β-unsaturated sulfonyl chloride **46** was prepared according to literature procedures.[52] Recently, **46** had been also used by our group in the synthesis of sulfonylated aminothiazoles, which were identified as new small molecule inhibitors

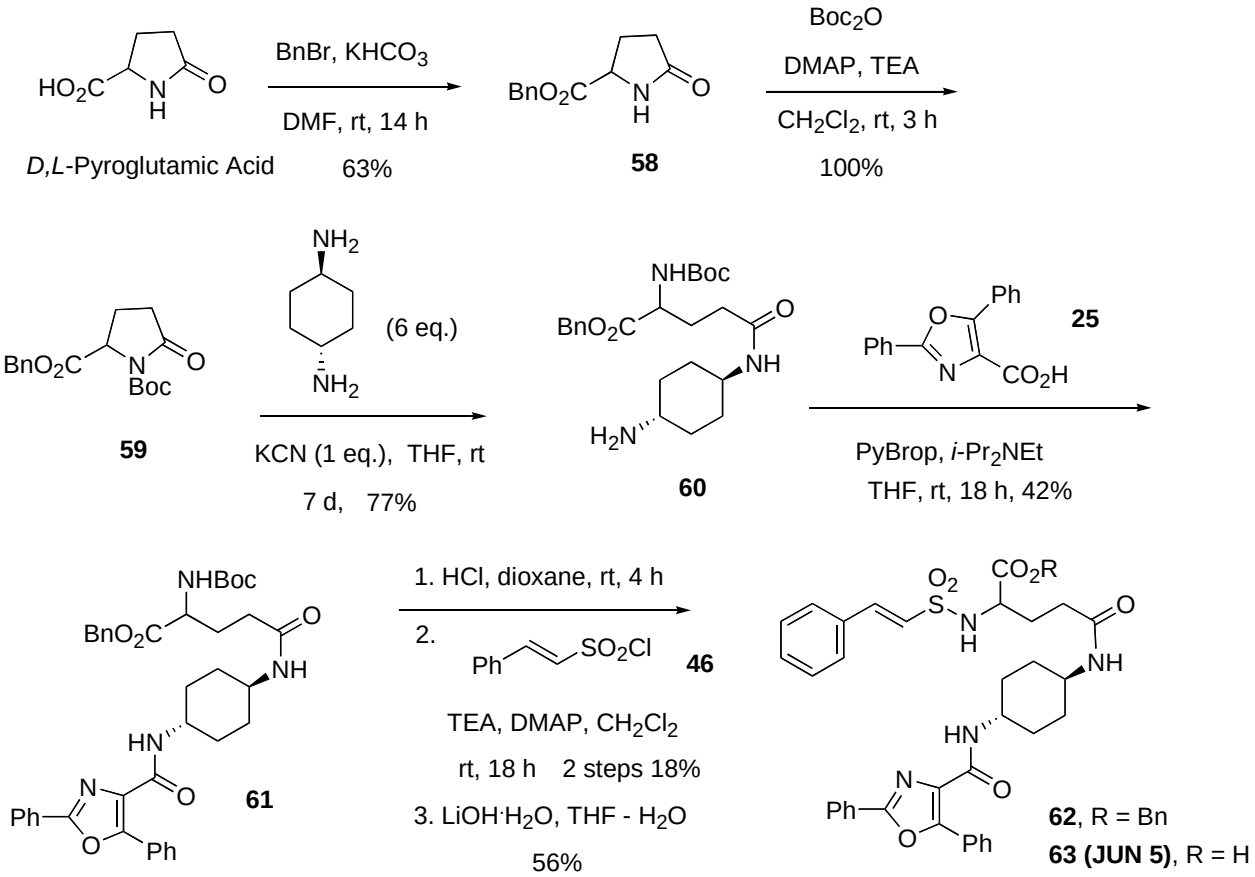
of protein phosphatases.[41] The coupling reaction of Boc-deprotected **24** with **46** proved to be not trivial. After considerable experimentation, we found that the use of TEA as a base and DMAP as an additive gave **47** at least in satisfactory yield (Scheme 7). Subsequent saponification of **47** gave **48** (**JUN 4**) in 75% yield.



Scheme 7. Synthesis of **JUN 4, 6, 7** and **8**

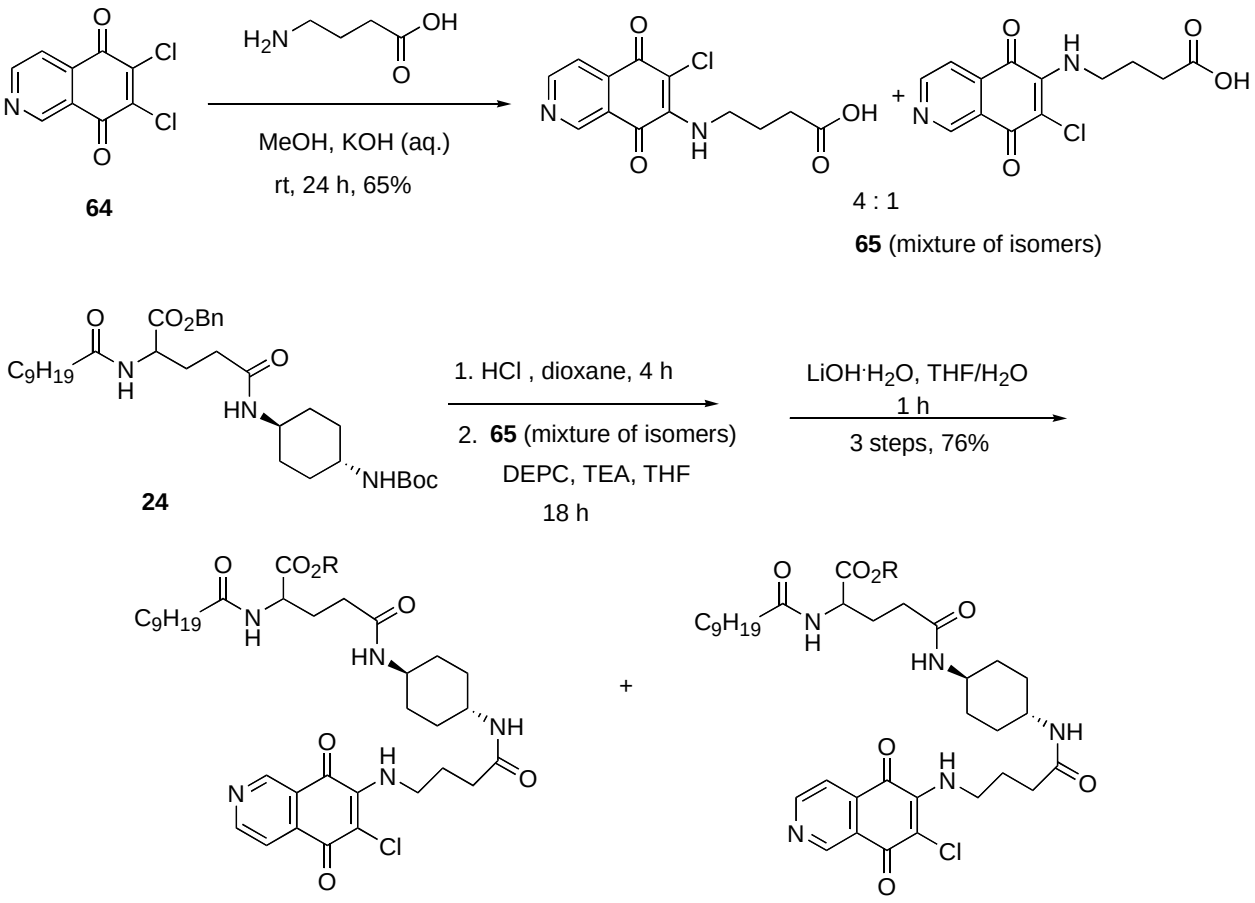
Syntheses of **JUN 6, JUN 7** and **JUN 8** were accomplished analogously to synthesis of **JUN 4** (Scheme 6). α,β-Unsaturated sulfonyl chlorides **49, 52** and **55** were also prepared according to literature protocols.[41,52]

The synthesis of **JUN 5** was mainly initiated to investigate the new synthetic route described in Scheme 2. Thus, for the synthesis of **JUN 5**, a different route using *D,L*-pyroglutamic acid as a starting material instead of glutamic acid was selected (Scheme 8). Initially, this new route was expected to be more concise than the previous one because the number of steps to amine **60** was smaller, however, the feasibility of this route had not been established. The key reaction was the lactam ring opening of pyroglutamic acid. Several attempts to open lactam **59** with 1,4-diaminocyclohexane or mono-protected 1,4-diaminocyclohexane were made, including alane-assisted and ultrasound-mediated reaction conditions. As the first step toward **JUN 5**, benzylation of *D,L*-pyroglutamic acid was performed to give **54** in moderate yield, and Boc-protection of the lactam nitrogen in **58** gave **59**[53] in good yield. After considerable experimentation, lactam-ring opening with 1,4-diaminocyclohexane was accomplished in THF after 7 d in the presence of 1 equiv. of KCN to give the desired product **60** in moderate yield. The long reaction time has to be considered a major drawback of this procedure. With **60** in hand, the coupling reaction with oxazole **25** was performed using PyBrop as a coupling reagent to provide **61.** Deprotection of the Boc group in **61**, followed by coupling with sulfonyl chloride **46** in the presence of TEA provided **62**. The low yield in this coupling reaction was presumably due to the elimination of SO_2 from **27** in the presence of a base such as TEA. Finally, saponification of **62** and acid extraction gave **63** (**JUN 5**). Although the synthesis of **JUN 5** was achieved successfully using this new route, further optimization of some reaction conditions would be desirable.



Scheme 8. Synthesis of **JUN 5**

For the synthesis of **JUN 9**, isoquinolinedione **64** was prepared according to literature procedures[54] and reacted with γ-aminobutyric acid in the presence of KOH to give **65** as an inseparable ~4:1 mixture of regioisomers (Scheme 9). All separation efforts failed and the structure assignment for these regioisomers was based on NMR analysis.[55] Coupling of this mixture with Boc-deprotected **66** using PyBrop as a coupling reagent failed to give the desired pure product. Substitution of PyBroP with DEPC provided **66,** however, and saponification afforded **67** (**JUN 9**). During the entire sequence, the regioisomers could not be separated, and **67** was characterized and assayed as a mixture.



Scheme 9. Synthesis of **JUN 9**

In summary, 9 analogues of FY-αα09 were synthesized. These compounds were tested against $Cdc25B_2$ and some of them were also tested against VHR. All biological assays were performed by the Lazo group at the Department of Pharmacology, University of Pittsburgh and assay methods are described in the experimental section of references 44 and 45. The results are summarized in Table 1. In this case, IC_{50} represents the concentration of a sample that inhibits 50% of enzyme activity.

Table 1. Biological assay results for analogues of FY21-αα09

Sample	IC_{50}[a] vs. $Cdc25B_2$ (n=2) (μM)	Percent Inhibition at 30 μM vs. VHR
FY21-αα09	7	N. D.
JUN 1	29.0	18
JUN 2	25.0	15
JUN 3	76.7	N. D.
JUN 4	345.5	N. D.
JUN 5	27.5	23
JUN 6	329.0	N, D.
JUN 7	78.0	4
JUN 8	165.5	N. D.
JUN 9[b]	9.4	6
JUN 197 (**65**)[b]	0.33	N. D.

N. D., not determined
[a] average value
[b] a mixture of regioisomers was tested.

As shown in Table 1, **JUN 1**, **2** and **5** exhibited less potent biological activity than FY21-αα09 and **JUN 3**, **4**, **6**, **7** and **8** showed much less activity. Though a limited number of compounds were tested, these results suggested that the oxazole moiety in FY21-αα09 might be important for the activity against $Cdc25B_2$ and that addition of a benzyl group to FY21-αα09 did not improve activity. Although, **JUN 9** was identified as the most potent phosphatase inhibitor in this series, this activity appeared to derive mainly from the isoquinolinedione moiety rather than the shared subunit with FY21-αα09. This was proven by the fact that isoquinolinedione **JUN 197**, which was prepared for the synthesis of **JUN 9**, showed greater potency than **JUN 9**. In conclusion, despite considerable synthetic efforts to modify FY21-αα09, no significant

improvement of the biological activity was achieved in this series of compounds (Figure 20). Therefore, we decided to select other molecules as potential Cdc25 phosphatase inhibitors.

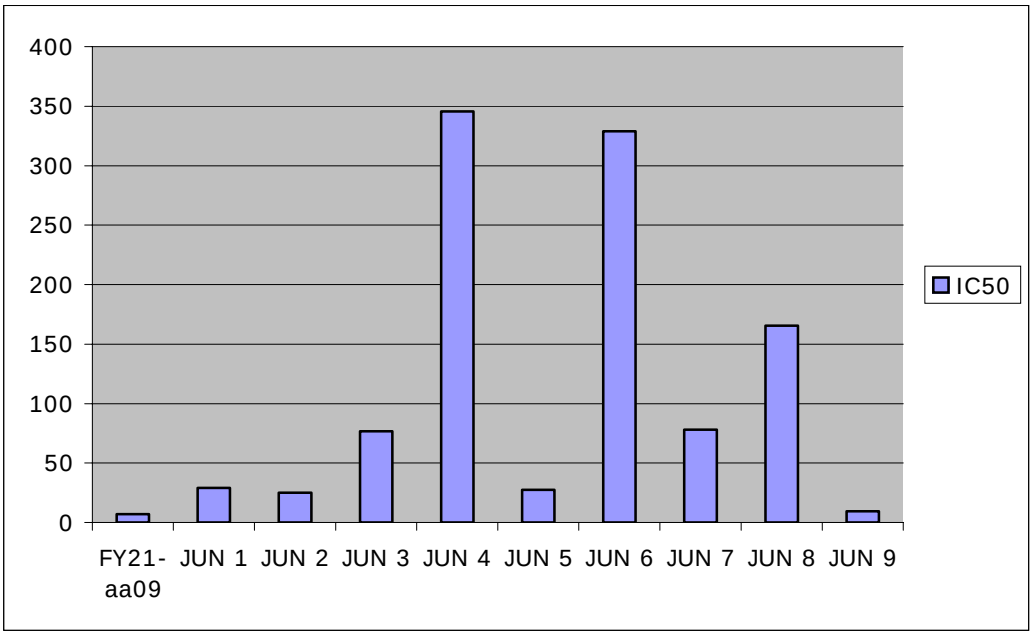


Figure 20. IC_{50} values (μM) of analogues of FY21-αα09 against $Cdc25B_2$

1.3.2. Synthesis of Analogues of NSC 663284

As mentioned in Section 1.2, NSC 663284 showed potent activity against Cdc25. Thus, we decided to synthesize NSC 663284 for scale-up and prepare analogues as shown in Figure 21.

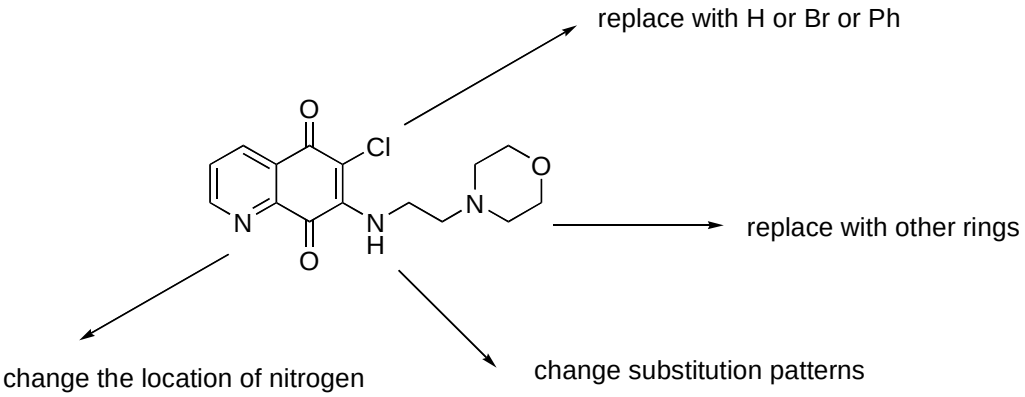
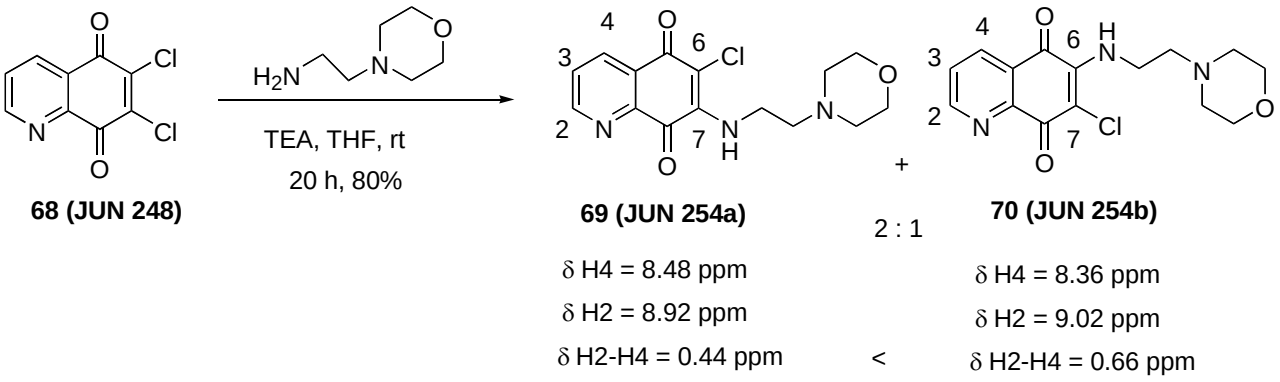


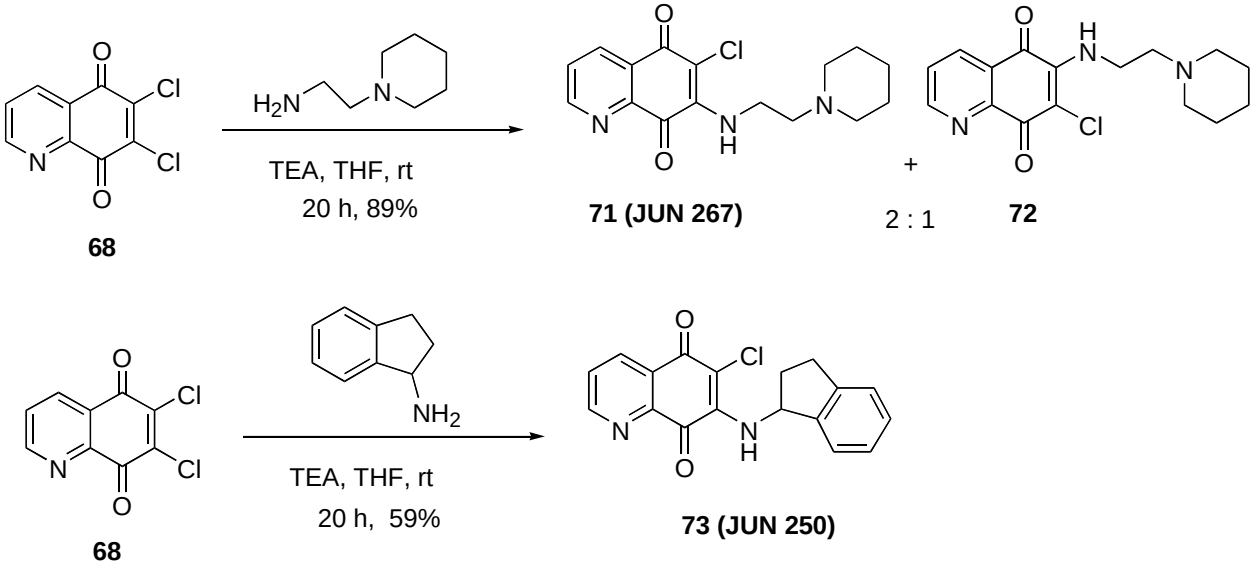
Figure 21. Modifications of NSC 663284

For the synthesis of NSC 663284, compound **68** (**JUN 248)** was prepared from quinolin-8-ol according to literature procedures.[54] Compound **69** (**JUN 254a** = NSC 663284 = DA3003-1) and **70** (**JUN 254b** = DA3003-2) were prepared from the coupling reaction of **68** with 2-morpholin-4-yl-ethylamine in the presence of TEA. The complete separation of these two regioisomers proved to be extremely difficult and only a small amount of pure isomer was obtained by chromatography on SiO_2. The exact structure assignment was mainly based on a literature study.[55] According to that study, we depended on the difference in ^{1}H NMR chemical shift between H(2) and H(4) of **69** and **70** for the assignment of each regioisomer (the chemical shift difference in the 6-isomer is larger than in the 7-isomer) (Scheme 10).



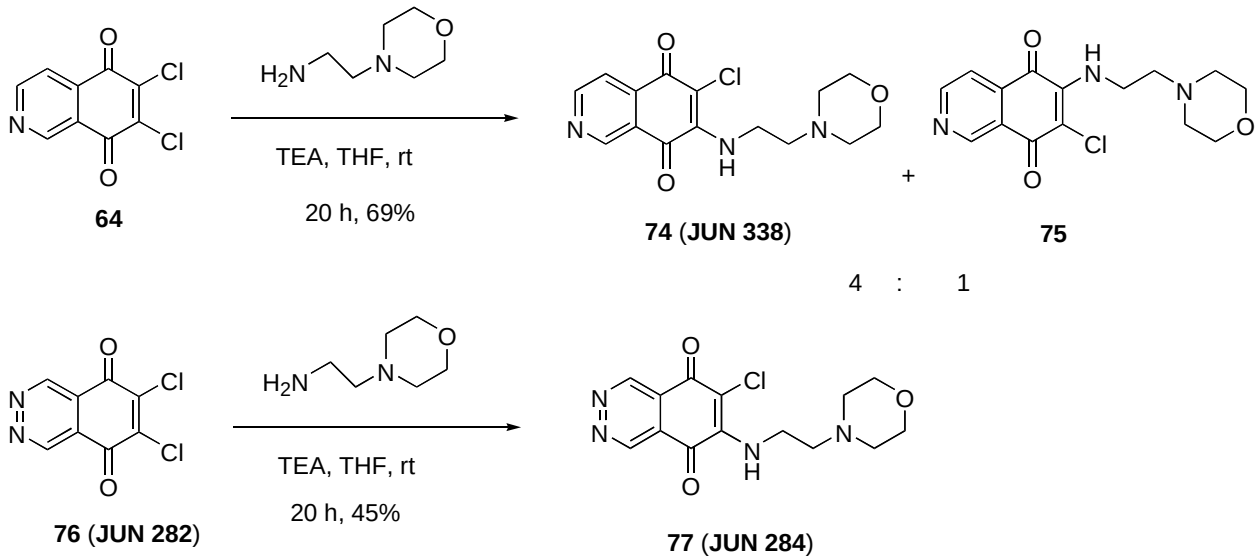
Scheme 10. Synthesis of NSC 663284 and its regioisomer

Coupling of **68** with 2-piperidin-1-yl-ethylamine and indan-1-ylamine, respectively, gave **71** (**JUN 267**) and **73** (**JUN 250**). In case of **JUN 250**, one regioisomer was obtained after work-up and chromatography on SiO_2, even though **JUN 267** was separated from a mixture of regioisomers (Scheme 11).



Scheme 11. Syntheses of **JUN 254a**, **254b**, **267** and **250**

Treatment of **64** with 2-morpholin-4-yl-ethylamine in the presence of TEA provided **74** (**JUN 338**) along with the regioisomer **75** (Scheme 12). Separation of these two regioisomers was performed by chromatography on SiO_2 to give **74** as the major product. The tentative assignment of the regiochemistry of **74** was achieved by ^{1}H-NMR analysis based on the same principles as for the assignment of **69** and **70**, and the putative electronic preference for the formation of the 7-regioisomer.[55,56] This assignment was later confirmed in the course of the synthesis of caulibugulones (*vide infra*). For the synthesis of **77** (**JUN 284**), **76** (**JUN 282**) was prepared from phthalazine in a three-step sequence according to literature procedures.[56] Exposure of **76** to 2-morpholin-4-yl-ethylamine in the presence of TEA provided **77**. The purity of all compounds was checked by reverse phase HPLC and almost uniformly exceeded 99%.[44]



Scheme 12. Synthesis of **JUN 338** and **284**

Biological assays for these compounds were performed by the Lazo group and are summarized in Table 2.

Table 2. Biological assay results for first analogues of NSC 663284

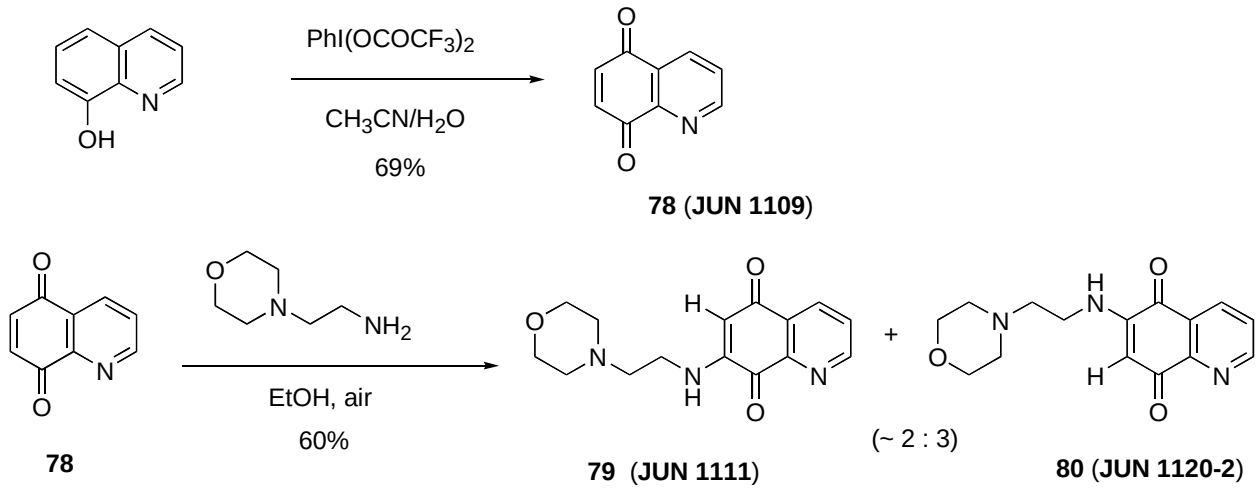
Sample	IC_{50} vs. $Cdc25B_2$ (μM)	IC_{50} vs. VHR (μM)	IC_{50} vs. PTP1B (μM)
JUN 248	4.6 ± 1.0	>10	>10
JUN 183	1.5 ± 0.7	>10	>10
JUN 282	8.9 ± 5.0	>10	>10
JUN 250	0.30 ± 0.03	N. D.	N. D.
JUN 254a	**0.18 ± 0.02**[a]	**4.0 ± 0.1**	**>10**
JUN 254b	0.78 ± 0.44[a]	>10	>10
JUN 267	0.17 ± 0.03[a]	N. D.	N. D.
JUN 284	0.45 ± 0.07	>10	>10
JUN 338	0.59 ± 0.18	1.1[b]	9.8[b]

* IC_{50} values were from 3 or more determinations with SEM indicated.
[a] Values are different from the report[44] since purer samples were retested.
[b] Single determination.
N. D. = not determined.

As shown in Table 2, all compounds in this series showed good activity against $Cdc25B_2$. Especially, **JUN 254a** (structurally identical to NSC 663284) was identified as one of the most potent inhibitors of $Cdc25B_2$ known to date. **JUN 267** also showed high activity against $Cdc25B_2$. **JUN 254a** and **254b** were also tested in antiproliferative and chemical complementation assays.[44] **JUN 254a** had a mean IC_{50} value of 1.5 ± 0.6 μM in the NCI 60 Cell Human Tumor Panel after 48 h. Human breast cancer MDA-MB-435 and MDA-N cells, which had IC_{50} value of 0.2 μM, were most sensitive. Also, 48-h continuous treatment of human breast MCF-7 cells in culture with **JUN 254a** showed an IC_{50} value of 1.7 μM. Even after only 3 h exposure to **JUN 254a**, an IC_{50} for growth inhibition of ~35 μM was observed. Consistent with its in vitro inhibition, **JUN 254a** was 3-fold more potent for growth inhibition after a 3 h

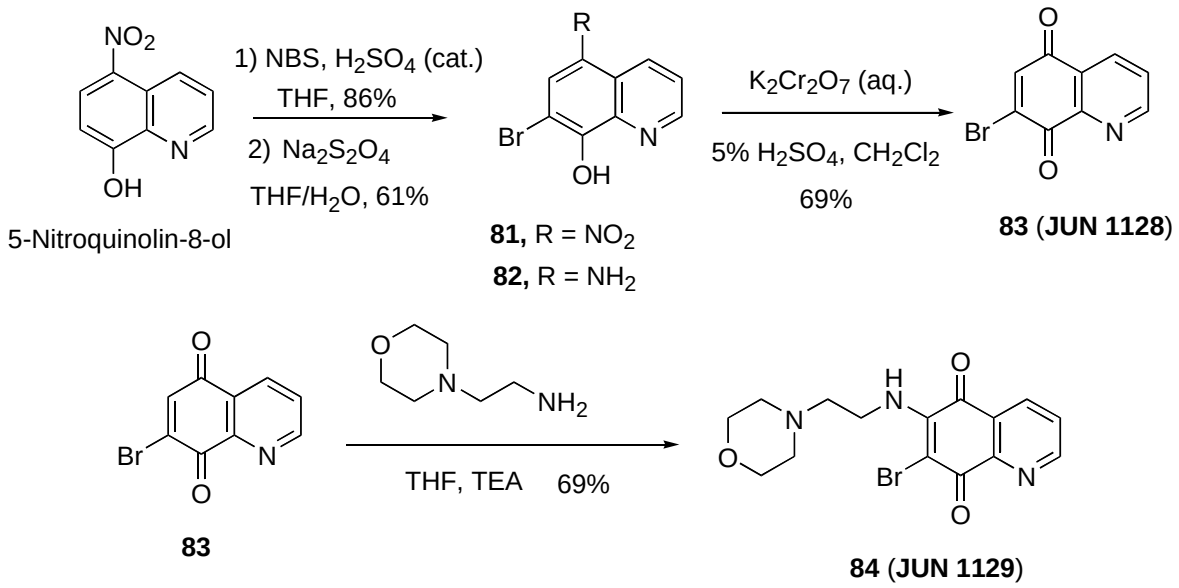
exposure than its regioisomer, **JUN 254b**. A chemical complementation assay was used to probe for inhibition of cellular Cdc25 activity by **JUN 254a**. This assay revealed the ability of a small molecule to complement or reverse a biochemical effect caused by ectopic Cdc25A expression. The results supported the hypothesis that **JUN 254a** blocked the biological effects of Cdc25A within cells. Some more biological assays were performed with **JUN 254a** and **254b** (*vide infra*).

On the basis of the results we described earlier in this section, we can suggest that quinolinediones have a rich potential as lead structures for the development of Cdc25 inhibitors and that they might serve as biochemical probes or even as pharmacophores in new agents for the treatment of cancer or other diseases.[44] Thus, we decided to synthesize more analogs of NSC 663284, which was identified as the most potent inhibitor of Cdc25B. At this time, we decided to replace the chlorine atom at the 6-position in NSC 663284 with other substituents such as hydrogen, bromine and phenyl groups, mainly because the replacement of chlorine may reduce liver toxicity in mice. First, we decided to synthesize the dechlorinated analog **JUN 1111** and we prepared quinoline-5.8-dione **78** by PIFA-oxidation of 8-hydroxyquinone in moderate yield according to a literature procedure[57] as a key intermediate for the synthesis of **JUN 1111** (Scheme 13). The PIFA oxidation proved to be much better for the preparation of **78** than Fremy's salt oxidation since we obtained **78** in only 10% yield with latter reagent. Dione **78** had to be used immediately for the next conversion because it decomposed readily. With **78** in hand, we tried the addition of 4-(2-aminoethyl)-morpholine, followed by air oxidation to give **79** (**JUN 1111**) along with its regioisomer **80** (**JUN 1120-2**) in ~2:3 ratio. Repeated separation of regioisomers by chromatography on SiO_2 provided pure **JUN 1111** and **JUN 1120-2** in several hundred mg quantities. The regiochemistry was assigned by the ^{1}H NMR chemical shift of the vinyl proton.[58]



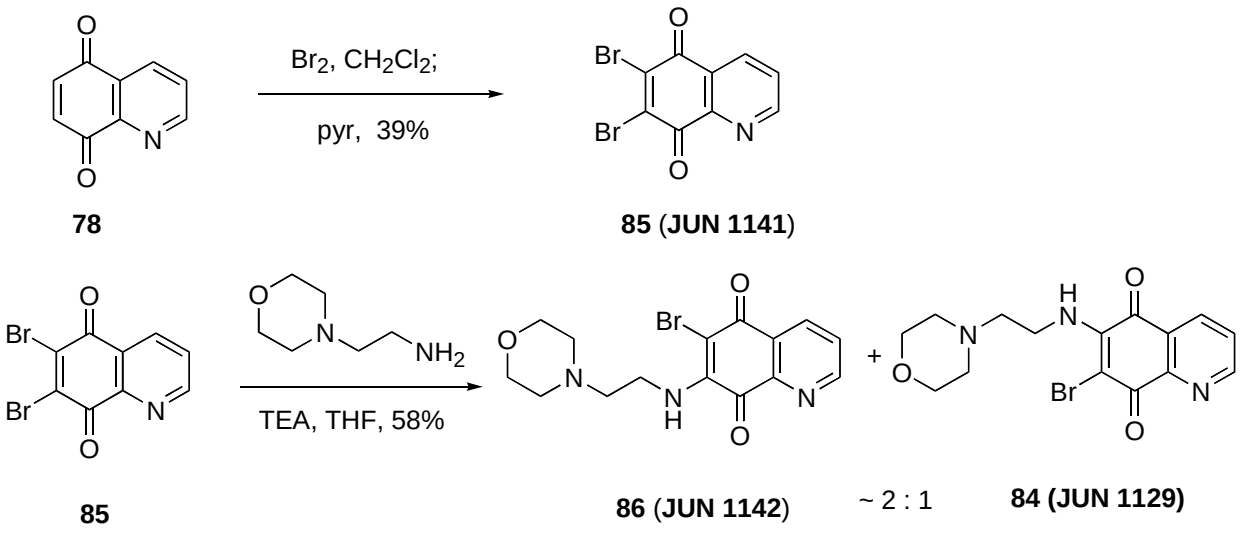
Scheme 13. Synthesis of **JUN 1111** and **1120-2**

Although the regioisomers could be separated by chromatography, we decided to investigate another route to produce **JUN 1111** selectively. Initially, we envisioned that the reaction of the known bromo compound **83**[59] with 4-(2-aminoethyl)-morpholine in the presence of TEA would give **JUN 1111** as the major product via an addition-elimination sequence. For that purpose, we prepared compound **83** in 3 steps according to literature procedures.[59] Bromination of 5-nitroquinolin-8-ol with NBS, reduction of the nitro group in **81** and oxidation of amine **82** provided bromo compound **83** (Scheme 14). With 7-bromoquinolinedione **83** in hand, we tried the conjugate addition-elimination reaction. However, in contrast to our expectation, the reaction of **83** with 4-(2-aminoethyl)-morpholine provide the bromo compound **84** (**JUN 1129**) as the major product instead of **JUN 1111** via an addition-oxidation sequence even in the presence of the base TEA. Based on this result, a regioselective synthesis of **JUN 1111** was not pursued any further.[60]



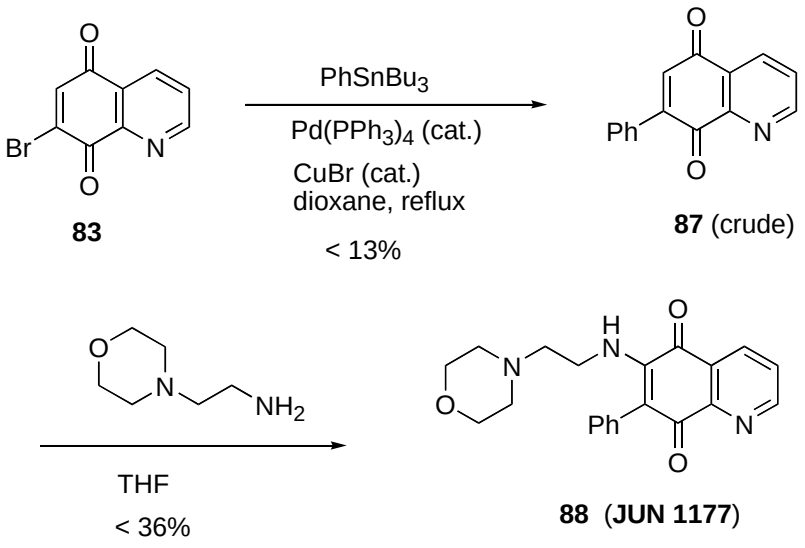
Scheme 14. Synthesis of **JUN 1129**

Next, we synthesized **JUN 1142**, the regioisomer of **JUN 1129** (Scheme 15). The dibromo compound **85** was prepared in 39% yield by the bromination of **78** in the presence of pyridine. Then, 6,7-dibromoquinolinedione **85** was reacted with 4-(2-aminoethyl)-morpholine in the presence of TEA to give **86** (**JUN 1142**) and **87** (**JUN 1129**) in a ~2:1 ratio. Two regioisomers were separated by chromatography on SiO_2, and the regiochemistry of the two compounds was unambiguously determined based on the assignment for **JUN 1129**. This assignment matched well with the previous assignment of the regiochemistry of **JUN 1111** and **1120-2** because the ^{1}H NMR spectrum of **JUN 1142** is very close to that of **JUN 1111** whereas the ^{1}H spectrum of **JUN 1129** is very close to that of **JUN 1120-2**.



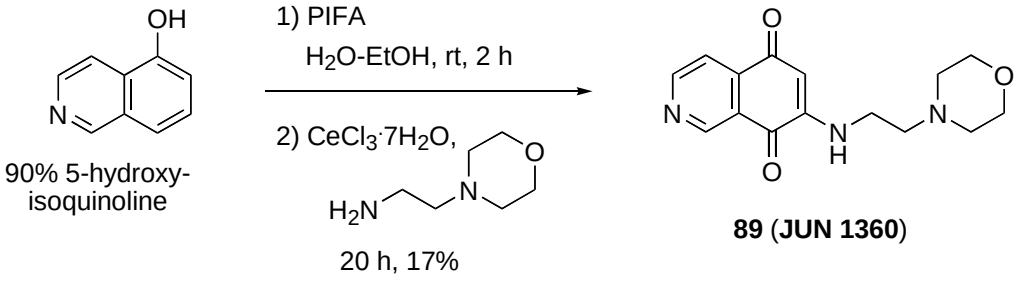
Scheme 15. Synthesis of **JUN 1142**

In addition to the replacement of the chlorine substituent in NSC 663824 with hydrogen or bromine, we wanted to introduce a phenyl group at this position (Scheme 16). Stille coupling of **83** with phenyl *tri*-butyl-tin, followed by addition of 4-(2-aminoethyl)-morpholine provided the phenyl-substituted derivative **88** (**JUN 1177**) in very low yield and purity even after several separation processes.



Scheme 16. Synthesis of **JUN 1177**

The isoquinolinedione **89** (**JUN 1360**) was synthesized from 5-hydroxyisoquinoline in 17% yield via a two step – one pot sequence shown in Scheme 17. Noteworthy is that a single regioisomer was isolated after the reaction and purification. The low yield can be attributed to the poor solubility of the product in organic solvents.



Scheme 17. Synthesis of **JUN 1360**

All analogues of NSC 663284 and their precursors were evaluated for biological activities against Cdc25A, Cdc25B, Cdc25C, VHR and PTB 1B by the Lazo group.[61] Table 3 summarizes the biological data for analogues of NSC 663284.

Table 3. Summary of IC_{50} values (μM concentration) of analogues of NSC 663284 and their precursors

Compounds	Cdc25A	Cdc25B	Cdc25C	VHR	PTB1B
JUN254a	0.50 ± 0.02	1.33 ± 0.59	0.6614[a]	10.1 ± 0.33	15.1 ± 0.52
JUN 254b	1.19 ± 0.11	3.69[a]	3.54[a]	180 ± 58	87.9 ± 7.3
JUN 1111	0.38 ± 0.10	2.78 ± 0.96	1.186[a]	27.9 ± 2.9	36.6 ± 0.26
JUN 1120-2	3.03 ± 0.09	44.6 ± 0.27	15.86[a]	329 ± 17.2	366 ± 40
JUN 1142-1	0.52 ± 0.07	1.18 ± 0.61	0.8589[a]	6.61 ± 1.1	11.9 ± 0.56
JUN 1129	1.92 ± 0.01	10.7 ± 4.17	3.736[a]	86.1 ± 12	93 ± 2.7
JUN 1177	5.45 ± 1.1	13.7 ± 2.5	6.27 ± 0.26	216 ± 42	273 ± 60
JUN 1360	1.76 ± 0.8	3.06 ± 0.7	1.99 ± 0.2	187 ± 33	424 ± 86
JUN 1141	7.45 ± 0.79	9.49 ± 1.4	8.08 ± 0.24	111 ± 30	203 ± 61
JUN 1128	9.21 ± 0.47	11.1 ± 0.85	10.1 ± 0.43	87 ±21	152 ± 15
JUN 1109	9.39 ± 1.9	11.8 ± 0.73	9.81 ± 1.6	132 ± 19	114 ± 23

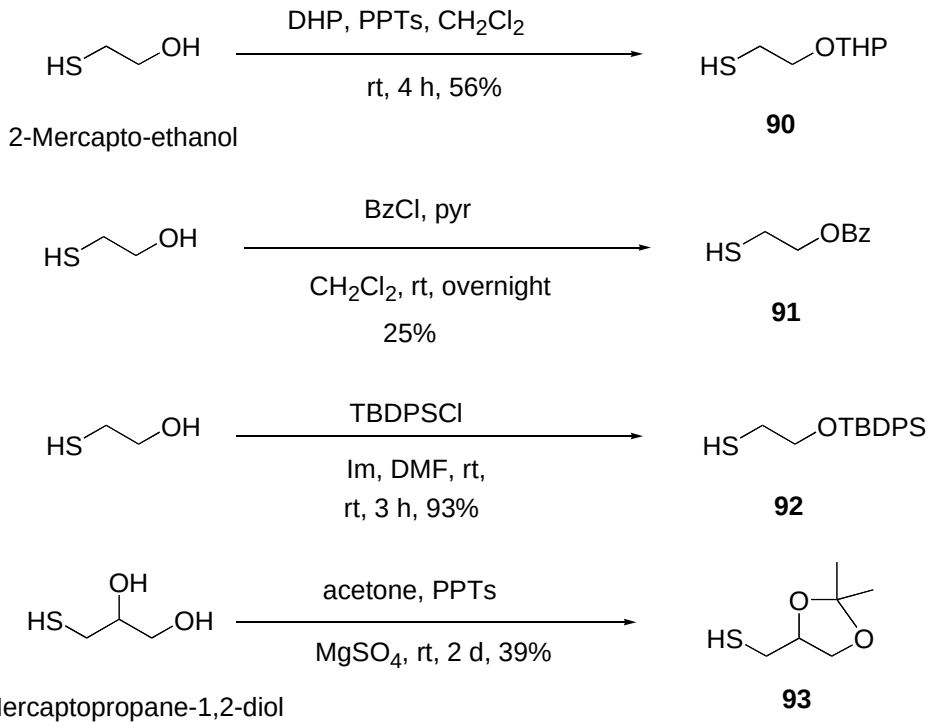
* IC_{50} values were from 3 or more determinations with SEM indicated.
* Specifically, activities against $Cdc25A_1$, $Cdc25B_2$ and $Cdc25C_1$ were measured.
[a] Single determination

Some aspects of the in vitro biological data were quite interesting. All compounds are potent inhibitors of Cdc25 phosphatases. The results show consistently that the 7-regioisomers (**JUN 254a**, **1111** and **1142-1**) are more potent but less selective than the 6-regioisomers (**JUN 254b**, **1120-2** and **1129**), and that compounds substituted with the 2-aminoethylmorpholine moiety are more potent than nonsubstituted precursors (**JUN 1109**, **1128** and **1141**). IC_{50} values are increased in the order Cdc25A < Cdc25C < Cdc25B, and the considerable range indicates that the synthesis of isomer-specific inhibitors is possible. Also, the substituents increase in potency in the order hydrogen ≈ chlorine > bromine > phenyl. Comparison of **JUN 1360** to **JUN 254a** demonstrated that the quinoline scaffold is more potent than the isoquinoline. Besides these

in vitro assays, some additional biological tests[61] were performed for **JUN 254a**, **254b**, **1111**, **1120-2** and **1360**. Reversibility assays using solid support (nickel bead) were performed by the Lazo group to determine whether these compounds are reversible inhibitors. The results suggested that they were all irreversible inhibitors, but **JUN 1111** and **1120-2** did not seem to form a tight covalent adduct. Flow cytometry experiments were also performed to determine if compounds arrested tsFT210 cells in G1 by inhibiting Cdc25A, or G2 by inhibiting Cdc25B or Cdc25C. The results showed that compounds might partially arrest the cell cycle at both G1 and G2. Especially, **JUN 1120-2** and **1360** caused a stronger G2 arrest. Cdc25C MEF cells were treated with **JUN 254a** and **1111** and cell viability (using trypan blue dye) was counted after 3 days of treatment. However, no clear differential effect on Cdc25C knockout and wild type MEF cells was found. More biological experiments are still in progress and will be reported in due course.[61]

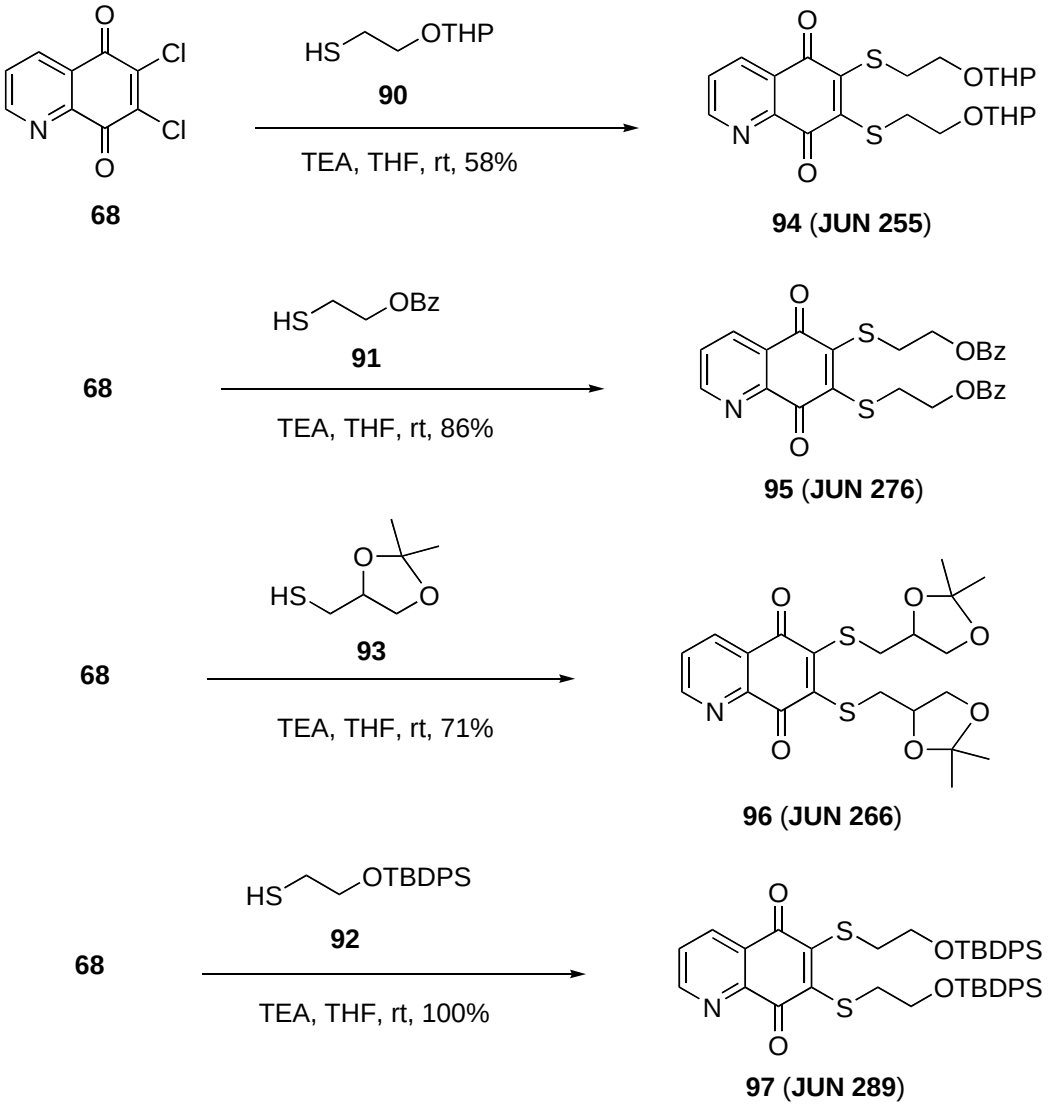
1.3.3. Synthesis of Analogues of NSC 95397

Syntheses of analogues of the NSC 95397 started with the selective protection of the hydroxy groups of 2-mercaptoethanol and 3-mercaptopropane-1,2-diol (Scheme 18). Successful mono-*O*-protection of 2-mercaptoethanol was achieved with THP, Bz and TBDPS groups, but in most cases sulfur-protected compounds were also formed and removed readily by column chromatography because the *O*-protected compounds were less polar than the *S*-protected compounds. It was also noted that the silicon-protecting group was the best in terms of selectivity due to the high affinity of silicon toward oxygen. Thus, **90**,[62] **91** and **92** were obtained in moderate to good yields. Finally, protection of 3-mercaptopropane-1,2-diol by acetone in the presence of PPTs and $MgSO_4$ gave **93**.[62]



Scheme 18. Synthesis of intermediates for the analogues of NSC 95397

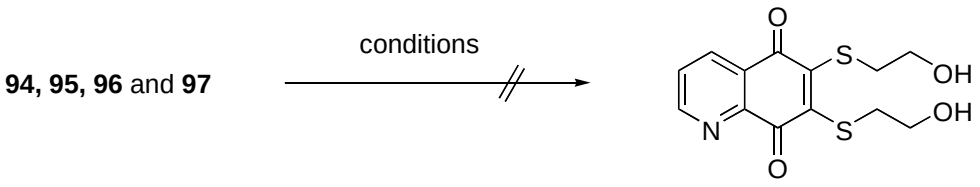
With the *O*-protected compounds in hand, we tried the coupling reaction with 6,7-dichloroquinolinedione **68** in the presence of TEA (Scheme 19). Consequently, compounds **94** (**JUN 255**), **95** (**JUN276**), **96** (**JUN 266**) and **97** (**JUN 289**) were obtained in good yields.



Scheme 19. Synthesis **of JUN 255**, **JUN 276**, **JUN 266** and **JUN 289**

Unfortunately, all attempts for deprotection of these compounds failed to generate the desired free alcohol **98** as described inTable 4. In entries 1-3 and 6, substrates decomposed

slowly after addition of acidic reagents, presumably due to protonations of the nitrogen atom in the quinoline rings. In entries 4, 5 and 7, unidentified polar product(s) were mainly obtained after purifications.

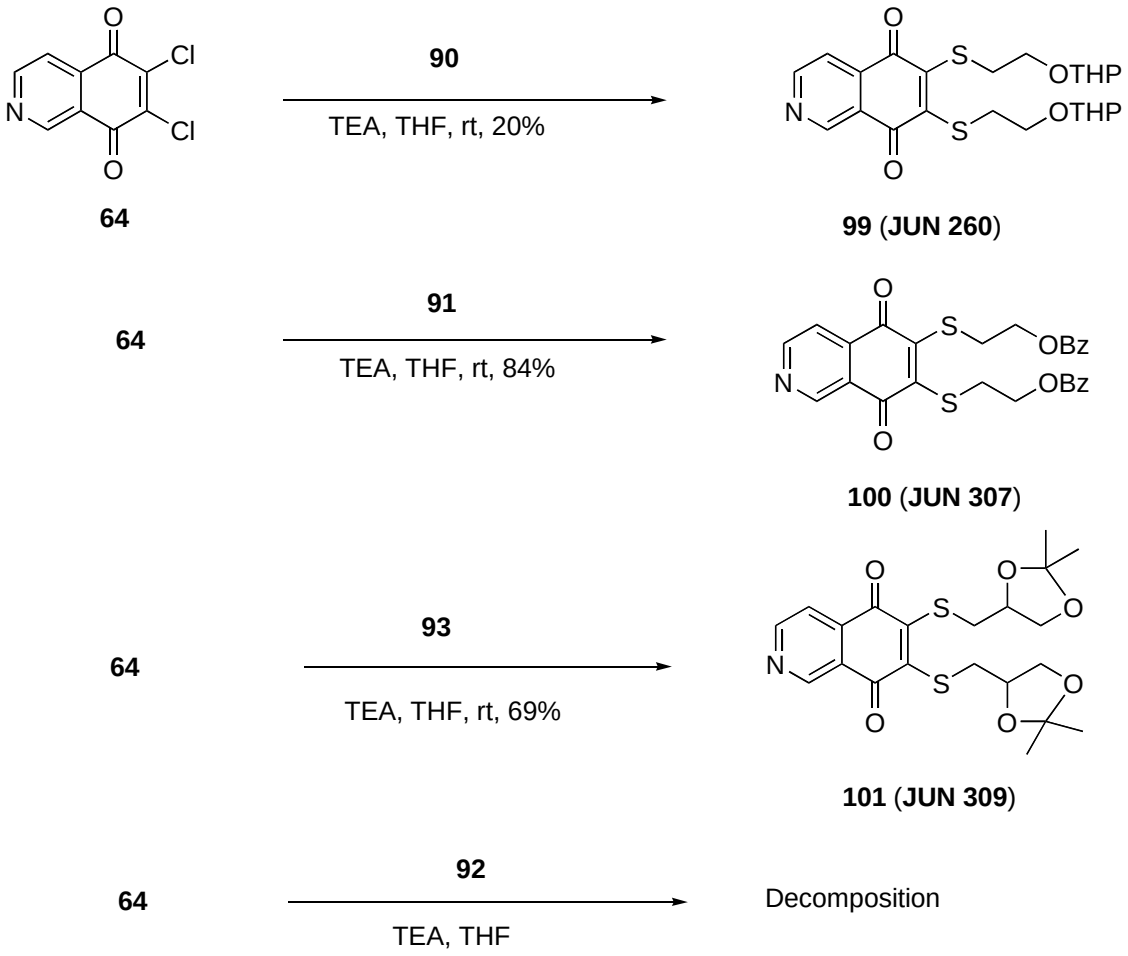


98

Table 4. Attempts for the synthesis of **98**

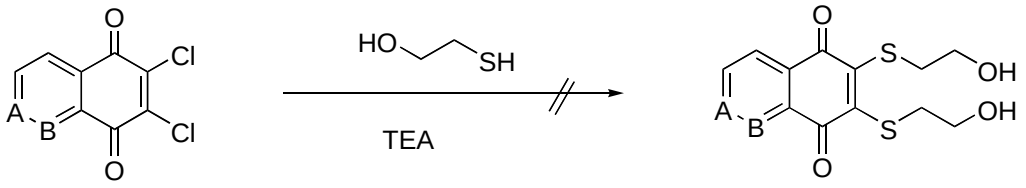
Entry	Substrate	Reaction Conditions	Results
1	**94**	HOAc-THF-H_2O (4:2:1)	Decomposed
2	**94**	PPTS, EtOH	Decomposed
3	**94**	p-TsOH, MeOH	Decomposed
4	**95**	LiOH•H_2O, THF-H_2O	Unidentified polar product(s)
5	**95**	NaOH, MeOH	Unidentified polar product(s)
6	**96**	p-TsOH, MeOH	Decomposed
7	**97**	TBAF, THF	Messy reaction

Compounds **99** (**JUN 289**), **100** (**JUN 307**) and **101** (**JUN 309**) were also prepared from the coupling reaction of 6,7-dichloroisoquinolinedione **64** with **90**, **91** and **93**, respectively (Scheme 20). The reaction of **64** with **92** in the presence of TEA led to decomposition.



Scheme 20. Synthesis of **JUN 260**, **307** and **309**

We also failed in obtaining the desired free alcohol **102** from **99**, **100** and **101**. Thus, we tried direct coupling reactions of **64** and **68** with 2-mercaptoethanol in the presence of TEA, but we could not isolate any desired products **98** and **102**. In most cases, we observed a complex mixture of products, which were not easily separated by standard chromatography conditions (Scheme 21).



64. A = N. B =CH

65. A = CH. B =CH

102. A = N. B =CH

98. A = CH. B =CH

Scheme 21. Attempted coupling of **64** and **68** with 2-mercaptoethanol

Despite our failure to prepare the highly desired free alcohols **98** and **102**, all synthetic compounds were tested against $Cdc25B_2$ by Lazo group. The results are summarized in Table 5.[45]

Table 5. Biological assay results for analogues of NSC 95397

Sample	IC_{50} (μM) vs. $Cdc25B_2$ (n=2)
JUN 255	7.9
JUN 260	2.1
JUN 266	6.3
JUN 276	4.9
JUN 289	Inactive at 10 μM
JUN 307	1.5
JUN 309	1.7

All analogues showed a lower activity than NSC 95397 (IC_{50} vs. $Cdc25B_2$ < 1 μM) presumably due to the increased steric hindrance by bulky alcohol protecting groups. It is also possible that the protection of the hydroxy group might reduce some interaction with an amino acid residue in Cdc25B.

1.3.4. Synthesis of Morpholine Derivatives

Based on the chemical structure of NSC 663284, three possible interactions between NSC 663284 and Cdc25A could be hypothesized. First, NSC 663284 might form a covalent bond with amino acid residues because it is an electrophile. For example, sulfhydryl arylation of a cysteine or etherification of a serine in the catalytic domain of Cdc25A might be possible. Second, NSC 663284 might strongly interact with Cdc25A by noncovalent bonding, such as hydrogen bonding. Finally, Cdc25A might be inactivated by NSC 663284 by inducing a disulfide linkage through a quinone redox reaction. Recent studies by the Lazo group supported the first hypothesis that NSC 663284 bound covalently in the Cdc25A catalytic domain as shown in Figure 22[46] and also suggested that the NSC 663284 modification likely occurred at Ser114. However the possibility that other hydroxyl- or thiol- containing species were involved cannot be eliminated.

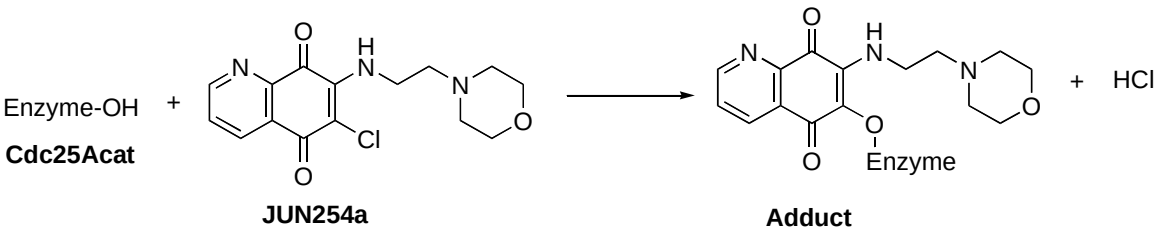


Figure 22. The schematic reaction model of NSC 663284 interacting with Cdc25A

Ham et al. also proposed a possible covalent bond formation of Vitamin K with enzyme as shown in Figure 23. [25(a)]

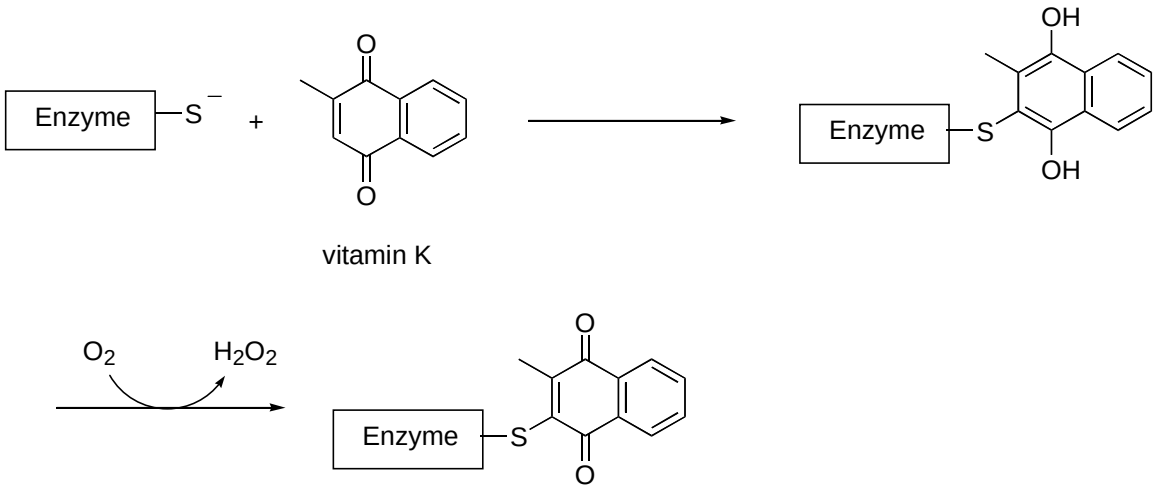
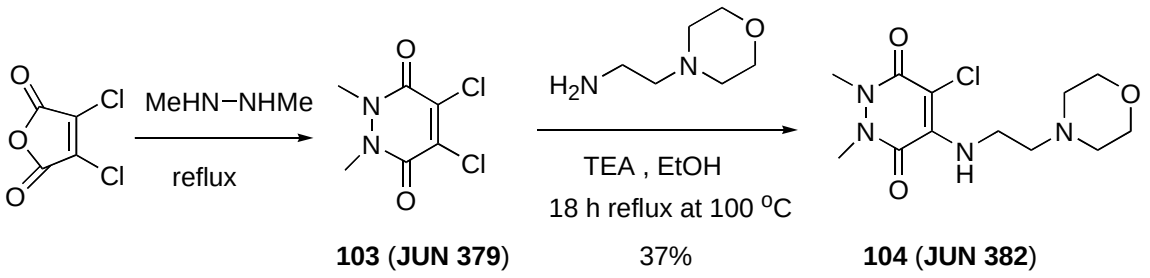


Figure 23. Possible covalent bond formation of Vitamin K with enzyme[25(a)]

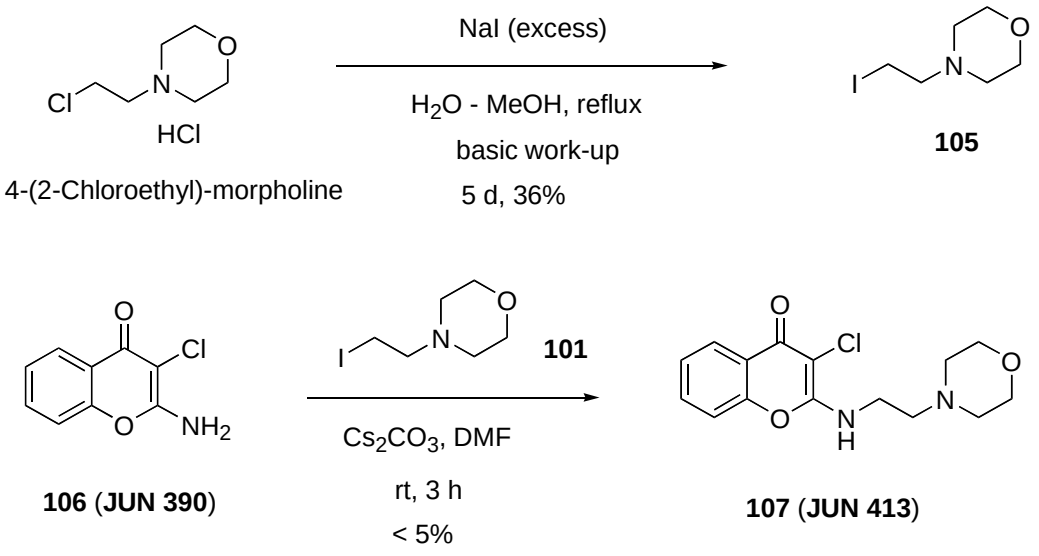
Even though quinone compounds have exhibited good inhibitory activities against Cdc25, covalent bond formation should be avoided in drug discovery. Thus, we decided to prepare alternative heterocycles with 4-(2-aminoethyl)-morpholine substituents to remove the possibility for covalent binding between the reactive residues (such as Cys or Ser) of Cdc25 and inhibitors while simultaneously increasing the affinity for the active site by establishing new noncovalent interactions. For this purpose, compound **103** (**JUN 379**) was prepared from dichloromaleic anhydride according to literature procedures[63] and treated with 2-morpholin-4-yl-ethylamine in the presence of TEA to afford **104** (**JUN 382**) (Scheme 22). In this case, more vigorous conditions such as heating at reflux in EtOH were required to get the desired addition-elimination product because of the low reactivity of **103**.



103 (**JUN 379**) **104** (**JUN 382**)

Scheme 22. Synthesis of **JUN 382**

Intermediate **106** (**JUN 390**) was prepared from 3-cyanochromone in two steps according to literature procedures[64] and iodide **105** was obtained from the substitution reaction of 4-(2-chloroethyl)-morpholine with sodium iodide (Scheme 23). After several attempts to couple **106** with **105**, the desired product **107** (**JUN 413**) was obtained in very low yield.

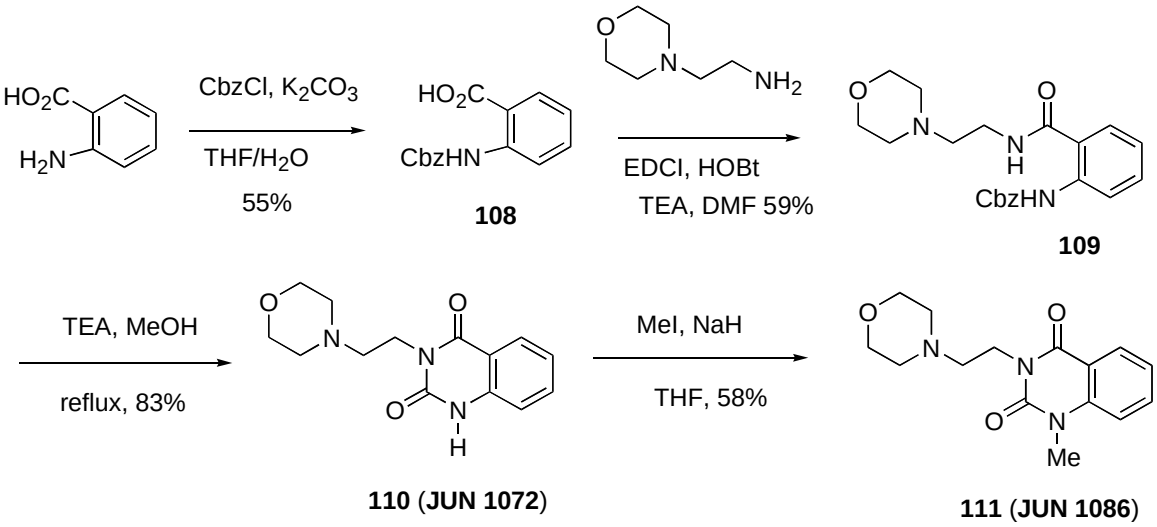


106 (**JUN 390**) **107** (**JUN 413**)

Scheme 23. Synthesis of **JUN 413**

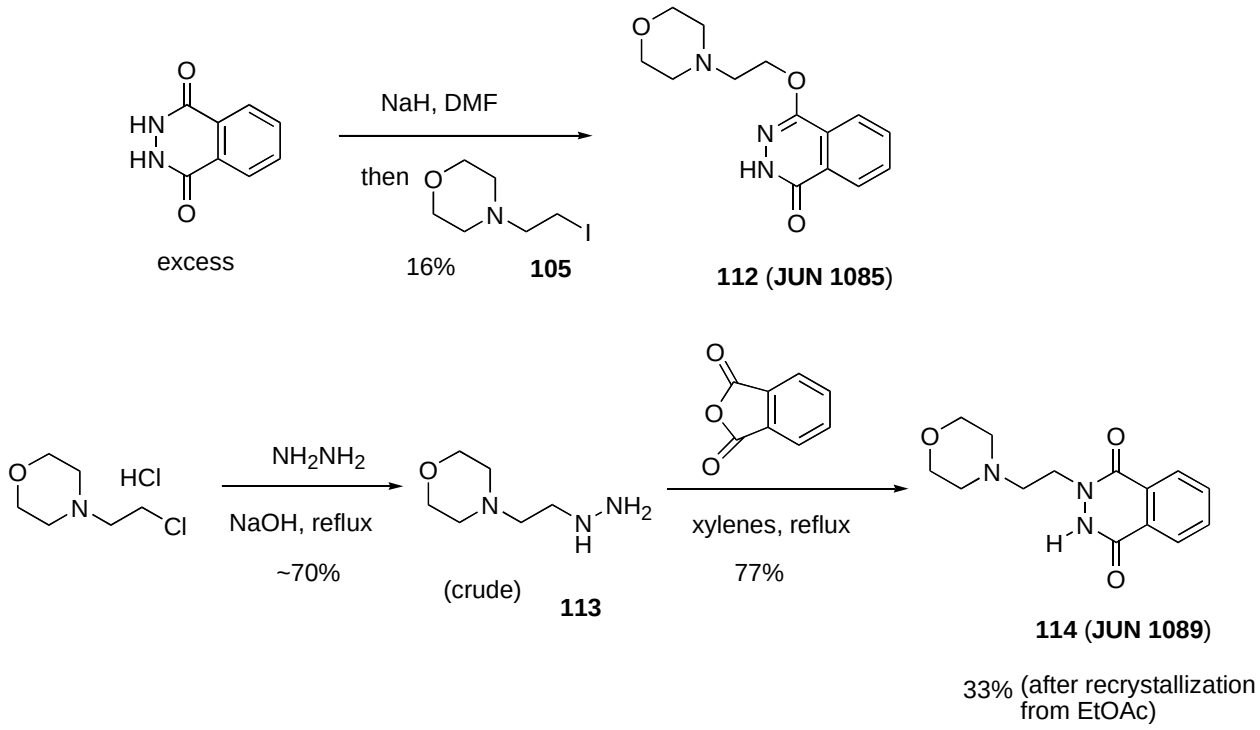
For the preparation of quinazolonodione **JUN 1072**, anthranilic acid was condensed with benzyl carbamate to give intermediate **108**[65] (Scheme 24). Coupling of **108** with 4-(2-aminoethyl)-morpholine in the presence of EDCI and HOBT led to amide **109**, which was

cyclized to the desired heterocycle **110** (**JUN 1072**) under mild basic conditions.[65,66] Subsequently, **110** was converted to **111** (**JUN 1086**) by *N*-alkylation with iodomethane.



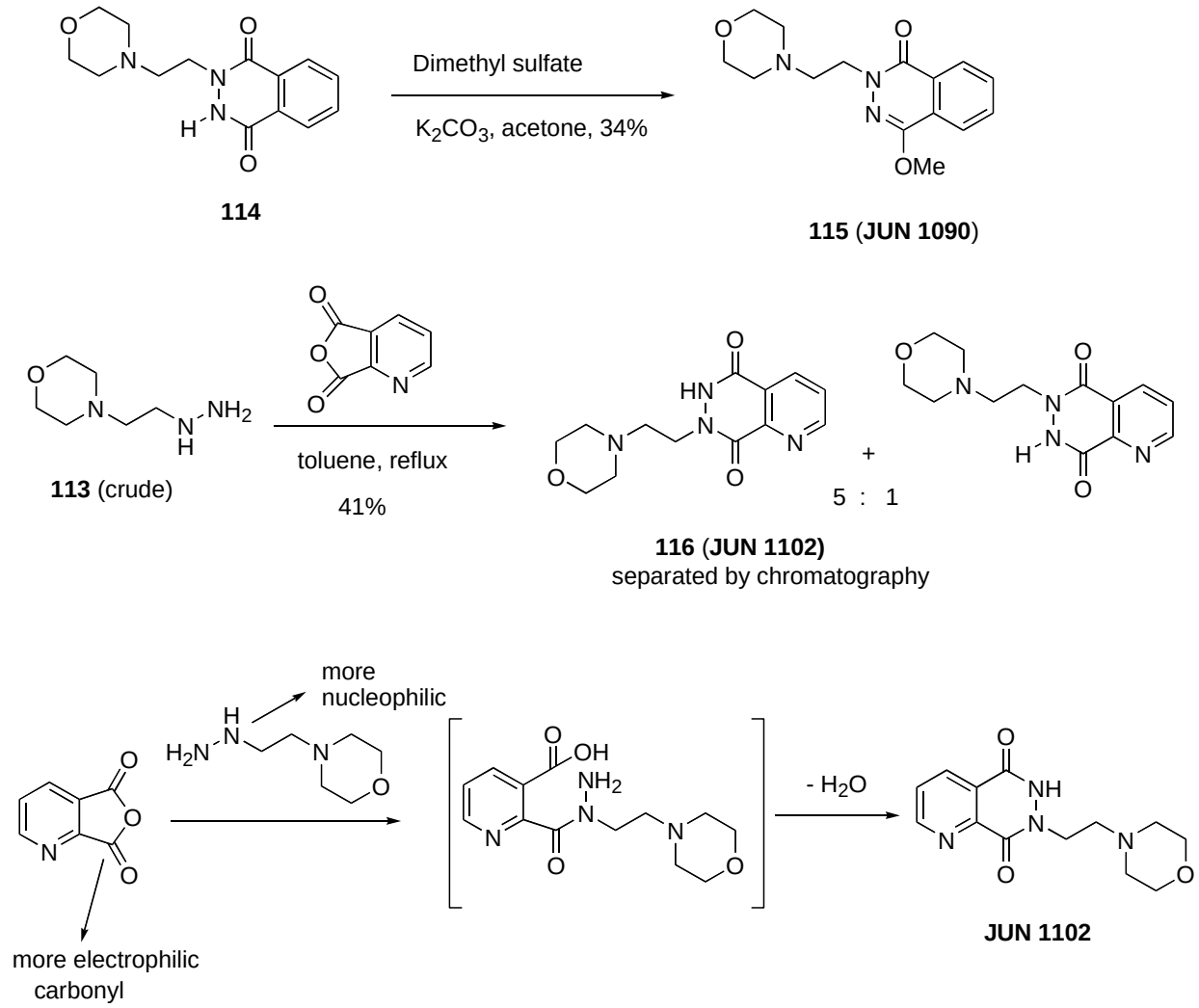
Scheme 24. Synthesis of **JUN 1072** and **1086**

After completing the syntheses of **JUN 1072** and **JUN 1086**, the phthalazine-1,4-dione **JUN 1089** was prepared (Scheme 25). Initially, we attempted the *N*-alkylation of phthalhydrazide with iodide **105** in the presence of NaH. However, the reaction gave the *O*-alkylated compound **112** (**JUN 1085**) as the only isolable product. Next, we tried a hydrazinolysis of phthalic anhydride with hydrazine **113**,[67] which was prepared in crude form from the reaction of 4-chloroethylmorpholine with hydrazine in the presence of NaOH in EtOH, and indeed the desired **114** (**JUN 1089**) was obtained in moderate yield.



Scheme 25. Synthesis of **JUN 1085** and **1089**

114 (**JUN 1089**) was *O*-alkylated with dimethyl sulfate in the presence of potassium carbonate to give **115** (**JUN 1090**) (Scheme 26). Pyridazinedione **116** (**JUN 1102**) was prepared according to the synthesis of **JUN 1089**. In this case, two regioisomers were obtained in a ~5:1 ratio and the major regioisomer was separated by chromatography on SiO_2. A tentative assignment of the two regioisomers was made based on the speculation that the more electrophilic[68] carbonyl group of pyridine-dicarboxylic anhydride reacts with the more nucleophilic[69] secondary amine of hydrazine **113**. Hydrazinolysis of pyrazine-dicarboxylic anhydride with hydrazine **113** led only to severe decomposition in refluxing toluene and xylene solution without producing the desired product.



Scheme 26. Synthesis of **JUN 1090** and **1102**

In conclusion, we prepared eight heterocyclic scaffolds with the 4-(2-aminoethyl)-morpholine side chains as analogues of the (iso)quinolinedione NSC 663284. All compounds were tested against Cdc $25B_2$ and found to be inactive. Accordingly, the morpholine portion of NSC 663284 is not sufficient for biological activity against phosphatases. These results allowed us to conclude that the quinone ring of NSC 663284 is essential for the activity against Cdc25B and mediates a covalent bond formation with enzymes. Based on the bioassay results for the

analogues of NSC663284 and morpholine derivatives, we could summarize the SAR as shown in Figure 24.

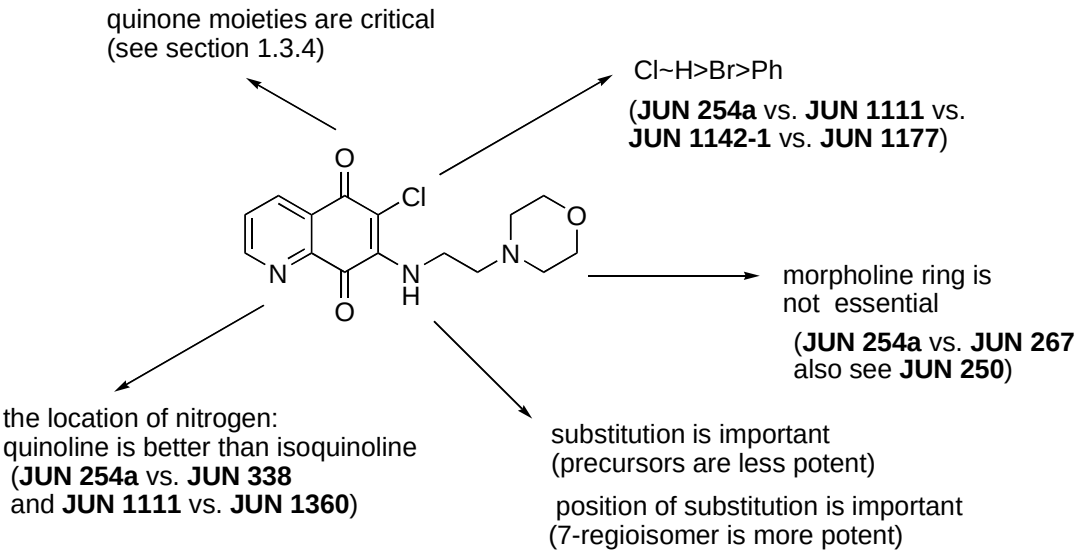


Figure 24. SAR model for NSC663284

The quinone moiety was essential for activity against Cdc25. This result strongly supported the hypothesis that NSC 663284 might bind covalently with Cdc25. The quinoline derivatives are more potent than the isoquinoline derivatives, indicating that the electronic properties of the aromatic ring in the analogues might be important. The substituted analogues showed increased activities over their precursors and the 7-regioisomer was more potent than the 6-regioisomer. Thus, substitution patterns were also important in terms of activity. The replacement of chlorine with hydrogen did not reduce the activity, whereas the replacement with bromine and phenyl decreased the biological effects.

1.3.5. Synthesis of Caulibugulones

Recently, the Gustafson group at the NCI isolated caulibugulones A-F, a series of novel cytotoxic isoquinoline diones and iminoquinones, from an extract of the marine bryozoan *Caulibugula intermis* (Figure 18).[47] They also reported that caulibugulones A-F exhibited IC_{50}'s of 0.03 – 1.67 μg/mL against murine tumor cells in an in vitro cytotoxicity assay (Table 6). These compounds attracted our attention because they showed close structural similarity with heterocyclic scaffolds that we had identified as potent phosphatase inhibitors.[44,45] Moreover, we envisioned that their demonstrated cytotoxicities could be related to their inhibition of phosphatases. Thus, we decided to synthesize several caulibugulones and evaluate their biological activity against Cdc25 phosphatases.[70]

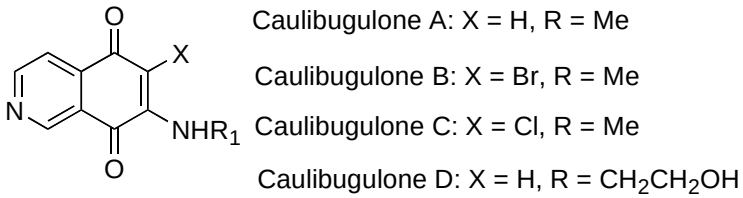


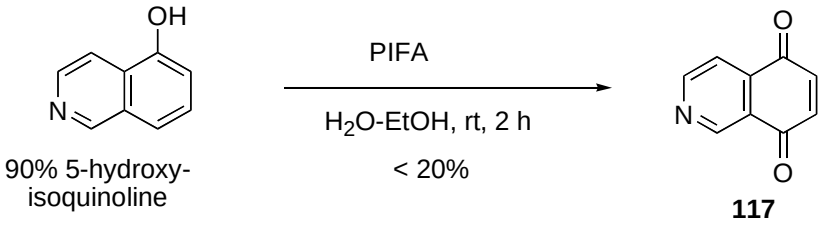
Figure 18. Caulibugulones

Table 6. IC_{50} of caulibugulones A-E against murine IC-2^{wt} cell line in an in vitro antiproliferative assay

Compound	IC_{50} (μg/mL)	Compound	IC_{50} (μg/mL)
Caulibugulone A	0.34	Caulibugulone D	1.67
Caulibugulone B	0.22	Caulibugulone E	0.03
Caulibugulone C	0.28	Caulibugulone F	0.10

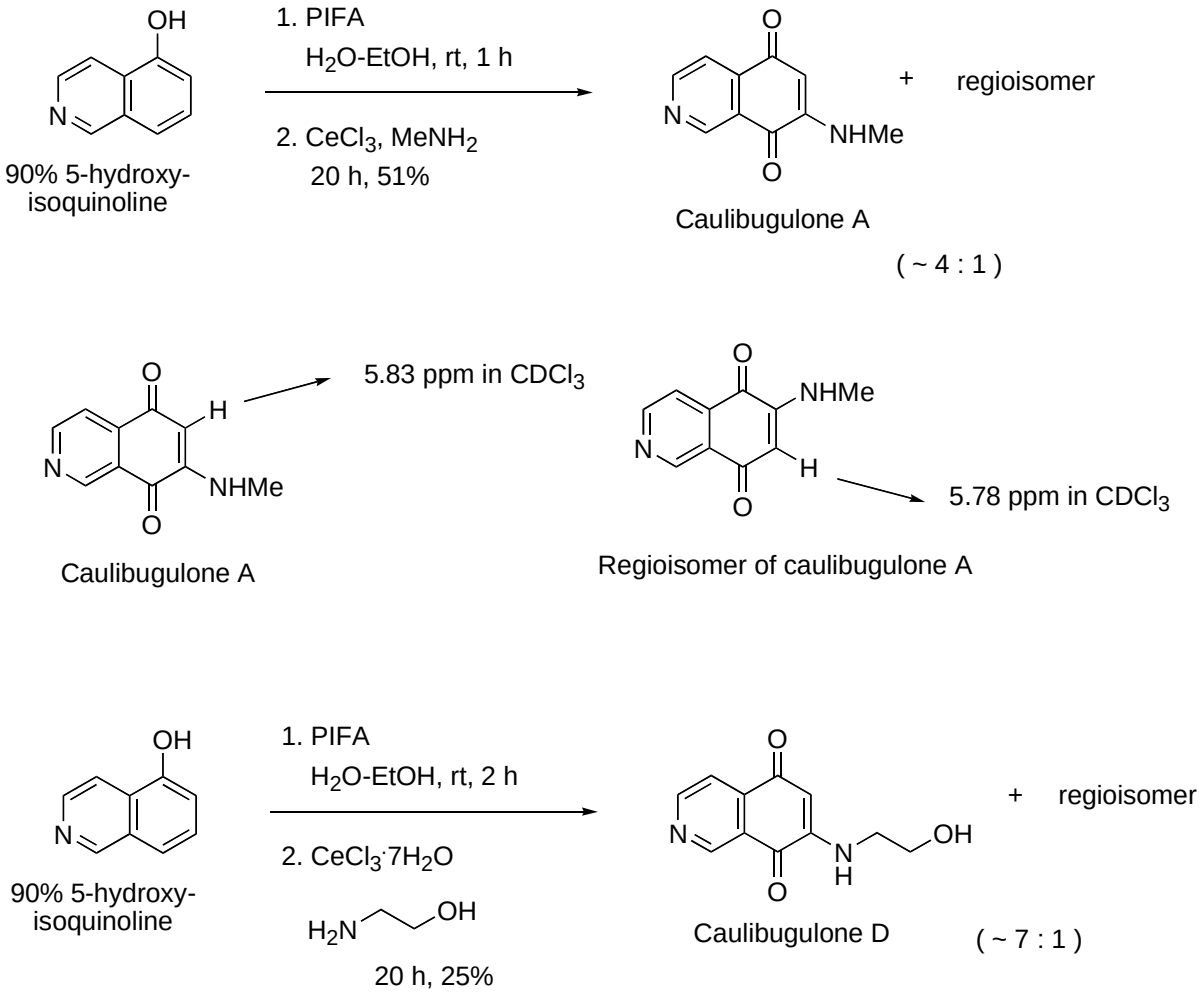
Our synthesis of caulibugulones began with the preparation of the isoquinolinedione **117** (Scheme 27). According to a literature procedure,[57] we prepared compound **117** from

isoquinolin-5-ol, but to our disappointment, **117** was too unstable to be isolated in high yield and purity.



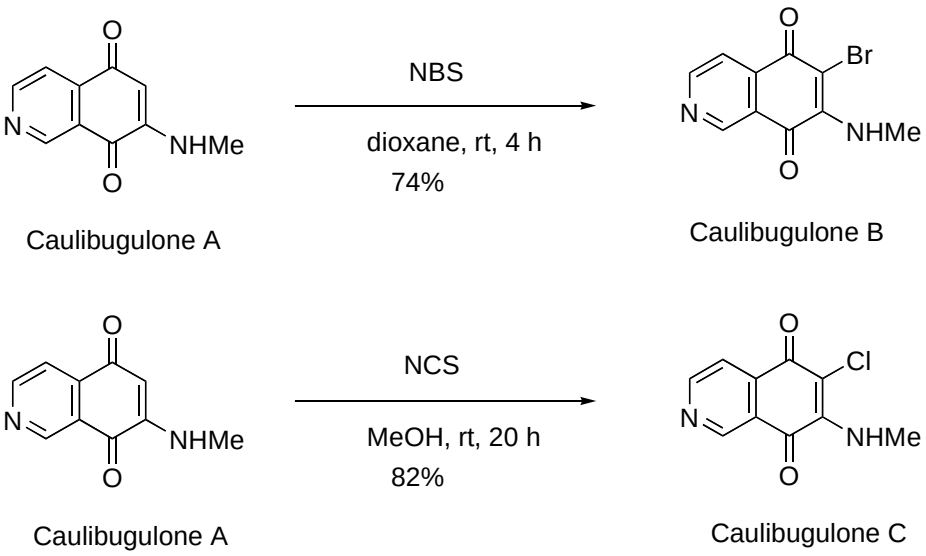
Scheme 27. Synthesis of **117**

Therefore, we proceeded without isolation of this compound. Oxidation of 5-hydroxyl-isoquinoline by PIFA in H_2O-EtOH solution and the subsequent *in situ* addition of $CeCl_3$[71] and methyl amine were performed without intermediate work-up and provided a ~ 4:1 mixture of caulibugulone A and its regioisomer in 51% yield after aqueous quench and chromatography (Scheme 28). The regiochemistry was determined by ^{1}H NMR spectroscopy as shown Scheme 28. The chemical shift of the vinyl proton of the 7-regioisomer (i.e. caulibugulone A) is more downfield than that of the 6-regioisomer. Further separation by repeated chromatography provided pure caulibugulone A as a red solid.[72] Caulibugulone D was subsequently synthesized from 5-hydroxyisoquinoline via a related two step – one pot sequence using 2-aminoethanol. The low yield can be attributed to the poor solubility of the product in organic solvents.



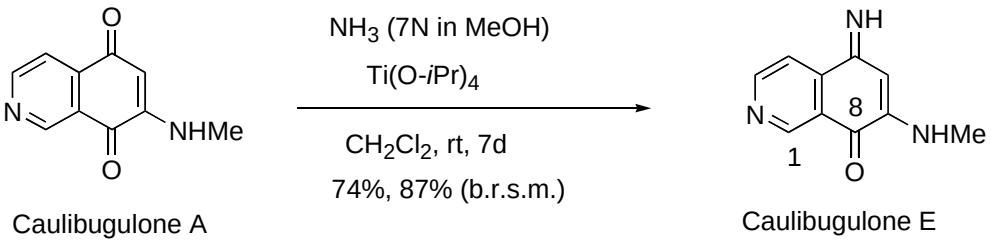
Scheme 28. Synthesis of caulibugulone A and D

Caulibugulones B and C were synthesized by halogenations of caulibugulone A according to literature procedures (Scheme 29).[47] Thus, treatment of caulibugulone A with NBS and NCS provided caulibugulone B in 74% yield and caulibugulone C in 82% yield, respectively. For the synthesis of caulibugulone C, MeOH was a better solvent than dioxane in terms of reaction time and yield. ^{1}H NMR and ^{13}C NMR spectra matched the reported data.[47]



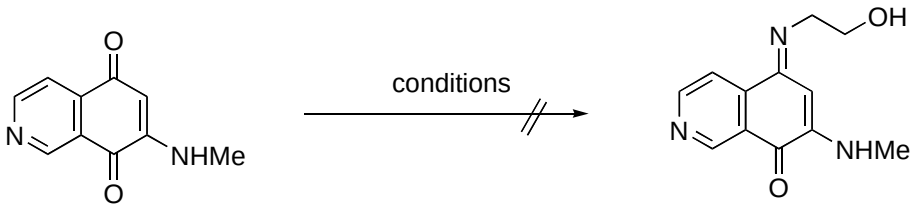
Scheme 29. Synthesis of caulibugulone B and C

Finally, caulibugulone E was prepared by treatment of caulibugulone A with ammonia in the presence of Ti(O-*i*Pr)$_4$ (Scheme 30). Although the reaction was sluggish, we obtained caulibugulone E in 74% yield, along with recovered calibugulone A in 15% yield. The regioselectivity of this reaction could be explained by steric hindrance around the C8-carbonyl group and a hydrogen-bond formation of the C8-carbonyl with the NHMe of caulibugulone A in CH_2Cl_2 solution. The structure assignment was confirmed by the HMBC spectrum of caulibugulone E.



Scheme 30. Synthesis of caulibugulone E

It is noteworthy that we failed to synthesize caulibugulone F despite significant efforts. First, we tried several reactions of caulibugulone A with 2-aminoethanol or 2-azidoethanol to obtain caulibugulone F, but failed to get the desired product as shown in Table 7. Interestingly, we isolated caulibugulone E instead of caulibugulone F in entry 3 and entry 4.



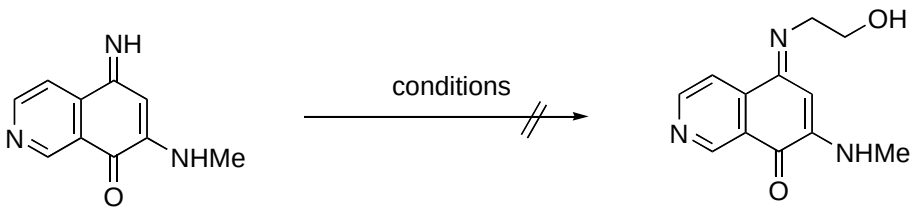
caulibugulone A

caulibugulone F

Table 7. Attempts toward the synthesis of caulibugulone F from caulibugulone A

Entry	Reagents	Reaction Conditions	Results
1	2-Aminoethanol (5 equiv.) p-TsOH•H_2O (0.1 equiv.)	CH_2Cl_2 Rt, 20h	No reaction S. M. (100%)
2	2-Aminoethanol (5 equiv.) p-TsOH•H_2O (1 equiv.)	Benzene Reflux, 18h	No reaction
3	2-Aminoethanol (5 equiv.) Ti(O-*i*Pr_4) (0.1 equiv.)	CH_2Cl_2 Rt, 4d	S. M. (40%) + Caulibugulone E (20%)
4	2-Aminoethanol (5 equiv.) Ti(O-*i*Pr_4), 4 A° M. S.	CH_2Cl_2 Rt, 3d	S. M. (48%) + Caulibugulone E (11%)
5	2-Azidoethanol (2.8 equiv.) PPh_3 (2.8 equiv.)	CH_2Cl_2 Rt to reflux	No reaction
6	2-Azidoethanol (5 equiv.) PPh_3 (5 equiv.)	Toluene Reflux, 20h	No reaction
7	2-Aminoethanol (10 equiv.) $POCl_3$ (5 equiv.)	CH_2Cl_2 Rt, 2h	Unidentified polar product + S. M. (48%)

Next, we also tried several reactions of caulibugulone E with 2-iodoethanol in the presence of bases, but also failed to obtain caulibugulone F as shown in Table 8.



caulibugulone E

caulibugulone F

Table 8. Attempts toward the synthesis of caulibugulone F from caulibugulone E

Entry	Reagents	Reaction Conditions	Results
1	2-Iodoethanol (10 equiv.) TEA (5 equiv.)	CH_2Cl_2 Rt to reflux, 18h	No reaction S. M. (80%)
2	2-Iodoethanol (10 equiv.) K_2CO_3 (5 equiv.)	CH_3CN Reflux, 20h	Undesired product(s) S. M. (trace)
3	2-Iodoethanol (10 equiv.) NaH (5 equiv.)	THF Rt, 30min	Undesired product(s) S. M. (83%)
4	2-Iodoethanol (10 equiv.) LHMDS (1.5 equiv.)	THF -78 °C to rt, 2h	No reaction S. M. (100%)
5	2-Iodoethanol (1 equiv.) Cs_2CO_3 (5 equiv.)	DMF Rt, 20h	No reaction

As illustrated in Table 9, all five caulibugulones inhibited full-length human Cdc25B in vitro with IC_{50} values ranging from 2.7 to 32.5 μM, with caulibugulone B and E being the most and least potent, respectively.[73] Moreover, all caulibugulones exhibited a great preference for inhibition of the dual specificity phosphatase Cdc25B.

Table 9. IC_{50} values of caulibugulones (μM)

	Cdc25A	Cdc25B	Cdc25C	VHR	PTP1B
Caulibugulone A	3.4 ± 0.6	6.7 ± 1.3	5.4 ± 1.2	>500	>1000
Caulibugulone B	1.5 ± 0.2	2.7 ± 0.5	2.7 ± 0.2	130 ± 23	183 ± 24
Caulibugulone C	2.6 ± 0.6	5.4 ± 0.7	3.3 ± 0.3	175 ± 2	322 ± 32
Caulibugulone D	4.9 ± 0.8	19.1 ± 0.3	10.8 ± 0.5	>1000	>1000
Caulibugulone E	18.2 ± 1.1	32.5 ± 3.6	16.6 ± 1.0	>1000	>1000

IC_{50} values were from 3 or more determinations with SEM indicated.
Specifically, activities against $Cdc25A_1$, $Cdc25B_2$ and $Cdc25C_1$ were measured.

IC_{50} values increased in the order Cdc25A < Cdc25C < Cdc25B. In addition to in vitro assays, more biological testings[74] were performed for caulibugulone A and E. The reversibility assays using solid support (nickel bead) were performed by the Lazo group to determine whether compounds were reversible inhibitors. The results suggested that caulibugulone A and E were irreversible inhibitors. Flow cytometry experiments were also performed to determine if compounds arrested tsFT210 cells in G1 by inhibiting Cdc25A, or G2 by inhibiting Cdc25A or Cdc25B. The results showed that caulibugulone A and E induced growth inhibition and produced a strong arrest at G2 of the cell cycle. In addition, inhibition of Cdc25A in Hela cells was assayed with caulibugulone A and E. The results indicated that caulibugulone A and E directly inhibited Cdc25A in Hela cells, and Cdc25A protein levels decreased after treatment of Hela cells with caulibugulone A. More biological assays are still in progress and will be reported soon.[74]

1.4. Conclusion

We prepared 9 compounds as analogues of FY21-αα09 by diverse synthetic methods in the hope that modification of the FY21-αα09 structure would improve the activity against the Cdc25 family. However, no significant improvements were achieved in this series, and therefore we selected other target molecules.

In the meantime, in the course of screening NSC compounds, the Lazo group identified new potent compounds, namely NSC 663284 and NSC 95397, which served as new lead structures. We prepared several analogs of NSC 663284 that proved to be potent inhibitors of Cdc25B. Since these compounds were highly potent against Cdc25B, they were also evaluated against Cdc25A, Cdc25C, VHR and PTBIB. The results showed that they were all specific inhibitors of Cdc25. Moreover, reversibility and flow cytometry experiments were performed. The results suggested that all compounds were irreversible inhibitors and induced cell arrest cell cycle at the G2 level.

For the synthesis of (iso)-quinoline analogs of NSC 95397, we prepared some key intermediates and tested their biological activities. However, the potency of these compounds did not exceed that of NSC 95397, and several desired derivatives could not be obtained despite considerable efforts.

We also prepared eight alternative heterocycles with 4-(2-aminoethyl)-morpholine substituents to remove the possibility for covalent binding between reactive residues (such as Cys or Ser) of Cdc25 and inhibitors while simultaneously increasing the affinity for the active site by establishing new noncovalent interactions. Accordingly, the major modification was directed toward the quinone ring. However, none of these compounds showed activity against

Cdc25B. These results allowed us to conclude that the quinone ring of NSC 663284 was essential for activity against Cdc25B.

Finally, the total synthesis of the naturally occurring cytotoxic caulibuguones proceeded efficiently in high overall yields from readily available isoquinolin-5-ol via hypervalent oxidation, regioselective halogenations and amination reactions. Biological assays established this new class of natural products as phosphatase inhibitors with considerable selectivity against the Cdc25 family of DSPases.

Based on the results of all synthesized and tested compounds, compound **118** can be proposed as a possible potent reversible inhibitor of Cdc25 as shown in Figure 25. The main motif for the proposal of **118** is to develop a reversible inhibitor without loss of activity against Cdc25. This goal might be achieved by the reversible intramolecular addition of thiol after covalent bond formation of enzyme with **118**. Moreover, the generation of HCl or H_2O_2, which might be harmful to cells, could be avoided in this reaction.

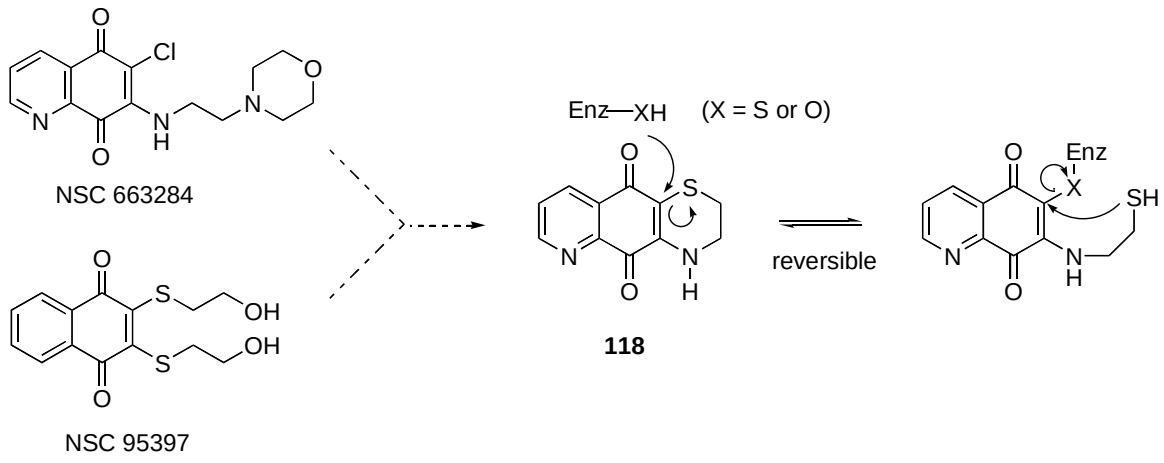


Figure 25. Proposal of **118** as a reversible inhibitor for Cdc25

1.5. Experimental Section

General Methods. All moisture-sensitive reactions were performed under an atmosphere of dry nitrogen and all glassware was dried in an oven prior to use. THF and ether were dried by distillation over Na/benzophenone and CH_2Cl_2 was dried by distillation over CaH_2. Unless otherwise stated, all commercially available materials were used without purification. IR spectra were recorded neat using NaCl cells. NMR spectra were obtained at 300MHz/75MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless noted otherwise. High and low resolution mass spectra were determined by introduction with a direct insertion probe into a VG- 70-70 HF spectrometer operating in the electron ionization (EI) mode.

4-(4-*tert*-Butoxycarbonylaminocyclohexylcarbamoyl)-2-decanoylaminobutyric acid benzyl ester (24). Prepared according to literature procedures:[2(a)] ^1H NMR δ 7.40-7.30 (m, 5 H), 6.75-6.65 (br, 1 H), 6.30-6.20 (br, 1 H), 5.19 (d, 1 H, *J* = 12 Hz), 5.13 (d, 1 H, *J* = 12 Hz), 4.60-4.50 (m, 1 H), 4.50-4.40 (m, 1 H), 3.80-3.60 (m, 1 H), 3.50-3.30 (m, 1 H), 2.27-2.10 (m, 5 H), 2.08-1.90 (m, 5 H), 1.70-1.50 (m, 2 H), 1.43 (s, 9 H), 1.40-1.20 (m, 16 H), 0.88 (t, 3 H, *J* = 6.8 Hz).

2-Decanoylamino-4-[4-(2-nitrobenzenesulfonylamino)-cyclohexylcarbamoyl]-butyric acid benzyl ester (31). HCl (conc., 0.3 mL) was added dropwise to a solution of **24** (294 mg, 0.500 mmol) in dioxane (10 mL) at room temperature. The solution was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL). To this solution was added collidine (0.40 mL, 3.0 mmol) and o-NsCl (0.12 g, 0.55 mmol). The reaction mixture was stirred for 18 h, diluted with CH_2Cl_2 (50 mL) and washed with 1 N

HCl solution (25 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give **31** (120 mg, 36%) as a white solid: ^{1}H NMR δ 8.20-8.05 (m, 1 H), 7.95-7.20 (m, 8 H), 6.59 (d, 1 H, *J* =7.5 Hz), 6.37 (d, 1 H, *J* = 7.6 Hz), 5.46 (d, 1 H, *J* = 7.6 Hz), 5.17 (d, 1 H, *J* = 12.4 Hz), 5.13 (d, 1 H, *J* = 12.4 Hz), 4.60-4.40 (m, 1 H), 3.72-3.52 (m, 1 H), 3.35-3.18 (m, 1 H), 2.23-2.04 (m, 5 H), 2.00-1.75 (m, 5 H), 1.70-1.45 (m, 2 H), 1.4-1.0 (m, 16 H), 0.90-0.70 (m, 3 H).

4-{4-[Benzyl-(2-nitrobenzenesulfonyl)-amino]-cyclohexylcarbamoyl}-2-decanoylaminobutyric acid benzyl ester (32). To a solution of **31** (86 mg, 0.13 mmol) in DMF (1 mL) was added K_2CO_3 (71 mg, 0.51 mmol) and BnBr (0.060 mL, 0.51 mmol). The reaction mixture was stirred for 40 h, diluted with EtOAc (50 mL) and washed with 1N HCl solution (25 mL×3). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give **32** (57 mg, 58%) as a white solid: IR (neat) 3301, 3064, 2927, 2855, 1732, 1638, 1544, 1438, 1372, 1170 cm^{-1}; ^{1}H NMR δ 7.78-7.21 (m, 14 H), 6.59 (d, 1 H, *J* = 7.5 Hz), 6.23 (d, 1 H, *J* = 7.8 Hz), 5.18 (d, 1 H, *J* = 12.2 Hz), 5.13 (d, 1 H, *J* = 12.2 Hz), 4.60-4.40 (m, 1 H) 4.49 (s, 2 H), 3.92-3.78 (m, 1 H), 3.62-3.46 (m, 1 H), 2.23-2.05 (m, 5 H), 1.89-1.77 (m, 3 H), 1.77-1.73 (m, 2 H), 1.63-1.59 (m, 2 H), 1.51-1.40 (m, 2 H), 1.40-1.15 (m, 14 H), 0.88 (t, 3 H, *J* = 6.2 Hz). MS (EI) *m/z* (relative intensity) 762 (M^+, 20), 576 (5), 270 (100); HRMS (EI) *m/z* calcd for $C_{41}H_{54}N_4O_8S$ 762.3662, found 762.3644.

4-(4-Benzylaminocyclohexylcarbamoyl)-2-decanoylaminobutyric acid benzyl ester (33). To a solution of **32** (57 mg, 0.075 mmol) in DMF (0.2 mL) was added PhSH (15 μL, 0.15 mmol) and K_2CO_3 (31 mg, 0.23 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (20 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2

(CH_2Cl_2/MeOH, 10:1) to give **33** (38 mg, 88%) as a white solid: ^{1}H NMR δ 7.41-7.22 (m, 10 H), 6.57 (d, 1 H, *J* = 7.4 Hz), 6.02 (d, 1 H, *J* = 7.8 Hz), 5.20 (d, 1 H, *J* = 12.1 Hz), 5.15 (d, 1 H, *J* = 12.1 Hz), 4.56-4.49 (m, 1 H), 3.81 (s, 2 H), 3.80-3.65 (m, 1 H), 2.55-2.40 (m, 1 H), 2.25-2.10 (m, 5 H), 2.10-1.85 (m, 5 H), 1.70-1.50 (m, 3 H), 1.4-1.1 (m, 14 H), 0.88 (t, 3 H, *J* = 6.3 Hz).

2,5-Diphenyloxazole-4-carboxylic acid (25). Prepared according to literature procedures:[50] ^{1}H NMR δ 8.36-8.34 (m, 2 H), 8.20-8.10 (m, 2 H), 7.60-7.40 (m, 6 H).

4-{4-[Benzyl-(2,5-diphenyloxazole-4-carbonyl)-amino]-cyclohexylcarbamoyl}-2-decanoylaminobutyric acid benzyl ester (34). To a solution of **33** (38 mg, 0.066 mmol) and **25** (19 mg, 0.072 mmol) in THF (1 mL) was added PyBrop (61 mg, 0.13 mmol) and *i*-Pr_2NEt (23 μL, 0.13 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature, diluted with EtOAc (20 mL) and washed with of 1N HCl solution (10 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **34** (41 mg, 76%) as a white solid: ^{1}H NMR (~1:1 mixture of rotamers) δ 8.20-7.10 (m, aromatic, 20 H), 6.58, 6.47 (2d, 1 H, *J* = 7.4 Hz), 6.11, 6.02 (2d, 1 H, *J* = 7 Hz), 5.19-5.12 (m, 2 H), 4.79, 4.62 (2s, 2 H), 4.60-4.40 (m, 1 H) 3.95-3.80, 3.75-3.50 (2m, 1 H), 2.30-1.50 (m, 14 H), 1.40-1.15 (m, 14 H), 0.90-0.75 (m, 3 H).

4-{4-[Benzyl-(2,5-diphenyloxazole-4-carbonyl)-amino]-cyclohexylcarbamoyl}-2-decanoylaminobutyric acid (35). To a solution of **34** (40 mg, 0.048 mmol) in THF (0.4 mL) was added a solution of LiOH•H_2O (6.0 mg, 0.15 mmol) in H_2O (0.4 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and for 20 min at room temperature, diluted with H_2O (20 mL) and washed with Et_2O (20 mL). The aqueous layer was acidified to pH 1 with 10 % HCl solution, salted out with NaCl and extracted with EtOAc (25 mL×3). The resulting organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **35** (21 mg, 60%) as a white

solid: Mp 170 ^{o}C (dec) IR (neat) 3307, 3061, 2918, 2851, 1735, 1632 cm^{-1}; ^{1}H NMR (rotamers) δ 8.02-7.10 (m, aromatic, 15 H), 6.75 (bd, 1 H, *J* = 7.3 Hz), 6.26 (bd, 1 H, *J* = 7.5 Hz) 4.78, 4.62 (2s, 2 H), 4.55-4.25 (m, 2 H) 4.00-3.80, 3.70-3.50 (m, 1 H), 2.50-1.50 (m, 14 H), 1.50-1.15 (m, 14 H), 0.95-0.80 (m, 3 H); MS (EI) *m/z* (relative intensity) 716 ([M–H_2O]$^{+}$, 2) 625 (15), 468 (30), 248 (100); HRMS (EI) *m/z* calcd for $C_{44}H_{52}N_4O_5$ (M–H_2O) 716.3938, found 716.3947.

(4-Aminocyclohexyl)-carbamic acid *tert*-butyl ester (36). Prepared according to literature procedures:[2(a)] ^{1}H NMR δ 4.50-4.30 (br, 1 H), 3.40-3.20 (m, 1 H), 2.70-2.50 (m, 1 H), 2.10-1.70 (m, 4 H), 1.60-1.40 (br, 2 H), 1.42 (s, 9 H), 1.30-1.00 (m, 4 H).

4-(2-Nitrobenzenesulfonylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (37). To a solution of **36** (93 mg, 0.43 mmol) in THF (5 mL) was added $NaHCO_3$ (146 mg, 1.74 mmol) and o-NsCl (96 mg, 0.43 mmol). The reaction mixture was stirred for 24 h at room temperature, concentrated, diluted with EtOAc (50 mL) and washed with H_2O (30 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **37** (147 mg, 85%) as a white solid: ^{1}H NMR δ 8.19–8.15 (m, 1 H), 7.90-7.86 (m, 1 H), 7.77-7.74 (m, 2 H), 5.20 (d, 1 H, *J* = 7.7 Hz), 4.40-4.30 (m 1 H), 3.45-3.20 (m, 2 H), 2.05-1.85 (m, 4 H), 1.43 (s, 9 H), 1.40-1.05 (m, 4 H).

{4-[Benzyl(2-nitro-benzenesulfonyl)-amino]-cyclohexyl}-carbamic acid *tert*-butyl ester (38). To a solution of **37** (133 mg, 0.333 mmol) in DMF (5 mL) was added K_2CO_3 (184 mg, 1.33 mmol) and BnBr (0.16 mL, 1.3 mmol). The reaction mixture was stirred for 14 h, diluted with EtOAc (50 mL) and washed with H_2O (30 mL×2). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:2) to give **38** (160 mg, 97%) as a white solid: ^{1}H NMR δ 7.81-7.78 (m, 1 H), 7.63-7.59 (m, 2 H), 7.54-7.49

(m, 1 H), 7.31-7.21 (m, 5 H), 4.49 (s, 2 H), 4.34-4.32 (m, 1 H), 3.90-3.82 (m, 1 H), 3.32-3.12 (m, 1 H), 2.02-1.90 (m, 2 H), 1.85-1.75 (m, 2 H), 1.41 (s, 9 H), 1.5-1.1 (m, 4 H).

(4-Benzylaminocyclohexyl)-carbamic acid *tert*-butyl ester (39). To a solution of **38** (158 mg, 0.323 mmol) in DMF (2 mL) was added PhSH (66 μL, 0.65 mmol) and K_2CO_3 (0.13 g, 0.97 mmol) at 0 °C. The reaction mixture was stirred for 24 h at room temperature, diluted with of EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (25 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (CH_2Cl_2/ MeOH, 15:1) to give **39** (89 mg, 91%) as a white solid: ^{1}H NMR δ 7.35-7.20 (m, 5 H), 4.51-4.34 (br, 1 H), 3.79 (s, 2 H), 3.51-3.31 (m, 1 H), 2.54-2.37 (m, 1 H), 2.05-1.90 (m, 4 H), 1.44 (s, 9 H), 1.35-1.00 (m, 4 H).

2-Decanoylaminopentanedioic acid 5-allyl ester 1-benzyl ester (22). Prepared according to the literature:[2(a)] ^{1}H NMR δ 7.40-7.20 (m, 5 H), 6.18 (d, 1 H, -N*H*, *J* = 7.6 Hz), 6.00-5.80 (m, 1 H), 5.35-5.10 (m, 2 H), 5.17 (s, 2 H), 4.75-4.60 (m, 1 H), 4.56 (d, 2 H, *J* = 5.6 Hz), 2.60-1.90 (m, 6 H), 1.75-1.55 (m, 2 H), 1.40-1.10 (m, 12 H), 1.00-0.80 (m, 3 H).

4-[Benzyl-(4-*tert*-butoxycarbonylaminocyclohexyl)-carbamoyl]-2-decanoylamino-butyric acid benzyl ester (40). To a solution of **22** (150 mg, 0.348 mmol) in THF (2 mL) was added morpholine (0.30 mL, 3.4 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) at room temperature. The reaction mixture was stirred for 1 h, concentrated under reduced pressure. The crude residue was diluted with EtOAc (50 mL) and washed with 10% aqueous HCl solution (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give crude deallylated product (136 mg, ~100%). The crude product was dissolved in THF and treated with **39** (89 mg, 0.29 mmol), PyBrop (272 mg, 0.584 mmol) and *i*-Pr_2NEt (0.10 mL, 0.58 mmol) at room temperature. The reaction mixture was stirred overnight at room

temperature and concentrated to remove THF. The residue was diluted with EtOAc (50 mL) and washed with H_2O (25 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 4:1 $\rightarrow$ 1:1) to give **40** (142 mg, 72%) as a white solid: IR (neat) 3311, 3061, 3030, 2927, 2856, 1741, 1711, 1646 cm^{-1}; ^1H NMR (rotamers) δ 7.35-7.10 (m, aromatic, 10 H), 6.92, 6.71 (2d, 1 H, *J* = 6.4, 6.7 Hz), 5.18-5.10 (m, 2 H), 4.65-4.25 (m, 4 H), 3.56-3.29 (m, 1 H), 2.68-2.32 (m, 1 H), 2.30-1.90 (m, 9 H), 1.75-1.49 (m, 4 H), 1.42 (s, 9 H), 1.35-1.15 (m, 14 H), 0.95-0.80 (m, 3 H); MS (EI) *m/z* (relative intensity) 677 (M^+, 20), 486 (40), 303 (100); HRMS (EI) *m/z* calcd for $C_{40}H_{59}N_3O_6$ 677.4404, found 677.4404.

4-(Benzyl-{4-[(2,5-diphenyloxazole-4-carbonyl)-amino]-cyclohexyl}-carbamoyl)-2-decanoylaminobutyric acid benzyl ester (41). HCl (conc., 0.1 mL) was added dropwise to a solution of **40** (118 mg, 0.174 mmol) in dioxane (3 mL) at room temperature. The solution was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was dissolved in THF (3 mL). To this solution was added **25** (51 mg, 0.19 mmol), PyBrop (162 mg, 0.348 mmol) and *i*-$PrNEt_2$ (0.09 mL, 0.5 mmol) at room temperature. The reaction mixture was stirred for 14 h, concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with 1N aqueous HCl solution (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **41** (92.0 mg, 85%) as a white solid: ^1H NMR (rotamers) δ 8.40-8.30 (m, 2 H), 8.15-8.05 (m, 2 H), 7.53-7.16 (m, 16 H), 6.95, 6.73 (2d, 1 H, *J* = 7.1 Hz), 5.25-5.05 (m, 2 H), 4.70-4.35 (m, 4 H), 3.95-3.60 (m, 2 H), 2.75-2.45 (m, 1 H), 2.40-2.05 (m, 6 H), 1.90-1.40 (m, 7 H), 1.35-1.15 (m, 14 H), 0.95-0.80 (m, 3 H).

4-(Benzyl-{4-[(2,5-diphenyloxazole-4-carbonyl)-amino]-cyclohexyl}-carbamoyl)-2-decanoylaminobutyric acid (42). To a solution of **41** (55 mg, 0.067 mmol) in THF (0.5 mL)

was added a solution of $LiOH \bullet H_2O$ (8.0 mg, 1.9 mmol) in H_2O (0.5 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and for 60 min at room temperature, diluted with H_2O (30 mL) and washed with Et_2O (20 mL). The aqueous layer was acidified to pH 1 with 10 % aqueous HCl solution, salted out with NaCl and extracted with EtOAc (25 mL×3). The resulting organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **42** (45 mg, 91 %) as a white solid: Mp 170 ^oC (dec); IR (neat) 3402, 3314, 3065, 3034, 2927, 2855, 1734, 1635 cm^{-1}; ^1H NMR (rotamers) δ 8.40-8.30 (m, 2 H), 8.15-8.05 (m, 2 H), 7.52-7.16 (m, 11 H), 4.70-4.30 (m, 3 H), 3.95-3.70 (m, 2 H), 3.25-1.40 (m, 14 H), 1.35-1.15 (m, 14 H), 0.95-0.80 (m, 3 H); ^{13}C NMR δ 175.4, 174.7, 174.6, 173.3, 161.0, 158.7, 152.6, 152.5, 138.4, 137.1, 131.2, 130.4, 130.3, 130.1, 129.2, 128.8, 128.5, 127.9, 127.5, 127.2, 126.8, 126.6, 125.9, 57.2, 54.1, 53.1, 47.7, 36.5, 32.1, 31.5, 30.5, 30.3, 29.9, 29.7, 29.6 (2C), 29.5 (2C), 29.0, 28.5, 25.8, 22.9, 14.4; MS (EI) *m/z* (relative intensity) 716 ($[M–H_2O]^+$, 2), 672 (3), 625 (5); HRMS (EI) *m/z* calcd for $C_{44}H_{52}N_4O_5$ ($M–H_2O$) 716.3938, found 716.3940.

Phenanthrene-9-carboxylic acid (43). A solution of 9-cyanophenanthrene (375 mg, 1.80 mmol) and NaOH (175 mg, 43.0 mmol) in diethylene glycol/H_2O (6 mL/2 mL) was heated at reflux for 14 h, cooled to room temperature and acidified to pH 1 with 1N aqueous HCl solution. The precipitate was filtered and concentrated under reduced pressure to give **43** (380 mg, 95%) as a white solid: ^1H NMR (DMSO-d_6) δ 8.84 (d, 1 H, J = 8.4 Hz), 8.81 (d, 1 H, J = 9.2 Hz), 8.31 (d, 1 H, J = 7.5 Hz), 8.02 (d, 1 H, J = 6.7 Hz), 7.96 (s, 1 H), 7.77-7.62 (m, 4 H); MS (EI) *m/z* (relative intensity) 222 (M^+, 100), 205 (50), 177 (65).

2-Decanoylamino-4-{4-[(phenanthrene-9-carbonyl)-amino]-cyclohexylcarbamoyl}-butyric acid benzyl ester (44). According to the procedure described for the synthesis of **34**, **44** (28 mg, 20%) was obtained from **22** (120 mg, 0.200 mmol) and **43** (44 mg, 0.20 mmol): ^1H

NMR (MeOH-d_4) δ 8.80 (d, 1 H, *J* = 7.7 Hz), 8.76 (d, 1 H, *J* = 8.2 Hz), 8.17 (d, 1 H, *J* = 7.7 Hz), 7.97 (d, 1 H, *J* = 7.4 Hz), 7.90 (s, 1 H), 7.66-7.53 (m, 9 H), 5.18 (d, 1 H, *J* = 12.2 Hz), 5.10 (d, 1 H, *J* = 12.2 Hz), 4.45-4.35 (m, 1 H), 3.63-3.35 (m, 5 H), 2.43-2.36 (m, 1 H), 2.25-2.09 (m, 5 H), 2.00-1.90 (m, 2 H), 1.60-1.40 (m, 4 H), 1.35-1.15 (m, 14 H), 0.88 (t, 3 H, *J* = 6.6 Hz).

2-Decanoylamino-4-{4-[(phenanthrene-9-carbonyl)-amino]-cyclohexylcarbamoyl}-butyric acid (45). According to the procedure described for the synthesis of **35**, **45** (14 mg, 57%) was obtained from **44** (28 mg, 0.040 mmol) as a white solid: Mp 210 ^{o}C (dec); IR (neat) 3646, 3412, 3282, 3058, 2921, 2848, 1724, 1631, 1524 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.80 (d, 1 H, *J* = 8.8 Hz), 8.76 (d, 1 H, *J* = 8.3 Hz), 8.16 (d, 1 H, *J* = 7.9 Hz), 7.97 (d, 1 H, *J* = 7.6 Hz), 7.86 (s, 1 H), 7.72-7.59 (m, 4 H), 4.35-4.30 (m, 1 H), 4.05-3.95 (m, 1 H), 3.70-3.45 (m, 4 H), 2.50-2.40 (m, 1 H), 2.30-1.90 (m, 8 H), 1.90 (m, 9 H), 1.70-1.40 (m, 5 H), 1.35-1.15 (m, 14 H), 0.95-0.80 (m, 3 H); MS (EI) *m/z* (relative intensity) 583 ($[M–H_2O]^+$, 20), 378 (15), 302 (15), 221 (35), 205 (100); HRMS (EI) *m/z* calcd for $C_{36}H_{45}N_3O_4$ (M–H_2O) 583.3410, found 583.3391.

2-Phenylethenesulfonyl chloride (46). Prepared according to literature procedures:[41,52] ^{1}H NMR δ 7.76 (d, 1 H, *J* = 15.1 Hz), 7.60-7.45 (m, 5 H), 7.26 (d, 1 H, *J* = 15.0 Hz).

2-Decanoylamino-4-[4-(2-phenylethenesulfonylamino)-cyclohexylcarbamoyl]-butyric acid benzyl ester (47). HCl (conc., 0.1 mL) was added dropwise to a solution of **24** (110 mg, 0.187 mmol) in dioxane (1 mL) at room temperature. The solution was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), treated with **46** (77 mg, 0.38 mmol), TEA (0.080 mL, 0.60 mmol) and DMAP (23 mg, 0.19 mmol), stirred for 18 h at room temperature, diluted with EtOAc (30 mL) and washed with 1N aqueous HCl solution (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2

(Hexanes/EtOAc, 1:2) to give **47** (38 mg, 31%) as a white solid: ^{1}H NMR δ 7.65-7.30 (m, 11 H), 6.76 (d, 1 H, *J* = 15.4 Hz), 6.49 (d, 1 H, *J* = 7.6 Hz), 6.21 (d, 1 H, *J* = 7.6 Hz), 5.20 (d, 1 H, *J* = 12.1 Hz), 5.14 (d, 1 H, *J* = 12.2 Hz), 4.55-4.52 (m, 1 H), 4.47 (d, 1 H, *J* = 7.8 Hz), 3.75-3.60 (m, 1 H), 3.30-3.15 (m, 1 H), 2.24-1.80 (m, 10 H), 1.70-1.50 (m, 4 H), 1.35-1.15 (m, 14 H), 0.88 (t, 3 H, *J* = 6.5 Hz).

2-Decanoylamino-4-[4-(2-phenylethenesulfonylamino)-cyclohexylcarbamoyl]-butyric acid (48). According to the procedure described for the synthesis of **35**, **48** (18 mg, 75%) was obtained from **47** (28 mg, 0.043 mmol) as a white solid: Mp 195 ^{o}C (dec); IR (neat) 3302, 3252, 3060, 2913, 2842, 1736, 1636, 1593, 1533, 1444, 1319, 1133, 1026, 869, 768 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.70-7.50 (m, 2 H), 7.50-7.30 (m, 4 H), 6.99 (d, 1 H, *J* = 15 Hz), 4.40-4.30 (m, 1 H), 3.70-3.55 (m, 1 H), 3.20-3.05 (m, 1 H), 2.30-1.50 (m, 12 H), 1.50-1.15 (m, 16 H), 0.95-0.80 (m, 3 H); MS (EI) *m/z* (relative intensity) 545 ([M–H_2O]$^+$, 3), 378 (40), 96 (100); HRMS (EI) *m/z* calcd for $C_{29}H_{43}N_3O_5S$ (M–H_2O) 545.2923, found 545.2931.

2-(3,4-Difluorophenyl)ethenesulfonyl chloride (49). Prepared according to literature procedures:[41,52] ^{1}H NMR δ 7.66 (d, 1 H, *J* = 15.1 Hz), 7.41–7.27 (m, 3 H), 7.18 (d, 1 H, *J* = 15.1 Hz).

2-Decanoylamino-4-{4-[2-(3,4-difluorophenyl)-ethenesulfonylamino]-cyclohexylcarbamoyl}-butyric acid benzyl ester (50). According to the procedure described for the synthesis of **47**, **50** (60 mg, 43%) was obtained from **49** (48 mg, 0.20 mmol) and **24** (118 mg, 0.201 mmol) as a white solid: ^{1}H NMR (acetone-d_6) δ 7.80-7.30 (m, 8 H), 7.15 (d, 1 H, *J* = 15.1 Hz), 7.2-7.1, 6.4-6.3 (2m, 1 H), 5.13 (bs, 2 H), 4.50-4.35 (m, 1 H), 3.70-3.40 (m, 1 H), 3.25-3.05 (m, 1 H), 2.10-1.80 (m, 10 H), 1.65-1.38 (m, 4 H), 1.30-1.10 (m, 14 H), 0.95-0.80 (m, 3 H).

2-Decanoylamino-4-{4-[2-(3,4-difluorophenyl)-ethenesulfonylamino]-cyclohexylcarbamoyl}-butyric acid (51). According to the procedure described for the synthesis of **35**, **51** (45 mg, 87%) was obtained from **50** (60 mg, 0.090 mmol) as a white solid: Mp 200 ^{o}C (dec); IR 3293, 3232, 3048, 2912, 2842, 1732, 1630, 1593, 1508, 1283 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.63-7.50 (m, 1 H), 7.40-7.25 (m, 2 H), 7.34 (d, 1 H, *J* = 15.6 Hz), 7.02 (d, 1 H, *J* = 15.6 Hz), 4.36-4.28 (m, 1 H), 3.60-3.50 (m, 1 H), 3.15-3.05 (m, 1 H), 2.25-2.02 (m, 5 H), 2.00-1.80 (m, 5 H), 1.62-1.50 (m, 2 H), 1.40-1.15 (m, 16 H), 0.87 (t, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (relative intensity) 581 ([M–H_2O]$^{+}$, 1), 378 (40); HRMS (EI) *m/z* calcd for $C_{29}H_{41}N_3O_5F_2S$ (M–H_2O) 581.2735, found 581.2746.

2-Decanoylamino-4-[4-(2-naphthalen-2-ylethenesulfonylamino)-cyclohexylcarbamoyl]-butyric acid benzyl ester (53). According to the procedure described for the synthesis of **47**, **53** (60 mg, 43%) was obtained from **52** (38 mg, 0.15 mmol) and **24** (88 mg, 0.15 mmol) as a white solid: ^{1}H NMR (acetone-d_6) δ 8.20-7.20 (m, 13 H), 7.22 (d, 1 H, *J* = 15.5 Hz), 7.02 (d, 1 H, *J* = 7.3 Hz), 6.30 (d, 1 H, *J* = 7.5 Hz), 5.16-5.10 (m, 2 H), 4.50-4.30 (m, 1 H), 3.70-3.30 (m, 3 H), 3.25-3.10 (m, 1 H), 2.20-1.88 (m, 12 H), 1.70-1.40 (m, 2 H), 1.30-1.10 (m, 14 H), 0.95-0.80 (m, 3 H).

2-Decanoylamino-4-[4-(2-naphthalen-2-yl-ethenesulfonylamino)-cyclohexylcarbamoyl]-butyric acid (54). According to the procedure described for the synthesis of **35**, **54** (27 mg, 69%) was obtained from **53** (45 mg, 0.064 mmol) as a white solid: Mp 210 ^{o}C (dec); IR 3253, 3053, 2918, 2846, 1729, 1630, 1545, 1437, 1315, 1134 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.02 (s, 1 H), 7.92-7.84 (m, 2 H), 7.75-7.70 (m, 1 H), 7.67-7.50 (m, 3 H), 7.56 (d, 1 H, *J* = 16 Hz), 7.10 (d, 1 H, *J* = 15.4 Hz), 4.34-4.32 (m, 1 H), 3.75-3.50 (m, 2 H), 3.15-

3.05 (m, 1 H), 2.22-1.95 (m, 6 H), 1.95-1.80 (m, 3 H), 1.65-1.50 (m, 2 H), 1.40-1.05 (m, 16 H), 0.86 (t, 3 H, J = 6.1 Hz); MS (EI) *m/z* (relative intensity) 595 ($[M\text{-}H_2O]^+$, <1).

2-(2-Chlorophenyl)ethenesulfonyl chloride (55). Prepared according to literature procedures:[41,52] ^{1}H NMR δ 8.16-8.11 (d, 1 H, J = 15 Hz), 7.63–7.28 (m, 4 H), 7.28 (d, 1 H, J = 15 Hz).

2-Decanoylamino-4-{4-[2-(2-chlorophenyl)-ethenesulfonylamino]-cyclohexylcarbamoyl}-butyric acid benzyl ester (56). According to the procedure described for the synthesis of **47**, **56** (61 mg, 27 %) was obtained from **55** (78 mg, 0.33 mmol) and **24** (193 mg, 0.329 mmol) as a white solid: ^{1}H NMR (acetone-d_6) δ 7.82 (d, 1 H, J = 7.5 Hz), 7.75-7.26 (m, 10 H), 7.13 (d, 1 H, J = 15.5 Hz), 7.07 (d, 1 H, J = 7.7 Hz), 6.50-6.40 (m, 1 H), 5.20-5.05 (m, 2 H), 4.50-4.35 (m, 1 H), 3.65-3.36 (m, 2 H), 3.20-3.05 (m, 1 H), 2.21-2.13 (m, 4 H), 2.03-1.96 (m, 4 H), 1.88-1.85 (m, 2 H), 1.60-1.38 (m, 4 H), 1.30-1.10 (m, 14 H), 0.90-0.80 (m, 3 H).

2-Decanoylamino-4-{4-[2-(2-chlorophenyl)-ethenesulfonylamino]-cyclohexylcarbamoyl}-butyric acid (57). According to the procedure described for the synthesis of **35**, **57** (40 mg, 75 %) was obtained from **56** (61 mg, 0.089 mmol) as a white solid: Mp 195 ^{o}C (dec); IR 3301, 3077, 2920, 2849, 1740, 1640, 1534, 1441, 1323 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.89-7.34 (m, 5 H), 7.05 (d, 1 H, J = 15.4 Hz), 4.33 (dd, 1 H, J = 9.0, 4.6 Hz), 3.70-3.45 (m, 2 H), 3.15-3.05 (m, 1 H), 2.25-1.85 (m, 10 H), 1.65-1.50 (m, 2 H), 1.45-1.15 (m, 16 H), 0.92-0.80 (m, 3 H); MS (EI) *m/z* (relative intensity) 579 ($[M–H_2O]^+$, 1), 562 (7); HRMS (EI) *m/z* calcd for $C_{29}H_{42}N_3O_5SCl$ (M–H_2O) 579.2534, found 579.2531.

5-Oxopyrrolidine-2-carboxylic acid benzyl ester (58). To a solution of DL-pyroglutamic acid (1.3 g, 10 mmol) in DMF (10 mL) was added $KHCO_3$ (1.5 g, 15 mmol) and BnBr (1.2 mL, 10 mmol). The reaction mixture was stirred for 14 h at room temperature, diluted

with EtOAc (50 mL) and washed with 1N aqueous HCl solution (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc) to give **58** (1.4 g, 63%) as a colorless oil: ^{1}H NMR δ 7.45-7.27 (m, 5 H), 6.51 (br, 1 H), 5.19 (s, 2 H), 4.31-4.23 (m, 1 H), 2.55-2.15 (m, 4 H).

5-Oxopyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester (59). Prepared according to the literature procedures:[53] ^{1}H NMR (rotamers) δ 7.36-7.27 (m, 5 H), 5.20-5.15 (m, 2 H), 4.65-4.55 (m, 1 H), 2.70-2.25 (m, 3 H), 2.05-1.90 (m, 1 H), 1.40, 1.37 (2s, 9 H), MS (EI) *m/z* (relative intensity) 263 ([M-C_4H_8]$^+$, 25), 219 (20); HRMS (EI) *m/z* calcd for $C_{13}H_{13}NO_5$ (M-C_4H_8) 263.0794, found 263.0792.

4-(4-Aminocyclohexylcarbamoyl)-2-*tert*-butoxycarbonylaminobutyric acid benzyl ester (60). To a solution of **59** (320 mg, 1.00 mmol) in THF (5 mL) was added 1,4-*trans*-diaminocyclohexane (685 mg, 6.00 mmol) and KCN (65 mg, 1.0 mmol) at room temperature. The reaction mixture was stirred for 7 d at room temperature, concentrated, diluted with water (25 mL) and treated with 4N aqueous NaOH solution until the pH reached 13-14. The solution was extracted with EtOAc (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **60** (330 mg, 77%) as a white solid: ^{1}H NMR δ 7.30-7.15 (m, 5 H), 6.06 (d, 1 H, *J* = 6.8 Hz), 5.55 (d, 1 H, *J* = 6.8 Hz), 5.15 (d, 1 H, *J* = 12.6 Hz), 5. 08 (d, 1 H, *J* = 12.6 Hz), 4.60 (s, 2 H), 4.30-4.15 (m, 1 H), 3.70-3.55 (m, 1 H), 2.65-2.45 (m, 1 H) 2.20-1.70 (m, 8 H) 1.43 (s, 9 H), 1.25-1.05 (m, 4 H); ^{13}C NMR δ 172.3, 171.4, 155.9, 141.9, 135.4, 128.6, 128.3, 127.1, 126.8, 79.9, 67.1, 64.1, 53.3, 49.9, 49.8, 47.9, 35.0 (2C), 31.5 (2C), 28.4, 28.3; MS (EI) *m/z* (relative intensity) 433 (M^+, 5); HRMS (EI) *m/z* calcd for $C_{23}H_{35}N_3O_5$ 433.2576, found 433.2570.

2-*tert*-Butoxycarbonylamino-4-{4-[(2,5-diphenyloxazole-4-carbonyl)-amino]-cyclohexylcarbamoyl}-butyric acid benzyl ester (61). To a solution of **60** (320 mg, 0.743 mmol) in THF (10 mL) was added acid **25** (200 mg, 0.743 mmol), PyBrop (520 mg, 1.11 mmol) and *i*-PrNEt$_2$ (0.20 mL, 1.1 mmol) at room temperature. The reaction mixture was stirred for 18 h at room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL) and washed with H_2O (20 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1 $\rightarrow$ EtOAc) to give **61** (210 mg, 42%) as a white solid: ^{1}H NMR δ 8.40-8.37 (m, 2 H), 8.15-8.12 (m, 2 H), 7.53 7.25 (m, 11 H), 5.92 (bd, 1 H, *J* = 7.2 Hz), 5.31 (d, 1 H, *J* = 7.5 Hz), 5.23 (d, 1 H, *J* = 12.2 Hz), 5.14 (d, 1 H, *J* = 12.2 Hz), 4.38-4.18 (m, 1 H), 4.00-3.90 (m, 1 H), 3.89-3.70 (m, 1 H), 2.30-1.85 (m, 8 H), 1.8-1.2 (m, 13 H), 1.45 (s, 9 H).

4-{4-[(2,5-Diphenyloxazole-4-carbonyl)-amino]-cyclohexylcarbamoyl}-2-(2-phenylethenesulfonylamino)-butyric acid benzyl ester (62). According to the procedure described for the synthesis of **49**, **62** (20 mg, 18%) was obtained from **61** (100 mg, 0.150 mmol) and **46** (61 mg, 0.30 mmol) as a white solid: ^{1}H NMR δ 8.45-8.30 (m, 2 H), 8.20-8.05 (m, 2 H), 7.52-7.00 (m, 17 H), 6.80-6.60 (m, 1 H), 5.70-5.50 (br, 1 H), 5.50-5.30 (m, 1 H), 5.10-4.90 (m, 2 H), 4.1-3.7 (m, 3 H), 2.5-1.8 (m, 7 H), 1.7-1.0 (m, 5 H).

4-{4-[(2,5-Diphenyloxazole-4-carbonyl)-amino]-cyclohexylcarbamoyl}-2-(2-phenylethenesulfonylamino)-butyric acid (63). According to the procedure described for the synthesis of **35**, **63** (9.0 mg, 56%) was obtained from **62** (18 mg, 0.024 mmol) as a white solid: Mp 195 ^{o}C (dec); IR (neat) 3302, 3252, 3060, 2913, 2842, 1736, 1636, 1593 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 8.30-8.27 (m, 2 H), 8.20-8.05 (m, 2 H), 7.80 (d, 1 H, *J* = 7.3 Hz), 7.63-7.24 (m, 11 H), 7.27 (d, 1 H, *J* = 15.4 Hz), 7.08 (d. 1 H, *J* = 15.4 Hz), 3.79-3.62 (m, 2 H), 3.46-3.44 (m, 1 H),

2.20-2.12 (m, 2 H), 2.00-1.72 (m, 4 H), 1.59-1.40 (m, 2 H), 1.30-1.00 (m, 4 H); MS (EI) *m/z* (relative intensity) 638 ($[M–H_2O]^+$, <1); HRMS (EI) *m/z* calcd for $C_{35}H_{35}N_4O_6S$ ($M–H_2O$) 638.2199, found 638.2183.

6,7-Dichloroisoquinoline-5,8-dione (64). Prepared according to literature procedures:[54] ^1H NMR (MeOH-d_4) δ 9.33 (s, 1 H), 9.08 (d, 1 H, *J* = 5.1 Hz), 8.08 (d, 1 H, *J* = 5.0 Hz); ^{13}C NMR (MeOH-d_4) δ 173.8 (2C), 153.5, 146.7, 141.8, 141.7, 135.8, 123.4, 118.0; MS (EI) *m/z* (relative intensity) 227 (M^+, 100), 199 (20), 192 (80), 164 (80); HRMS (EI) *m/z* calcd for $C_9H_3NO_2Cl_2$ 226.9541, found 226.9544.

4-(6-Chloro-5,8-dioxo-5,8-dihydroisoquinolin-7-ylamino)-butyric acid (65). A solution of **64** (280 mg, 1.20 mmol) and 4-aminobutyric-acid (0.13 g, 1.2 mmol) in MeOH (20 mL) was treated with a solution of KOH (70 mg, 1.2 mmol) in H_2O (5 mL). The reaction mixture was stirred for 24 h, acidified with 10% aqueous HCl solution and extracted with EtOAc (50 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 15:1) to give **65** (0.24 g, 69%) as a dark yellow sticky oil (4:1 mixture of regioisomers): ^1H NMR (major isomer) δ 9.13 (s, 1 H), 8.94 (d, 1 H, *J* = 4.9 Hz), 7.92 (d, 1 H, *J* = 5.0 Hz), 3.91-3.83 (m, 2 H), 2.42-2.37 (m, 2 H), 2.03-1.93 (m, 2 H); MS (EI) *m/z* (relative intensity) 294 (M^+, 26), 221 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{11}N_2O_4Cl$ 294.0407, found 294.0413.

4-{4-[4-(6-Chloro-5,8-dioxo-5,8-dihydroisoquinolin-7-ylamino)-butyrylamino]-cyclohexylcarbamoyl}-2-decanoylaminobutyric acid (66). HCl (conc., 0.12 mL) was added dropwise to a solution of **24** (118 mg, 0.200 mmol) in dioxane (1.2 mL) at room temperature. The solution was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was dissolved in THF (3 mL), treated with **65** (24 mg, 0.081 mmol), TEA (0.08 mL,

0.6 mmol) and DEPC (0.036 mL, 0.24 mmol) and stirred for 14 h at room temperature. The reaction mixture was diluted with EtOAc (30 mL) and washed with of 1N aqueous HCl solution (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 10:1) to give crude **66** (110 mg) as a dark red amorphous sticky solid (mixture of regioisomers): ^{1}H NMR (MeOH-d_4) δ 9.13 (s, 1 H), 8.95 (d, 1 H, *J* = 5.1 Hz), 7.93 (d, 1 H, *J* = 5.0 Hz), 7.35-7.30 (m, 5 H), 5.13 (s, 2 H), 4.45-4.34 (m, 1 H), 3.90-3.80 (m, 2 H), 3.65-3.50 (m, 2 H), 2.30-2.05 (m, 6 H), 2.00-1.85 (m, 8 H), 1.60-1.50 (m, 2 H), 1.35-1.15 (m, 16 H), 0.88 (t, 3 H, *J* = 6.4 Hz).

4-{4-[4-(6-Chloro-5,8-dioxo-5,8-dihydroisoquinolin-7-ylamino)-butyrylamino]-cyclohexylcarbamoyl}-2-decanoylamino-butyric acid (67). According to the procedure described for the synthesis of **35**, **67** (42 mg, two steps 76%) was obtained from **66** (110 mg) as a dark red amorphous sticky solid (mixture of regioisomers): Mp 210 ^{o}C (dec); IR 3282, 3074, 2918, 2849, 1705, 1636, 1543 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 9.21 (bs, 1 H), 9.00 (br, 1 H), 7.98 (d, 1 H, *J* = 4.9 Hz), 4.40-4.30 (m, 1 H), 3.65-3.50 (m, 2 H), 2.30-2.10 (m, 6 H), 1.95-1.80 (m, 8 H), 1.65-1.50 (m, 2 H), 1.35-1.15 (m, 16 H), 0.95-0.80 (m, 3 H).

6,7-Dichloroquinoline-5,8-dione (68). Prepared in 30-40% yield from quinoline-8-ol according to a literature procedure:[54] ^{1}H NMR δ 9.11 (dd, 1 H, *J* = 3.8, 1.2 Hz), 8.54 (dd, 1 H, *J* = 7.3, 1.2 Hz), 7.77 (dd, 1 H, *J* = 7.3, 3.8 Hz); ^{13}C NMR δ 175.8, 174.5, 156.0, 147.0, 144.5, 143.3, 135.8, 128.5 (2C); MS (EI) *m/z* (relative intensity) 227 (M^+, 100), 199 (80), 192 (25), 136(100); HRMS (EI) *m/z* calcd for $C_9H_3NO_2Cl_2$ 226.9541, found 226.9545.

6-Chloro-7-(2-morpholin-4-yl-ethylamino)-quinoline-5,8-dione (69) and 7-chloro-6-(2-morpholin-4-yl-ethylamino)-quinoline-5,8-dione (70). A solution of **68** (228 mg, 1.00 mmol) and 2-morpholin-4-ylethylamine (130 mg, 1.00 mmol) in THF (5 mL) was treated with

TEA (0.14 mL, 1.0 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 15:1) to give a mixture of **69** and **70** (260 mg, 80%). The ratio of isomers in this mixture was determined by ^{1}H NMR (**69**:**70** = 2:1). Further separation of isomers by chromatography on SiO_2 (CH_2Cl_2/MeOH, 50:1) gave pure **69** and **70** as dark red amorphous sticky solids. **69**: IR (neat) 3275, 2958, 2855, 1695, 1636, 1600, 1568, 1109 cm^{-1}; ^{1}H NMR δ 8.92 (dd, 1 H, *J* = 4.7, 1.6 Hz), 8.48 (dd, 1 H, *J* = 7.8, 1.6 Hz), 7.66 (dd, 1 H, *J* = 7.8, 4.7 Hz), 7.09 (br, 1 H), 4.10-3.90 (m, 2 H), 3.80-3.70 (m, 4 H), 2.70 (t, 2 H, *J* = 5.7 Hz), 2.60-2.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 179.0, 175.4, 153.4, 146.2, 145.3, 134.6, 129.8, 128.4, 67.0(2C), 56.7, 53.0(2C), 40.9; MS (EI) *m/z* (relative intensity) 323 ([M+2H]$^+$, 7), 210 (25); HRMS (EI) *m/z* calcd for $C_{15}H_{18}N_3O_3Cl$ (M+2H) 323.1037, found 323.1034. **70**: IR (neat) 3275, 2958, 2851, 1687, 1647, 1600, 1564, 1106 cm^{-1}; ^{1}H NMR δ 9.02 (dd, 1 H, *J* = 4.6, 1.6 Hz), 8.36 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.59 (dd, 1 H, *J* = 8.0, 4.6 Hz), 6.98 (br, 1 H), 4.0-3.9 (m, 2 H), 3.85-3.70 (m, 4 H), 2.70 (t, 2 H, *J* = 5.4 Hz), 2.62-2.48 (m, 4 H); ^{13}C NMR δ 180.3, 175.2, 155.4, 148.6, 144.4, 134.8, 127.0, 126.7, 67.1 (2C), 56.8, 53.1 (2C), 40.8; MS (EI) *m/z* (relative intensity) 323 ([M+2H]$^+$, 40), 285 (8) 267 (10); HRMS (EI) *m/z* calcd for $C_{15}H_{18}N_3O_3Cl$ (M+2H) 323.1037, found 323.1027.

6-Chloro-7-(2-piperidin-1-ylethylamino)-quinoline-5,8-dione (71). According to the procedure described for **69** and **70**, a mixture of **71** and its regioisomer **72** (2:1, 286 mg, 89%) was obtained from **68** (228 mg, 1.00 mmol) and 1-(2-aminoethyl)-piperidine (128 mg, 1.00 mmol). Further separation of isomers by chromatography on SiO_2 (CH_2Cl_2/MeOH, 50:1) gave pure **71** as an amorphous red sticky solid: IR (neat) 3267, 2922, 2856, 1699, 1607, 1563, 1497,

1325, 1296, 728 cm^{-1}; ^1H NMR (MeOH-d_4) δ 8.90 (d, 1 H, *J* = 3.5 Hz), 8.42 (d, 1 H, *J* = 7.6 Hz), 7.73 (dd, *J* = 7.6, 3.5 Hz), 3.97 (m, 2 H), 2.68 (t, 2 H, *J* = 6.2 Hz), 2.60-2.40 (m, 4 H), 1.80-1.60 (m, 4 H), 1.60-1.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 179.2, 175.4, 153.4, 146.4, 145.5, 134.7, 130.0, 128.4, 57.0, 54.2 (2C), 41.4, 25.9 (2C), 24.3; MS (EI) *m/z* (relative intensity) 319 (M^+, 15), 281 (40), 220 (92), 208 (37); HRMS (EI) *m/z* calcd for $C_{16}H_{18}N_3O_2Cl$ 319.1087, found 319.1080.

6-Chloro-7-(indan-2-ylamino)-quinoline-5,8-dione (73). According to the procedure described for **69** and **70**, pure **73** (192 mg, 59%) was obtained from **68** (228 mg, 1.00 mmol) and 1-aminoindane (133 mg, 1.00 mmol) as a dark red amorphous sticky solid: IR (neat) 3323, 3065, 2939, 2844, 1695, 1640, 1592, 1560, 1315, 721 cm^{-1}; ^1H NMR δ 8.92 (dd, 1 H, *J* = 4.6, 1.4 Hz), 8.49 (dd, 1 H, *J* = 7.8, 1.4 Hz), 7.67 (dd, 1 H, *J* = 7.8, 4.6 Hz), 7.40-7.20 (m, 4 H), 6.40 (br, 1 H), 6.14 (dd, 1 H, *J* = 15.2, 7.2 Hz), 3.13-3.04 (m, 1 H), 3.00-2.92 (m, 2 H), 2.78-2.72 (m, 1 H), 2.13-2.06 (m, 2 H); ^{13}C NMR δ 178.6, 175.6, 153.4, 145.9, 144.1, 143.5, 142.4, 134.7, 129.8, 128.7, 128.5, 127.2, 125.1, 124.4, 59.7, 36.2, 20.2; MS (EI) *m/z* (relative intensity) 324 (M^+, 6), 287 (3), 220 (15), 205 (35), 117 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{13}N_2O_2Cl$ 324.0666, found 324.0656.

6-Chloro-7-(2-morpholin-4-yl-ethylamino)-isoquinoline-5,8-dione (74). A solution of **64** (114 mg, 0.500 mmol) and 2-morpholin-4-yl-ethylamine (65 mg, 0.50 mmol) in THF (5 mL) was treated with TEA (0.07 mL, 0.5 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 15:1) to give a mixture of **74** and its regioisomer **75** (4:1, 110 mg, 69%). The

regiochemistry of each isomer was tentatively determined by ^{1}H NMR.[55] Further separation of isomers by chromatography on SiO_2 (CH_2Cl_2/MeOH, 50:1) or recrystallization gave **74** (~90% purity) as a dark red amorphous sticky solid: IR (neat) 3271, 2958, 2851, 1683, 1640, 1600, 1564, 1113 cm^{-1}; ^{1}H NMR δ 9.24 (s, 1 H), 9.00 (d, 1 H, *J* = 5.0 Hz), 7.94 (d, 1 H, *J* = 5.0 Hz), 7.13 (br, 1 H), 4.02-3.96 (m, 2 H), 3.78-3.75 (m, 4 H), 2.71-2.67 (m, 2 H), 2.60-2.50 (m, 4 H); ^{13}C NMR δ 179.9, 175.0, 156.3, 154.3, 148.5, 148.2, 123.7, 119.1, 118.2, 67.0 (2C), 56.6, 53.0 (2C), 40.9; MS (EI) *m/z* (relative intensity) 323 ([M+2H]$^+$, 2), 221 (35), 101 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{18}N_3O_3Cl$ (M+2H) 323.1037, found 323.1037.

6,7-Dichlorophthalazine-5,8-dione (76). Prepared according to a literature procedure:[56] ^{1}H NMR δ 9.93 (s, 1 H); MS (EI) *m/z* (relative intensity) 228 (M$^+$, 100), 200 (30); HRMS (EI) *m/z* calcd for $C_8H_2N_2O_2Cl_2$ 227.9493, found 227.9492.

6-Chloro-7-(2-morpholin-4-ylethylamino)-phthalazine-5,8-dione (77). A solution of **76** (67 mg, 0.29 mmol) and 2-morpholin-4-yl-ethylamine (38 mg, 0.29 mmol) in THF (5 mL) was treated with TEA (0.04 mL, 0.3 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature, concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 15:1) to give pure **77** (42 mg, 45%): IR (neat) 3271, 2958, 2923, 2855, 2808, 1695, 1636, 1556, 1311, 1295, 1113 cm^{-1}; ^{1}H NMR δ 9.83 (s, 1 H), 9.65 (s, 1 H), 7.18 (br, 1 H), 4.10-3.90 (m, 2 H), 3.80-3.65 (m, 4 H), 2.69 (t, 2 H, J = 6.0 Hz), 2.60-2.45 (m, 4 H); ^{13}C NMR δ 180.5, 174.2, 171.4, 147.2, 145.3, 144.5, 124.8, 123.3, 67.1 (2C), 56.3, 53.0 (2C), 41.0; MS (EI) *m/z* (relative intensity) 324 ([M+2H]$^+$, 10), 286 (12), 256 (8), 235 (12) 100 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{17}N_4O_3Cl$ (M+2H) 324.0989, found 323.0989.

Quinoline-5,8-dione (78). Prepared from isoquinoline-8-ol according to literature procedures:[57] ^{1}H NMR δ8.88 (s, 1 H), 8.23 (d, 1 H, *J* = 7.8 Hz), 7.60 (d, 1 H, *J* = 7.8 Hz), 7.00, 6.91 (AB, 2 H, *J* = 10.4 Hz).

7-(2-Morpholin-4-yl-ethylamino)-quinoline-5,8-dione (79) and **6-(2-Morpholin-4-yl-ethylamino)-quinoline-5,8-dione (80).** To a solution of quinoline-5,8-dione **78** (0.33 g, 2.1 mmol) in EtOH (20 mL) was added 4-(2-aminoethyl)-morpholine (0.27 mL, 2.1 mmol) at room temperature. The reaction mixture was stirred for 16 h and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 1:30) to give a ~2:3 mixture of **79** and **80** (0.36 g, 60%). Pure **79** and **80** were obtained as red solids by further chromatography separation on SiO_2 ($MeOH/CH_2Cl_2$, 1:100) as red solids. **79**: Mp. 180 °C (dec.); IR (neat) 3329, 2966, 2837, 1696, 1618, 1598 cm^{-1}; ^{1}H NMR δ 8.88 (dd, 1 H, *J* = 4.5, 1.6 Hz), 8.39 (dd, 1 H, *J* = 7.9, 1.6 Hz), 7.63 (dd, 1 H, *J* = 7.9, 4.5 Hz), 6.62 (bs, 1 H), 5.75 (s, 1 H), 3.80-3.60 (m, 4 H), 3.27-3.21 (m, 2 H), 2.69 (t, 2 H, *J* = 6.1 Hz), 2.55-2.35 (m, 4 H); ^{13}C NMR δ 181.5, 180.1, 153.0, 148.3, 146.8, 134.3, 130.8, 128.3, 100.6, 66.9 (2C), 55.5, 53.3 (2C), 38.8; MS (EI) *m/z* (relative intensity) 289 ($[M+2]^+$, 1), 189 (4), 160 (2), 100 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{19}N_3O_3$ (M+2H) 289.1426, found 289.1427. **80**: Mp. 182 °C (dec.); IR (neat) 3293, 2945, 2837, 1685, 1588, 1562, 1490 cm^{-1}; ^{1}H NMR δ 8.97 (dd, 1 H, *J* = 4.8, 1.6 Hz), 8.33 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.55 (dd, 1 H, *J* = 8.0, 4.8 Hz), 6.53 (bs, 1 H), 5.87 (s, 1 H), 3.80-3.60 (m, 4 H), 3.27-3.18 (m, 2 H), 2.69 (t, 2 H, *J* = 6.0 Hz), 2.55-2.35 (m, 4 H); ^{13}C NMR δ 181.5, 181.2, 155.1, 149.3, 147.6, 134.2, 127.4, 126.3, 102.1, 66.9 (2C), 55.5, 53.2 (2C), 38.4; MS (EI) *m/z* (relative intensity) 289 ($[M+2]^+$, 2), 261 (2), 100 (75), 91 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{19}N_3O_3$ (M+2H) 289.1426, found 289.1429.

7-Bromo-5-nitroquinolin-8-ol (81). Prepared according to literature procedures:[59] ^{I}H NMR (DMSO-d_6) δ9.32 (d, 1 H, *J* = 8.9 Hz), 8.97 (d, 1 H, *J* = 4.4 Hz), 8.74 (s, 1 H), 7.98 (dd, 1 H, *J* = 8.9, 4.4 Hz).

5-Amino-7-bromoquinolin-8-ol (82). Prepared according to literature procedures:[59] ^{I}H NMR (DMSO-d_6) δ□□bs, 1 H), 8.79 (d, 1 H, *J* = 4.2 Hz), 8.48 (d, 1 H, *J* = 8.5 Hz), 7.48 (dd, 1 H, *J* = 8.5, 4.2 Hz), 6.84 (s, 1 H), 5.53 (bs, 2 H).

7-Bromoquinoline-5,8-dione (83). Prepared according to literature procedures:[59] Mp. 175-178 °C (dec.); IR (neat) 3053, 1695, 1650, 1568, 1296, 1245 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.02 (dd, 1 H, *J* = 3.2, 1.6 Hz), 8.36 (dd, 1 H, *J* = 7.9, 1.6 Hz), 7.87 (dd, 1 H, *J* = 7.9, 3.2 Hz), 7.80 (s, 1 H); ^{13}C NMR δ 182.5, 176.0, 154.1, 146.8, 140.1, 139.2, 134.3, 128.9, 128.2; MS (EI) *m/z* (relative intensity) 237 (M^+, 91), 209 (12), 158 (32), 130 (45), 102 (100); HRMS (EI) *m/z* calcd for $C_9H_4NO_2Br$ 236.9425, found 236.9421.

7-Bromo-6-(2-morpholin-4-yl-ethylamino)-quinoline-5,8-dione (84). A solution of **83** (0.14 g, 0.59 mmol) in THF (5 mL) was treated with TEA (82 μL, 0.59 mmol) and 4-(2-aminoethyl)-morpholine (77 μL, 0.59 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:30) to give **84** (0.15 g, 69%) as a red sticky amorphous solid: IR (neat) 3247, 2955, 2848, 1680, 1562, 1122 cm^{-1}; ^{1}H NMR δ 8.92 (dd, 1 H, *J* = 4.5, 1.4 Hz), 8.24 (dd, 1 H, *J* = 7.7, 1.4 Hz), 7.54 (dd, 1 H, *J* = 7.7, 4.5 Hz), 7.03 (bs, 1 H), 3.95-3.85 (m, 2 H), 3.80-3.60 (m, 4 H), 2.63 (t, 2 H, *J* = 5.9 Hz), 2.55-2.35 (m, 4 H); ^{13}C NMR δ 179.7 (2C), 174.4, 154.9, 147.9, 146.4, 134.6, 126.8, 126.4, 67.0 (2C), 56.3, 52.8

(2C), 41.2; MS (EI) *m/z* (relative intensity) 365 (M^+, 3); HRMS (EI) *m/z* calcd for $C_{15}H_{14}N_3O_2Br$ (M-2H) 363.0219, found 363.0214.

6,7-Dibromoquinoline-5,8-dione (85). To a solution of **78** (0.80 g, 5.0 mmol) in CH_2Cl_2 (50 mL) was added slowly Br_2 (0.77 mL, 15 mmol) in CH_2Cl_2 (20 mL) for 30 min at room temperature. The reaction mixture was stirred for 20 h at room temperature and treated with pyridine (1.2 mL, 15 mmol) at room temperature. The reaction mixture was stirred for 20 h, diluted with CH_2Cl_2 (200 mL) and washed with H_2O (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give crude **85** (620 mg, 39%) as a dark yellow solid. Crude **85** was recrystallized from EtOAc to give pure **85** (225 mg, 14%) as a yellow solid: Mp. 225 °C (EtOAc); IR (neat) 1685, 1665, 1541, 1568, 1265, 1188, 1107 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.01 (dd, 1 H, *J* = 4.6, 1.6 Hz), 8.42 (dd, 1 H, *J* = 7.9, 1.6 Hz), 7.86 (dd, 1 H, *J* = 7.9, 4.6 Hz); ^{13}C NMR δ 176.1, 174.2, 154.3, 146.7, 142.6, 140.9, 135.3, 135.0, 128.2; MS (EI) *m/z* (relative intensity) 315 (M^+, 5); HRMS (EI) *m/z* calcd for $C_9H_3NO_2Br_2$ 314.8531, found 314.8521.

6-Bromo-7-(2-morpholin-4-yl-ethylamino)-quinoline-5,8-dione (86). A solution of **85** (74 mg, 0.23 mmol) in THF (3 mL) was treated with TEA (0.033 □L, 0.23 mmol) and 4-(2-aminoethyl)-morpholine (0.030 □L, 0.23 mmol) at room temperature. The reaction mixture was stirred for 18 h at room temperature, diluted with EtOAc (25 mL) and washed with brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:30) to give a ~2:1 mixture of regioisomers **86** and **84** (50 mg, 58%). Further separation by chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:100) gave pure **86** as a red sticky amorphous solid: IR (neat) 3257, 2955, 2848, 1690, 1588, 1547, 1122 cm^{-1}; ^1H NMR δ 8.91 (dd, 1 H, *J* = 4.7, 1.7 Hz), 8.47 (dd, 1 H, *J* =

7.9, 1.7 Hz), 7.63 (dd, 1 H, *J* = 7.9, 4.7 Hz), 7.18 (bs, 1 H), 4.03-3.97 (m, 2 H), 3.85-3.65 (m, 4 H), 2.69 (t, 2 H, *J* = 5.9 Hz), 2.65-2.50 (m, 4 H); ^{13}C NMR δ 178.7 (2C), 175.1, 153.5, 147.8, 146.3, 135.0, 129.6, 128.4, 67.1 (2C), 56.7, 53.0 (2C), 41.5; MS (EI) *m/z* (relative intensity) 365 (M^+, 4), 228 (20), 100 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{16}N_3O_2Br$ 365. 0375, found 365. 0389.

6-(2-Morpholin-4-yl-ethylamino)-7-phenyl-quinoline-5,8-dione (88). To a solution of **83** (0.24 g, 1.0 mmol) in dioxane (10 mL) was added *n*-Bu_3SnPh (370 mg, 1.0 mmol), $Pd(PPh_3)_4$ (58 mg, 0.050 mmol) and CuBr (7.2 mg, 0.050 mmol) at room temperature. The reaction mixture was heated at reflux for 14 h, cooled to room temperature and filtered through a silica gel pad. The filtered solution was concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give crude **87**, which was dissolved in THF (1.5 mL). To this solution was added 4-(2-aminoethyl)-morpholine. The reaction mixture was stirred for 3 h at room temperature and purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 1:50) several times to give **88** (~3 mg, <1%) as a red sticky amorphous solid: IR (neat) 3324, 2955, 2929, 2858, 1680, 1562 cm^{-1}; ^{1}H NMR δ 9.03 (dd, 1 H, *J* = 3.2, 1.6 Hz), 8.40 (dd, 1 H, *J* = 7.8, 1.6 Hz), 7.58 (dd, 1 H, *J* = 7.8, 3.2 Hz), 7.46-7.30 (m, 5 H), 6.80 (bs, 1 H), 3.75-3.65 (m, 4 H), 2.80-2.60 (m, 2 H), 2.50-2.30 (m, 6 H); MS (EI) *m/z* (relative intensity) 365 ($[M+2]^+$, 30), 262 (45), 100 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{23}N_3O_3$ 365.1739, found 365.1731.

7-(2-Morpholin-4-yl-ethylamino)-isoquinoline-5,8-dione (89). To a solution of 5-hydroxyisoquinoline (90%, 200 mg, 1.25 mmol) in $EtOH/H_2O$ (10 mL/1 mL) was added PIFA (1.07 g, 2.50 mmol) at room temperature. The reaction mixture was stirred for 2 h and treated with $CeCl_3$ (0.60 g, 2.5 mmol) and 4-(2-aminoethyl)-morpholine (1.3 mL, 10 mmol) at room temperature. The solution was stirred for 20 h, diluted with EtOAc (100 mL) and washed with

brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 50:1) to give a crude product. Further separation by chromatography on SiO_2 (EtOAc) gave **89** as a red sticky solid. IR (film) 3346, 2960, 2849, 2815, 1683, 1631, 1601, 1554, 1511, 1352, 1327, 1262, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.25 (s, 1 H), 9.00 (d, 1 H. *J* = 5.0 Hz), 7.90 (d, 1 H, *J* = 5.0 Hz), 6.67 (bs, 1 H, -N*H*), 5.79 (s, 1 H), 3.80-3.65 (m, 4 H), 3.30-3.15 (m, 2 H), 2.71 (t, 2 H, *J* = 6.1 Hz), 2.60-2.40 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 181.3, 181.0, 156.4, 148.0 (2C), 132.3, 124.4, 119.0, 101.6, 67.0 (2C), 55.5, 53.2 (2C), 38.4; MS (EI) *m/z* (relative intensity) 288 (M^+, 3), 199 (3.5), 100 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{18}N_3O_3$ 288.1348, found 288.1338.

2-(Tetrahydropyran-2-yloxy)-ethanethiol (90). Prepared according to literature procedures:[62] IR (neat) 2939, 2871, 2558, 1446, 1346, 1203, 1137, 1034, 974, 906 cm^{-1}; ^1H NMR δ 4.61 (t, 1 H, *J* = 2.9 Hz), 3.87 – 3.81 (m, 2 H), 3.55 – 3.49 (m, 2 H), 2.69 (dt, 2 H, *J* = 6.5, 5 Hz), 1.69 – 1.49 (m, 7 H); ^{13}C NMR δ 98.8, 69.2, 62.3, 30.5, 25.4, 24.6, 19.4; MS (CI) *m/z* (relative intensity) 163 ($[M+H]^+$, 30), 85 (100), 61 (45).

Benzoic acid 2-mercaptoethyl ester (91). A solution of 2-mercaptoethanol (1.4 mL, 20 mmol) and benzoylchloride (2.3 mL, 20 mmol) in CH_2Cl_2 (20 mL) was treated with pyridine (2.0 mL, 20 mmol). The reaction mixture was stirred for 5 h at room temperature, diluted with CH_2Cl_2 (50 mL) and washed with 1N HCl solution (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give **91** (900 mg, 25%) as a colorless oil: IR (neat) 3065, 2954, 2895, 2578, 1715, 1608, 1580, 1453, 1378, 1279, 1184, 1101 cm^{-1}; ^1H NMR δ 8.05 – 8.06 (m, 2 H), 7.61–7.55 (m, 1 H), 7.48–7.43 (m, 2 H), 4.52 (t, 2 H, *J* = 6.7 Hz), 2.93–2.86 (m, 2 H), 1.58 (t, 1 H, *J* = 14.5 Hz); ^{13}C NMR δ 166.4, 133.3, 130.0, 129.9, 129.8 (2C),

128.6, 66.3, 23.6; MS (EI) *m/z* (relative intensity) 182 (M^+, 1), 149 (2), 123 (26), 105 (85), 77 (100), 60 (35); HRMS (EI) *m/z* calcd for $C_9H_{10}NO_2S$ 182.0402, found 182.0407.

2-(*tert*-Butyldiphenylsilanyloxy)-ethanethiol (92). A solution of 2-mercaptoethanol (0.70 mL, 10 mmol) and TBDPSCl (2.8 g, 10 mmol) in DMF (20 mL) was treated with imidazole (0.68 g, 10 mmol). The reaction mixture was stirred for 5 h at room temperature, quenched with saturated NH_4Cl solution (1 mL), diluted with EtOAc (50 mL) and washed with of saturated $NaHCO_3$ solution (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give **92** (2.95 g, 93%) as a colorless oil: IR (neat) 3069, 2946, 2859, 1473, 1434, 1117, 832, 709 cm^{-1}; ^1H NMR δ 7.75–7.72 (m, 4 H), 7.48–7.41 (m, 6 H), 3.83 (t, 2 H, *J* = 6.4 Hz), 2.75-2.65 (m, 2 H), 1.64 (t, 1 H, *J* = 8.3 Hz), 1.13 (s, 9 H); ^{13}C NMR δ 135.7 (4C), 133.5 (2C), 129.9 (2C), 127.8 (4C), 65.7, 27.3, 27.0 (3C), 19.4; MS (EI) *m/z* (relative intensity) 259 ($[M-tBu]^+$, 15), 199 (10), 181 (65), 84 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{15}OSSi$ (M-*t*Bu) 259.0613, found 259.0607.

(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methanethiol (93). Prepared according to literature procedures:[62] IR (neat) 2990, 2930, 2883, 2554, 1453, 1378, 1228, 1152, 1065, 859cm^{-1}; ^1H NMR δ 4.16-4.12 (m, 1 H), 4.07-4.01 (m, 1 H), 3.72-3.68 (m, 1 H), 2.70-2.63 (m, 1 H), 2.59-2.51 (m, 1 H), 1.43 (t, 1 H, *J* = 8.5 Hz), 1.37 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR δ 109.8, 77.1, 68.4, 27.7, 27.0, 25.6; MS (EI) *m/z* (relative intensity) 148 (M^+, 6), 133 (40), 101 (70), 73 (100); HRMS (EI) *m/z* calcd for $C_6H_{12}O_2S$ 148.0558, found 148.0560.

6,7-Bis-[2-(tetrahydropyran-2-yloxy)-ethylsulfanyl]-quinoline-5,8-dione (94). A solution of **68** (98 mg, 0.43 mmol) and **90** (210 mg, 1.30 mmol) in THF (8 mL) was treated with TEA (0.18 mL, 1.3 mmol) at room temperature. The reaction mixture was stirred at room

temperature for 20 h, concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **94** (270 mg, 58%) as a dark red amorphous sticky oil: IR (neat) 2943, 2863, 1663, 1580, 1485, 1287, 1204, 1125, 1073, 1022 cm^{-1}; ^1H NMR δ 8.96 (dd, 1 H, *J* = 4.7, 1.6 Hz), 8.37 (dd, 1 H, *J* = 7.8, 1.6 Hz), 7.63 (dd, 1 H, *J* = 7.8, 4.6 Hz), 4.64-4.54 (m, 2 H), 4.05-3.90 (m, 2 H), 3.85-3.44 (m, 10 H), 1.65-1.26 (m, 12 H); ^{13}C NMR δ 178.1, 177.4, 154.2, 149.5, 148.6, 146.3, 134.8, 129.9, 127.3, 98.7 (2C), 67.5, 67.4, 62.0 (2C), 34.6, 34.4, 30.3 (2C), 25.3 (2C), 19.1, 18.9; MS (EI) *m/z* (relative intensity) 479 (M^+, 6), 397 (6), 351 (5), 313 (40), 85 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{29}NO_6S_2$ 479.1436, found 479.1438.

6,7-Bis-[2-(benzoyloxy)-ethylsulfanyl]-quinoline-5,8-dione (95). According to the procedure described for **94, 95** (220 mg, 86 %) was obtained from **68** (114 mg, 0.500 mmol) and **91** (228 mg, 1.25 mmol) as a dark red amorphous sticky oil: IR (neat) 3061, 2951, 2883, 1723, 1663, 1271, 1113, 709 cm^{-1}; ^1H NMR δ 8.93 (dd, 1 H, *J* = 4.6, 1.7 Hz), 8.24 (dd, 1 H, *J* = 7.8, 1.7 Hz), 7.96-7.90 (m, 3 H), 7.58-7.46 (m, 4 H), 7.34-7.28 (m, 4 H), 4.62-4.48 (m, 4 H), 3.71-3.57 (m, 4 H); ^{13}C NMR δ 178.1, 177.3, 166.1 (2C), 154.4, 148.8, 148.3, 146.2, 134.9, 133.3, 133.2, 129.8 (8C), 128.5 (2C), 127.6 (2C), 64.6, 64.4, 33.9, 33.7; MS (EI) *m/z* (relative intensity) 519 (M^+, 7), 397 (12), 369 (10), 84 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{21}NO_6S_2$ 519.0810, found 519.0821.

6,7-Bis-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylsulfanyl)-quinoline-5,8-dione (76). According to the procedure described for **94, 96** (160 mg, 71 %) was obtained from **68** (114 mg, 0.500 mmol) and **93** (222 mg, 1.50 mmol) as a dark red amorphous sticky oil: IR (neat) 2943, 2863, 1663, 1580, 1485, 1287, 1204, 1125, 1073, 1022 cm^{-1}; ^1H NMR δ 8.98 (d, 1 H, *J* = 4.1

Hz), 8.38 (dd, 1 H, *J* = 7.8 Hz), 7.65 (dd, 1 H, *J* = 7.8, 4.6 Hz), 4.43-4.30 (m, 2 H), 4.15-4.10 (m, 2 H), 3.85-3.77 (m, 2 H), 3.62-3.25 (m, 4 H), 1.31 (s, 6 H), 1.27 (s, 6 H); ^{13}C NMR δ 178.0, 177.3, 154.3, 149.4, 148.5, 145.9, 134.8, 129.9, 127.5, 109.8 (2C), 75.6 (2C), 68.4 (2C), 37.1 (2C), 26.7 (2C), 25.4 (2C); MS (EI) *m/z* (relative intensity) 451 (M^+, 20), 337 (40), 236 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{25}NO_6S_2$ 451.1123, found 451.1125.

6,7-Bis-[2-(*tert*-butyldiphenylsilanyloxy)-ethylsulfanyl]-quinoline-5,8-dione (97). According to the procedure described for **94, 97** (390 mg, 99%) was obtained from **68** (114 mg, 0.500 mmol) and **92** (228 mg, 1.25 mmol) as a dark red amorphous sticky oil: IR (neat) 3049, 2956, 2890, 2860, 1657, 1587, 1468, 1423, 1278, 1204, 1100, 1026, 903, 818, 714 cm^{-1}; ^{1}H NMR δ 8.94 (dd, 1 H, *J* = 4.6, 1.6 Hz), 8.28 (dd, 1 H, *J* = 7.9, 1.6 Hz), 7.67-7.58 (m, 9 H), 7.67-7.58 (m, 12 H), 3.93, 3.90 (2t, 4 H, *J* = 6.1 Hz), 3.55, 3.49 (2t, 4 H, *J* = 5.9 Hz), 1.00 (s, 18 H); ^{13}C NMR δ 177.7, 177.0, 153.8, 148.7, 148.1, 145.7, 135.3 (8C), 134.4, 132.9 (4C), 129.5 (4C), 127.5 (8C), 127.0 (2C), 63.7, 63.5, 37.2, 36.8, 26.5 (6C), 18.9 (2C); MS (EI) *m/z* (relative intensity) 789 ($[M+2H]^+$, 10), 732 (20), 448 (15), 225 (100); HRMS (EI) *m/z* calcd for $C_{45}H_{51}NO_4Si_2S_2$ (M+2H) 789.2798, found 789.2813.

6,7-Bis-[2-(tetrahydropyran-2-yloxy)-ethylsulfanyl]-isoquinoline-5,8-dione (99). A solution of **64** (74 mg, 0.32 mmol) and **90** (160 mg, 0.960 mmol) in THF (5 mL) was treated with TEA (0.13 mL, 0.96 mmol) at room temperature. The reaction mixture was stirred at room temperature for 20 h, concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:2) to give **99** (31 mg, 20%) as a dark red amorphous sticky oil: IR (neat) 2936, 2863, 1663, 1580, 1282, 1119, 1026 cm^{-1}; ^{1}H NMR δ 9.28 (s, 1 H), 8.98 (d, 1 H, *J* = 5 Hz), 7.83 (d, 1 H, *J* =

5 Hz), 4.63-4.55 (m, 2 H), 3.98–3.46 (m, 8 H), 1.60-1.25 (m, 8 H); ^{13}C NMR δ 178.3, 177.9, 155.0, 149.3, 148.9, 147.2, 138.4, 126.4, 119.0, 98.9 (2C), 67.7(2C), 62.2 (2C), 34.7, 34.5, 30.5 (2C), 25.4 (2C), 19.3, 19.2; MS (EI) *m/z* (relative intensity) 479 (M^+, 40), 313 (100), 85 (85); HRMS (EI) *m/z* calcd for $C_{23}H_{29}NO_6S_2$ 479.1436, found 479.1429.

6,7-Bis-[2-(benzoyloxy)-ethylsulfanyl]-isoquinoline-5,8-dione (100). According to the procedure described for **99, 100** (190 mg, 84 %) was obtained from **64** (98 mg, 0.43 mmol) and **91** (222 mg, 1.30 mmol) as a dark red amorphous sticky oil: IR (neat) 3065, 2943, 2887, 1723, 1659, 1580, 1450, 1283, 1109, 705 cm^{-1}; ^{1}H NMR δ 9.15 (s, 1 H), 8.92 (d, 1 H, *J* = 4.1 Hz), 7.94-7.88 (m, 4 H), 7.70 (d, 1H, *J* = 4.1 Hz), 7.48-7.46 (m, 2 H), 7.34-7.26 (m, 4 H), 4.58, 4.56 (2t, 4 H, *J* = 5.9 Hz), 3.69, 3.64 (t, 4 H, *J* = 6.0 Hz); ^{13}C NMR δ 177.9, 177.6, 166.0 (2C), 154.9, 148.7, 148.6, 146.6, 137.8, 133.3, 133.2, 129.6 (8C), 128.4 (4C), 125.8, 118.8, 64.4, 64.3, 33.8, 33.5; MS (EI) *m/z* (relative intensity) 519 (M^+, 4), 397 (18), 105 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{21}NO_6S_2$ 519.0810, found 519.0829.

6,7-Bis-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylsulfanyl)-isoquinoline-5,8-dione (101). According to the procedure described for **99, 101** (37 mg, 69%) was obtained from **64** (27 mg, 0.12 mmol) and **93** (53 mg, 0.36 mmol) as a dark red amorphous sticky oil: IR (neat) 2986, 2923, 2851, 1659, 1279, 1061 cm^{-1}; ^{1}H NMR δ 9.30 (bs, 1 H), 9.02 (bs, 1 H), 7.84 (d, 1 H, *J* = 4.2 Hz), 4.38-4.26 (m, 2 H), 4.15-4.09 (m, 2 H), 3.84-3.79 (m, 2 H), 3.60-3.25 (m, 4 H), 1.30 (s, 6 H), 1.25 (s, 6 H); ^{13}C NMR δ 178.0, 177.7, 154.8, 149.0, 148.7, 146.8, 138.5, 126.5, 119.2, 110.0 (2C), 75.8 (2C), 68.5, 68.4, 37.2 (2C), 26.8, 26.7, 25.5, 25.4; MS (EI) *m/z* (relative intensity) 451 (M^+, 12); HRMS (EI) *m/z* calcd for $C_{21}H_{25}NO_6S_2$ 451.1123, found 451.1132.

4,5-Dichloro-1,2-dimethyl-1,2-dihydro-pyridazine-3,6-dione (103). Prepared according to literature procedures:[62] IR (neat) 3272, 3042, 2959, 2917, 1671, 1635, 1585, 1471

cm^{-1}; ^1H NMR δ 3.68 (s, 6 H); ^{13}C NMR δ 152.6 (2C), 138.2 (2C), 34.3 (2C); MS (EI) *m/z* (relative intensity) 208 (M^+, 100), 180 (55); HRMS (EI) *m/z* calcd for $C_6H_6N_2O_2Cl_2$ 207.9806, found 207.9802.

4-Chloro-1,2-dimethyl-5-(2-morpholin-4-yl-ethylamino)-1,2-dihydropyridazine-3,6-dione (104). A solution of **103** (420 mg, 2.01 mmol) in EtOH (20 mL) was treated with TEA (0.28 mL, 2.0 mmol) and 2-morpholin-4-ylethylamine (260 mg, 2.00 mmol) at room temperature. The reaction mixture was heated at reflux for 18 h at 100 ^oC, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL) and washed with water (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give pure **104** (260 mg, 37%) as a yellow solid: Mp 110-115 ^oC; IR (neat) 3492, 3302, 2947, 2850, 2807, 1617, 1507, 1353, 1293, 1116 cm^{-1}; ^1H NMR δ 6.54 (br, 1 H), 3.85 (t, 2 H, *J* = 5.8 Hz), 3.69 (t, 4 H, *J* = 4.6 Hz), 3.59 (s, 3 H), 3.57 (s, 3 H), 2.58 (t, 2 H, *J* = 6.0 Hz), 2.50 (t, 4 H, *J* = 4.5 Hz); ^{13}C NMR δ 157.1, 153.6, 140.7, 103.4, 66.9 (2C), 57.1, 53.1 (2C), 40.1, 33.9, 33.8; MS (EI) *m/z* (relative intensity) 303 (M^+, 5), 267 (45), 100 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{19}N_4O_3Cl$ 302.1146, found 302.1144.

4-(2-Iodoethyl)-morpholine (105). A solution of 4-(2-chloroethyl)-morpholine hydrochloric salt (1.9 g, 10 mmol) in MeOH (10 mL) was treated with NaI (15 g, 0.10 mol). The reaction mixture was heated at reflux for 5 d at 100 ^oC, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ solution (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **105** (800 mg, 36%) as a yellow oil: ^1H NMR δ 3.73-3.70 (m, 4 H), 3.21 (t, 2 H, *J* = 7.9 Hz), 2.72 (t, *J* = 7.9 Hz), 2.51-2.48 (m, 4 H); ^{13}C NMR δ 66.9

(2C), 61.1, 53.1 (2C), 1.9; MS (EI) *m/z* (relative intensity) 241 (M^+, 80), 155 (65), 114 (100); HRMS (EI) calcd for $C_6H_{12}NOI$ 240.9964, found 240.9962.

2-Amino-3-chlorochromen-4-one (106). Prepared according to the literature:[64] ^{1}H NMR δ 8.04 (2 H, br), 7.93-7.91 (m, 1 H), 7.65-7.60 (m, 1 H), 7.40-7.35 (m, 2 H); ^{13}C NMR δ 169.2, 161.5, 152.3, 133.1, 125.5, 122.4, 117.1, 92.3; MS (EI) *m/z* (relative intensity) 195 (M^+, 100), 167 (20), 121 (45), 91 (40); HRMS (EI) *m/z* calcd for $C_9H_6NO_2Cl$ 195.0087, found 195.0090.

3-Chloro-2-(2-morpholin-4-yl-ethylamino)-chromen-4-one (107). A solution of **106** (190 mg, 1.00 mmol) and **105** (240 mg, 1.00 mmol) in DMF (10 mL) was treated with Cs_2CO_3 (1.6 g, 5.0 mmol) and stirred for 3 h at room temperature. The reaction mixture was diluted with EtOAc (50 mL) and washed with $NaHCO_3$ solution (50 mL×2). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes /EtOAc, 2:1) to give **107** (14 mg, 5%) as a pale yellow liquid: IR (neat) 3422, 2962, 2852, 1636, 1623, 1600, 1450, 1353, 1145, 1113; ^{1}H NMR δ 7.68-7.65 (m, 1 H), 7.53-7.48 (m, 1 H), 7.43-7.40 (m, 1 H), 7.33-7.26 (m, 1 H), 4.62 (t, 2 H, *J* = 5.3 Hz), 3.75-3.71 (m, 4 H), 2.89 (t, 2 H, *J* = 5.3 Hz), 2.62-2.59 (m, 4 H); ^{13}C NMR δ 154.2, 152.3, 129.5, 123.7, 120.6, 120.5, 113.2, 112.4, 110.4, 70.6, 67.0 (2C), 57.7, 54.1 (2C); MS (EI) *m/z* (relative intensity) 241 ($[M\text{-}HCl]^+$, 40), 213 (10), 85 (15); HRMS (EI) *m/z* calcd for $C_{15}H_{16}N_2O_3$ (M-HCl) 272.1161, found 272.1157.

2-Benzyloxycarbonylamino-benzoicacid (108). To a solution of anthranilic acid (1.37 g, 10.0 mmol) in THF (60 mL) was added K_2CO_3 (2.76 g, 20.0 mmol) in H_2O (20 mL) at room temperature. The reaction mixture was cooled to 0 °C, treated with CbzCl (1.7 mL, 12 mmol), stirred for 2 h at room temperature, washed with Et_2O (40 mL) and acidified to pH 1 with 1 N aqueous HCl solution. The resulting aqueous solution was extracted with EtOAc (50 mL×2),

dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **108** (1.5 g, 55%) as a white solid: ^{1}H NMR δ 11.4 (bs, 1 H), 10.4 (s, 1 H), 8.53 (d, 1 H. *J* = 8.5 Hz), 8.13 (d, 1 H, *J* = 8.0 Hz), 7.59 (dd, 1 H, *J* = 8.5, 7.2 Hz), 7.50-7.30 (m, 5 H), 7.07 (dd, 1 H, *J* = 8.0, 7.2 Hz).

[2-(2-Morpholin-4-yl-ethylcarbamoyl)-phenyl]-carbamic acid benzyl ester (109). To a solution of **108** (1.36 g, 5.01 mmol) in DMF (50 mL) was added TEA (1.4 mL, 10 mmol), 4-(2-aminoethyl)-morpholine (0.73 mL, 5.5 mmol), HOBt (0.88 g, 6.5 mmol) and EDCI (1.24 g, 6.51 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ solution (100 mL×2). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (EtOAc) to give **109** (1.13 g, 59%) as a colorless oil: IR (neat) 3324, 2950, 2858, 2822, 1746, 1649, 1582, 1516, 1450 cm^{-1}; ^{1}H NMR δ 10.6 (s, 1 H), 8.39 (d, 1 H. *J* = 8.4 Hz), 7.50-7.30 (m, 7 H), 7.04 (dd, 1 H, *J* = 8.4, 7.4 Hz), 6.88 (bs, 1 H), 5.20 (s, 2 H), 3.85-3.65 (m, 4 H), 3.55-3.45 (m, 2 H), 2.61-2.53 (m, 2 H), 2.50-2.40 (m, 4 H); ^{13}C NMR δ 168.8, 153.7, 139.9, 136.3, 132.6, 128.6 (2C), 128.4 (2C), 128.3 (2C), 126.7, 122.0, 67.1 (2C), 66.9, 56.7, 53.4 (2C), 36.0; MS (EI) *m/z* (relative intensity) 383 (M^+, 3). 271 (4), 275 (3); HRMS (EI) *m/z* calcd for $C_{21}H_{25}N_3O_4$ 383.1845, found 383.1870.

3-(2-Morpholin-4-yl-ethyl)-1*H*-quinazoline-2,4-dione (110). To a solution of **109** (720 mg, 1.88 mmol) in MeOH (188 mL) was added TEA (2.6 mL, 19 mmol) at room temperature. The reaction mixture was heated at reflux for 2 d, cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:5) to give **110** (430 mg, 83%) as a white solid: Mp. 205-207 °C (CH_2Cl_2); IR (neat) 3278, 3196, 3048, 2950, 1726, 1649, 1501, 1450 cm^{-1}; ^{1}H NMR δ 10.6 (s, 1 H), 8.09 (d, 1

H. *J* = 7.9 Hz), 7.61 (dd, 1 H, *J* = 8.1, 7.9 Hz), 7.22 (dd, 1 H, *J* = 8.1, 7.5 Hz), 7.09 (d, 1 H, *J* = 8.1 Hz), 4.26 (t, 2 H, *J* = 6.7 Hz), 3.80-3.60 (m, 4 H,), 2.72 (t, 2 H, *J* = 6.7 Hz), 2.65-2.50 (m, 4 H); ^{13}C NMR δ 162.5, 152.3, 138.8, 135.1, 128.4, 123.5, 115.0, 114.6, 67.1 (2C), 56.1, 53.9 (2C), 37.8; MS (EI) *m/z* (relative intensity) 275 (M^+, 3.5), 232 (1.5), 189 (3.5), 163 (4.5), 100 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{17}N_3O_3$ 275.1270, found 275.1267.

1-Methyl-3-(2-morpholin-4-yl-ethyl)-1*H*-quinazoline-2,4-dione (111). To a solution of **110** (0.10 g, 0.36 mmol) in THF (5 mL) was added NaH (17 mg, 0.72 mmol) at room temperature. The reaction mixture was stirred for 1 h, treated with MeI (23 μL, 0.36 mmol) at room temperature, stirred for 2 d, quenched with brine (25 mL) and extracted with EtOAc (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 1:50) to give **111 (**61 mg, 58%) as a white solid: Mp. 138-140 °C (CH_2Cl_2); IR (neat) 2950, 2853, 2811, 1716, 1660, 1598, 1480 cm^{-1}; ^{1}H NMR δ 8.18 (d, 1 H. *J* = 7.9 Hz), 7.70-7.60 (m 2 H), 7.27-7.16 (m, 2 H), 4.22 (t, 2 H, *J* = 6.9 Hz), 3.80-3.60 (m, 4 H), 3.58 (s, 3 H), 2.64 (t, 2 H, *J* = 6.9 Hz), 2.60-2.45 (m, 4 H); ^{13}C NMR δ 161.8, 151.0, 140.6, 135.2, 128.9, 123.0, 115.6, 113.6, 67.1 (2C), 56.0, 53.9 (2C), 38.8, 30.8; MS (EI) *m/z* (relative intensity) 289 (M^+, 15), 246 (10), 203 (15); HRMS (EI) *m/z* calcd for $C_{15}H_{19}N_3O_3$ 289.1426, found 289.1428.

4-(2-Morpholin-4-yl-ethoxy)-2*H*-phthalazin-1-one (112). To a solution of phthalhydrazide (6.49 g, 40.0 mmol) in DMF (125 mL) was added NaH (960 mg, 40.0 mmol) at room temperature. The reaction mixture was stirred for 1 h and treated with 4-(2-iodoethyl)-morpholine (980 mg, 4.07 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature, quenched with saturated aqueous $NaHCO_3$ solution (125 mL) and extracted with EtOAc (500 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced

pressure to give crude product (180 mg, 16%). The crude product was recrystallized from Et_2O to give pure **112** (60 mg, 5%) as a white solid: Mp. 167-169 °C (Et_2O); IR (neat) 3170, 3011, 2909, 2883, 1654, 1593, 1485 cm^{-1}; ^1H NMR δ 11.6 (s, 1 H), 8.40-8.33 (m, 1 H), 7.97-7.90 (m, 1 H), 7.78-7.70 (m, 2 H), 4.47 (t, 2 H, *J* = 5.5 Hz), 3.74 (t, 4 H, *J* = 4.3 Hz), 2.88 (t, 2 H, *J* = 5.5 Hz), 2.62 (bt, 4 H, *J* = 4.3 Hz); ^{13}C NMR δ 160.7, 151.0, 133.3, 131.9, 128.9, 126.8, 125.2, 123.7, 66.9 (2C), 64.7, 57.3, 54.1 (2C); MS (EI) *m/z* (relative intensity) 275 (M^+, <1), 232 (1.5), 189 (2), 100 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{16}N_3O_3$ (M-H) 274.1192, found 274.1192.

2-(2-Morpholin-4-yl-ethyl)-2,3-dihydro-phthalazine-1,4-dione (114). To a solution of NaOH (4.0 g, 0.10 mol) in hydrazine-hydrate (20 mL) was added 4-(2-chloroethyl)-morpholine•HCl salt (1.86 g, 10.0 mmol) at room temperature. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, diluted with H_2O (30 mL) and extracted with chloroform (50 mL×2). The organic layer was dried (MgSO4) and concentrated under reduced pressure to give crude **113** (1.02 g, ~70%) as a yellow oil. A solution of crude **113** (1.02 g, 7.02 mmol) and phthalic anhydride (1.04 g, 7.02 mmol) in xylenes (50 mL) was heated at reflux for 14 h, cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:15) to give crude product (1.49 g, 77%). The crude product was recrystallized from EtOAc to give pure **114** (640 mg, 33%) as a dark white solid: Mp. 167-169 °C (EtOAc); IR (neat) 3468, 2966, 2863, 1614, 1583 cm^{-1}; ^1H NMR δ 11.7 (bs, 1 H), 8.20-8.14 (m, 1 H), 7.87-7.81 m, 3 H), 4.07 (t, 2 H, *J* = 6.8 Hz), 3.55-3.40 (m, 4 H), 2.64 (t, 2 H, *J* = 6.8 Hz), 2.50-2.35 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 159.1, 151.6, 131.9, 130.9, 128.6, 126.4, 124.9, 123.5, 65.4 (2C), 56.5, 52.7 (2C), 43.5; MS (EI) *m/z* (relative intensity) 275 (M^+, 2), 257 (2), 189 (3), 175 (3), 162 (3), 133 (55), 100 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{17}N_3O_3$ 275.1270, found 275.1272.

4-Methoxy-2-(2-morpholin-4-yl-ethyl)-2*H*-phthalazin-1-one (115). A solution of **114** (138 mg, 0.500 mmol) in acetone (5 mL) was treated with K_2CO_3 (69 mg, 0.50 mmol) and dimethyl sulfate (47 μL, 0.50 mmol) at room temperature. The reaction mixture was stirred for 14 h at room temperature, diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 1:50 → 1:5) to give **115** (50 mg, 34%) as a white solid: Mp. 73-75 °C (CH_2Cl_2); IR (neat) 2946, 2849, 2815, 1651, 1590, 1340, 1115 cm^{-1}; ^1H NMR δ□ □ □ □ □m, 1 H), 7.97-7.92 (m, 1 H), 7.87-7.72 (m, 2 H), 4.28 (t, 2 H, *J* = 6.9 Hz), 3.97 (s, 3 H), 3.80-3.60 (m, 4 H), 2.82 (t, 2 H, *J* = 6.9 Hz), 2.65-2.50 (m, 4 H); ^{13}C NMR δ 158.7, 150.3, 132.7, 131.9, 129.0, 127.2, 124.7, 123.4, 67.1 (2C), 56.4, 54.2, 53.7 (2C), 47.4; MS (EI) *m/z* (relative intensity) 289 (M^+, 1), 271 (4), 203 (5), 177 (7), 113 (70), 100 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{19}N_3O_3$ 289.1426, found 289.1425.

7-(2-Morpholin-4-yl-ethyl)-6,7-dihydro-pyrido[2,3-*d*]pyridazine-5,8-dione (116). A solution of (2-morpholin-4-yl-ethyl)-hydrazine (0.75 g, 5.0 mmol) and pyridine dicarboxylic anhydride (1.09 g, 7.50 mmol) in toluene (50 mL) was heated at reflux for 16 h, cooled to room temperature and concentrated under reduced pressure. The crude residue was washed with Et_2O and recrystallized from EtOAc to give a ~5:1 mixture of regioisomers (570 mg, 41%). A sample of pure major regioisomer **116** was obtained by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 1:15 → 1:5): Mp. 192-195 °C (CH_2Cl_2); IR (neat) 3375, 3006, 2950, 2878, 1634, 1567 cm^{-1}; ^1H NMR (MeOH-d_4) δ□ □ □ (b□, 1 H, *J* = 1.6 Hz), 7.65 (d, 1 H, *J* = 7.8 Hz), 7.35 (dd, 1 H, *J* = 7.8, 1.6 Hz), 4.16 (t, 2 H, *J* = 5.2 Hz), 3.80-3.60 (m, 4 H), 3.12 (bt, 2 H, *J* = 5.2 Hz), 3.00-2.80 (m, 4 H); ^{13}C NMR (MeOH-d_4) δ 159.4, 155.1, 154.4, 144.9, 134.8, 128.6, 124.5, 66.1 (2C), 57.1, 53.9

(2C), 46.1; MS (EI) *m/z* (relative intensity) 276 (M^+, 3), 190 (2); HRMS (EI) *m/z* calcd for $C_{13}H_{16}N_4O_3$ 276.1222, found 276.1222.

Caulibugulone A. To a solution of 5-hydroxy-isoquinoline (90%, 0.80 g, 5.0 mmol) in EtOH/H_2O (20 mL/2 mL) was added PIFA (4.28 g, 12.0 mmol) at room temperature. The reaction mixture was stirred for 1 h and treated with $CeCl_3$ (2.4 g, 10 mmol) and methylamine (2.0 M in MeOH, 20 mL, 40 mmol) at room temperature. The reaction mixture was stirred for 20 h and concentrated under reduced pressure. The crude residue was diluted with EtOAc (250 mL) and washed with brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give a mixture of caulibugulone A and its regioisomer (0.48 g, 51%, ~4:1 ratio by ^1H NMR). Further separation by chromatography on SiO_2 (CH_2Cl_2/MeOH, 200:1 → 100:1) gave **caulibugulone A** as a red solid: Mp. 228-230 °C (Dec.); IR (neat) 3263, 1685, 1598, 1501, 1419, 1173, 1075, 830 cm^{-1}; ^1H NMR ($CDCl_3$/CD_3OD, 1:1) δ 9.14 (s, 1 H), 8.92 (d, 1 H, *J* = 4.5 Hz), 7.91 (d, 1 H, *J* = 4.5 Hz), 5.76 (s, 1 H), 2.92 (s, 3 H); ^{13}C NMR ($CDCl_3$/CD_3OD, 1:1) δ 181.4 (2C), 156.1, 150.7, 147.8, 140.7, 125.6, 120.0, 100.6, 29.3; MS (EI) *m/z* (relative intensity) 188 (M^+, 100), 173 (30), 159 (14), 131 (20), 105 (21), 82 (64); HRMS (EI) *m/z* calcd for $C_{10}H_8N_2O_2$ 188.0586, found 188.0583.

Caulibugulone B. To a solution of caulibugulone A (30 mg, 0.16 mmol) in dioxane (4 mL) was added NBS (29 mg, 0.16 mmol) in dioxane (1 mL) at room temperature. The reaction mixture was stirred for 4 h and concentrated under reduced pressure. The crude residue was directly purified by chromatography on SiO_2 (CH_2Cl_2 → CH_2Cl_2/MeOH, 50:1) to give **caulibugulone B** (32 mg, 74%) as a dark red solid: Mp. 182-184 °C (Dec.); IR (neat) 3278, 1690, 1583, 1542, 1419, 1291 cm^{-1}; ^1H NMR (pyridine-d_5) δ 9.36 (s, 1 H), 9.00 (d, 1 H. *J* = 5.0

Hz), 8.20 (bs, 1 H, -N*H*), 7.98 (d, 1 H, *J* = 4.9 Hz), 3.39 (d, 3 H, *J* = 5.7 Hz); ^{13}C NMR (pyridine-d_5) δ 180.1 (2C), 156.1, 148.4 (2C), 138.2, 119.2, 33.0 (2 carbons are missing in solvent peaks); MS (EI) *m/z* (relative intensity) 266 (M^+, 100), 187 (49), 160 (39), 82 (23); HRMS (EI) *m/z* calcd for $C_{10}H_7BrN_2O_2$ 265.9691, found 265.9695.

Caulibugulone C. To a solution of caulibugulone A (9.4 mg, 0.050 mmol) in MeOH (5 mL) was added NCS (6.7 mg, 0.050 mmol) at room temperature. The reaction mixture was stirred for 20 h and concentrated under reduced pressure. The crude residue was directly purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **caulibugulone C** (9.1 mg, 82%) as a dark red solid: Mp. 219-221 °C (Dec.); IR (neat) 3274, 1689, 1588, 1563, 1417, 1316 cm^{-1}; ^{1}H NMR (pyridine-d_5) δ 9.35 (s, 1 H), 9.01 (d, 1 H, *J* = 5.0 Hz), 8.35 (bs, 1 H, -N*H*), 7.98 (d, 1 H, *J* = 5.0 Hz), 3.38 (d, 3 H, *J* = 5.6 Hz); ^{13}C NMR (pyridine-d_5) δ 180.5 (2C), 156.3, 148.4 (2C), 146.6, 138.6, 119.2, 32.5 (1 carbon is missing in solvent peaks); MS (EI) *m/z* (relative intensity) 222 (M^+, 100), 187 (51), 160 (35), 131 (25); HRMS (EI) *m/z* calcd for $C_{10}H_7ClN_2O_2$ 222.0196, found 222. 0194.

Caulibugulone D. To a solution of 5-hydroxy-isoquinoline (90%, 200 mg, 1.25 mmol) in EtOH/H_2O (10 mL/1 mL) was added PIFA (1.07 g, 2.50 mmol) at room temperature. The reaction mixture was stirred for 2 h and treated with $CeCl_3{\cdot}7H_2O$ (930 mg, 2.50 mmol) and ethaolamine (0.60 mL, 10 mmol) at room temperature. The reaction mixture was stirred for 20 h, diluted with EtOAc (100 mL) and washed with brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (EtOAc → CH_2Cl_2/MeOH, 50:1→ 10:1) to give a mixture of caulibugulone D and its regioisomer (68 mg, 25%, ~7:1 ratio by ^{1}H NMR). Further separation by chromatography on SiO_2 (CH_2Cl_2/MeOH, 100: 1) gave **caulibugulone D** as a dark orange solid:

Mp. 189-191 °C (Dec.); IR (neat) 3335, 3168, 2921, 2846, 1680, 1633, 1593, 1562, 1301, 1059 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$ = 1: 1) δ 9.17 (s, 1 H), 8.94 (d, 1 H. *J* = 4.2 Hz), 7.91 (d, 1 H, *J* = 5.0 Hz), 5.86 (s, 1 H), 3.78 (t, 2 H, *J* = 5.4 Hz), 3.35 (t, 2 H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$, 1:1) δ 181.0, 180.5, 155.4, 149.2, 147.2, 140.0, 125.0, 119.3, 100.5, 59.0, 44.7; MS (EI) *m/z* (relative intensity) 218 (M^+, 22), 200 (23), 187 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{10}N_2O_3$ 218.0691, found 218.0691.

Caulibugulone E. To a solution of caulibugulone A (230 mg, 1.22 mmol) in CH_2Cl_2 (25 mL) was added $Ti(O\text{-}iPr)_4$ (1.7 mL, 6.1 mmol) and ammonia (7N in MeOH, 3.6 mL, 25 mmol) at room temperature. The reaction mixture was stirred for 7 d and directly purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 50:1 → 10:1) to give caulibugulone A (34 mg, 15%) and **caulibugulone E** (170 mg, 74%) as an orange solid: Mp. 228-230 °C (Dec.); IR (neat) 3351, 3210, 1618, 1571, 1545, 1519, 1413, 1365, 1280, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.1 (bs, 1 H, =N*H*) 9.06 (s, 1 H), 8.89 (d, 1 H. *J* = 4.9 Hz), 8.00 (d, 1 H, *J* = 4.9 Hz), 6.80 (bs, 1 H, -NH), 5.78 (s, 1 H), 3.00 (d, 3 H, *J* = 5.3 Hz); ^{13}C NMR (DMSO-d_6) δ 179.5, 158.3, 153.5, 153.2, 147.1, 137.3, 123.8, 118,6, 98.4, 29.5; MS (EI) *m/z* (relative intensity) 187 (M^+, 100), 158 (29), 130 (57), 103 (28), 76 (29); HRMS (EI) *m/z* calcd for $C_{10}H_9N_2O$ 187.0746, found 187.0744.

2. Fragmentation Studies toward the Total Synthesis of Parvistemonine

2.1. Introduction

2.1.1. Parvistemonine & Other Stemona Alkaloids

The *Stemona* alkaloids are a class of structurally relatively complex polycyclic alkaloids (Figure 26). They have attracted considerable attention from organic chemists since the structural elucidation of tuberostemonine ca. 40 years ago.[75] The chemical investigation of Stemonaceae plants was initially motivated by their use in the Chinese and Japanese folk medicine as insecticides and drugs for the treatment of respiratory diseases such as bronchitis, pertussis, and tuberculosis, as well as antihelmintics.[75] To date, the structures of ca. 50 *Stemona and Croomia* alkaloids have been elucidated by a combination of crystallographic, spectroscopic and degradative techniques. In spite of their highly attractive spectrum of biological effects, synthetic studies towards the Stemona alkaloids are still quite limited.[75] So far syntheses of stenine,[76] croomine,[77] isostemofoline,[78] stemoamide,[79] stemospironine,[80] stemonamide,[81] isostemonamide,[81] stemonine,[82] tuberostemonine,[83] didehydrostemofoline[84] and isodehydrostemofoline[84] have been reported. Thus, a concise and general entry into this structurally challenging and pharmaceutically attractive class of natural products appears highly desirable.

Parvistemonine was isolated from the roots of Stemona parviflora collected in Heinan, China.[85] It has probably the most unique and interesting functional group array of the *Stemona* alkaloids. A γ-butyrolactone and a fused furanofuranone are attached to the central azepinopyrrolidine. In addition to a total of 10 chiral centers, ring systems are connected via asymmetric carbons. Parvistemonine represents therefore one of the most challenging and unusual synthetic targets in the *Stemona* family.

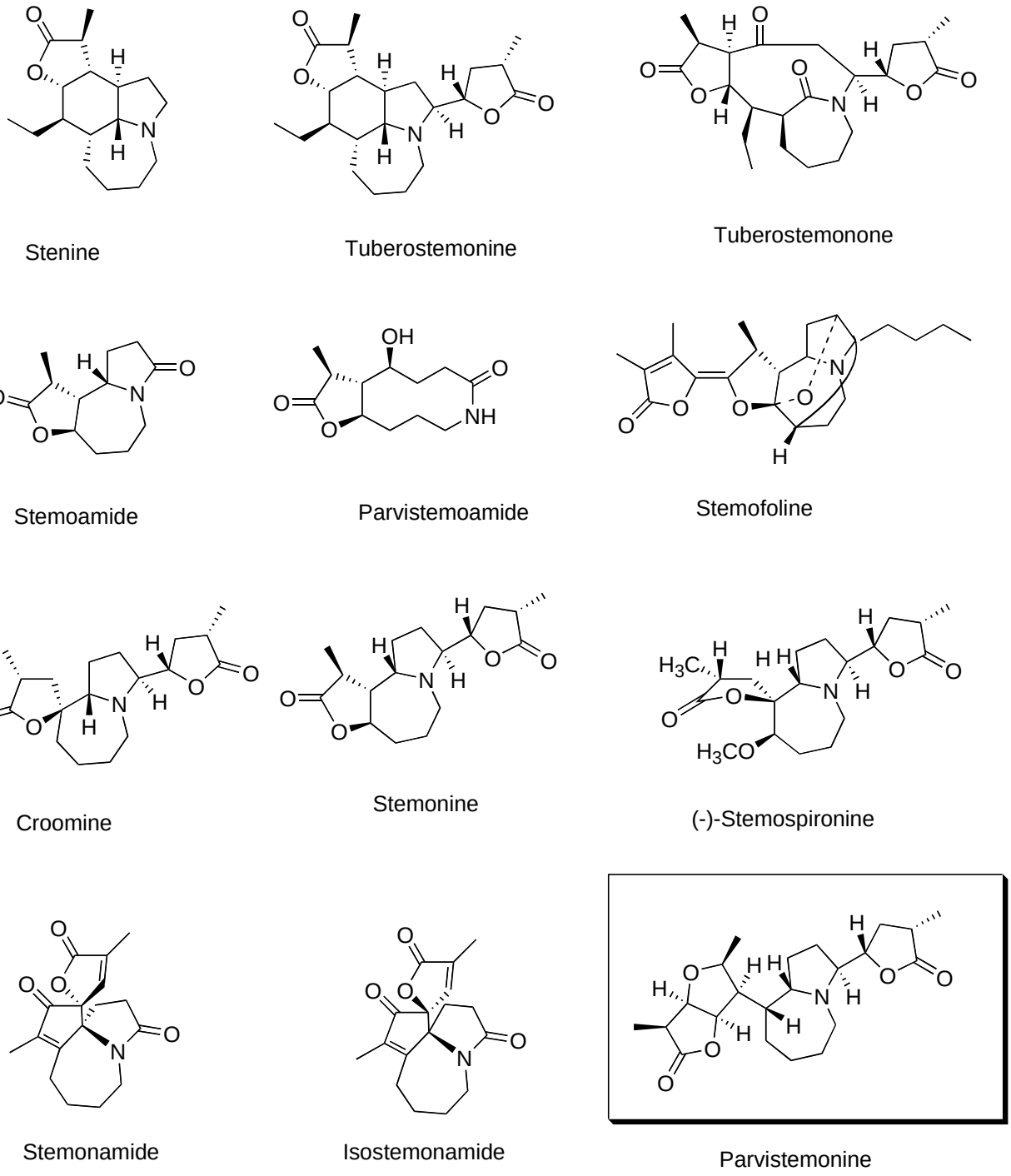
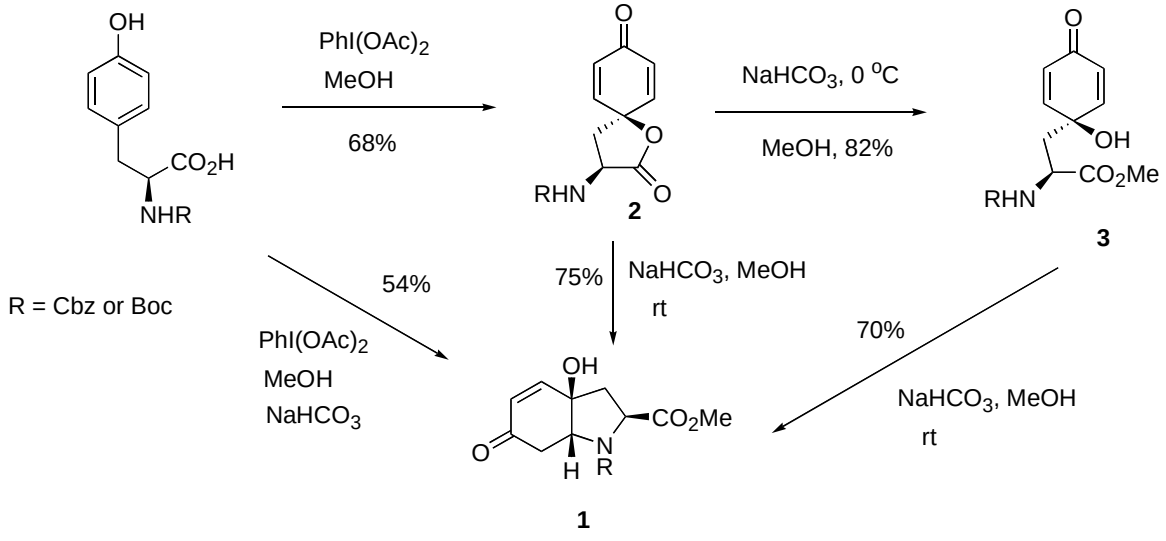


Figure 26. Stemona alkaloids and parvistemonine

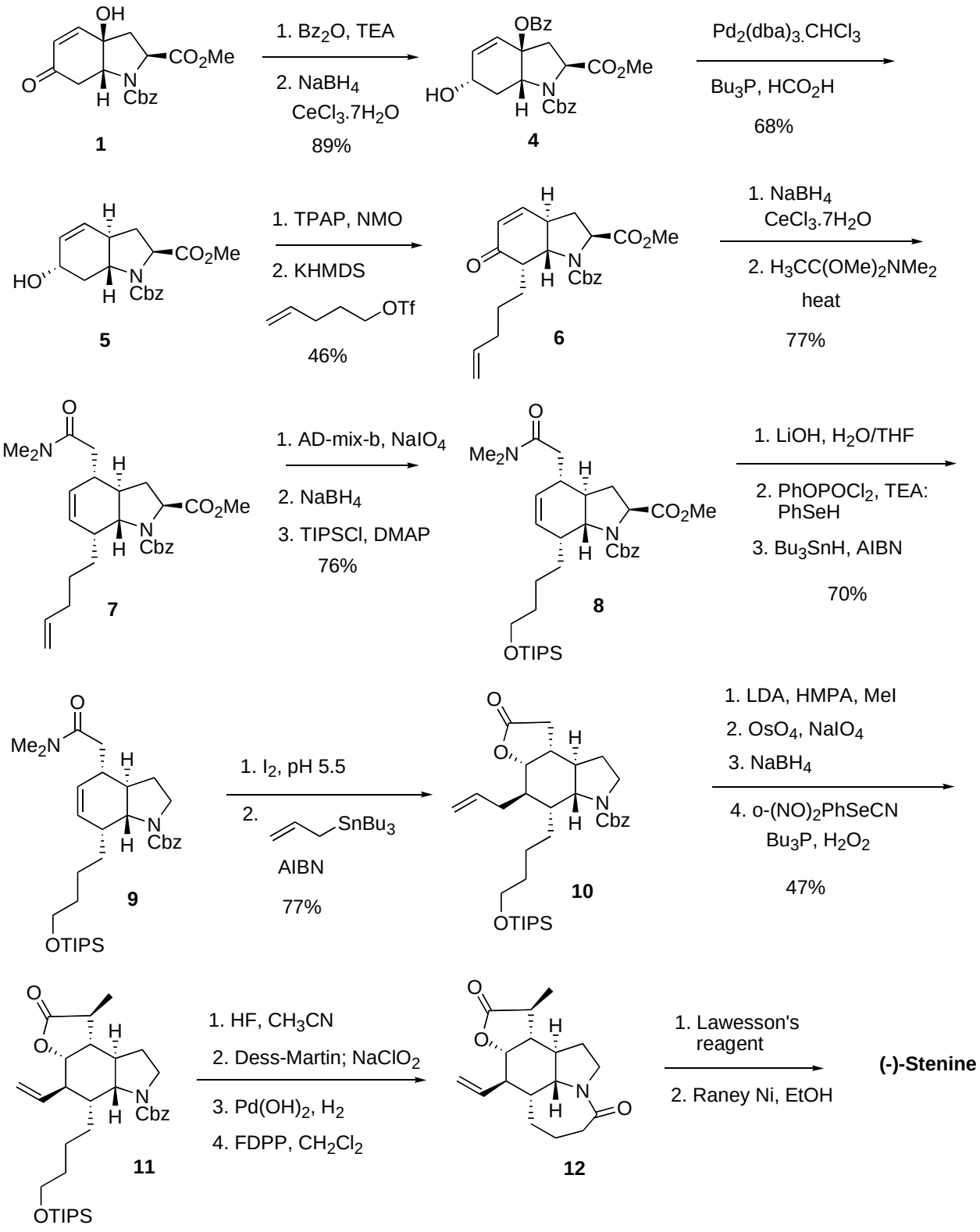
2.1.2. Wipf Group Research on Stemona Alkaloids

The Wipf group has had a long-standing interest in the synthesis of *Stemona alkaloids* since the report of the synthesis of the novel hydroindole **1**.[86] Hydroindole **1** was synthesized in a highly stereoselective manner from very readily available tyrosine (Scheme 31). After some optimization of the oxidizing reagent, N-protected tyrosine was cyclized to give spirolactone **2** by treatment with a slight excess of iodobenzene diacetate. Then, methanolysis of lactone **2** at ambient temperature in the presence of $NaHCO_3$ cleanly lead to the hydroindole **1** as the major diastereomer. In contrast, methanolysis of lactone **2** at 0 °C provided exclusively dienone **3**, which was converted to hydroindole **1** in MeOH in the presence of $NaHCO_3$. Hydroindole **1** could also be obtained directly from N-protected tyrosine by oxidation in the presence of sodium bicarbonate.



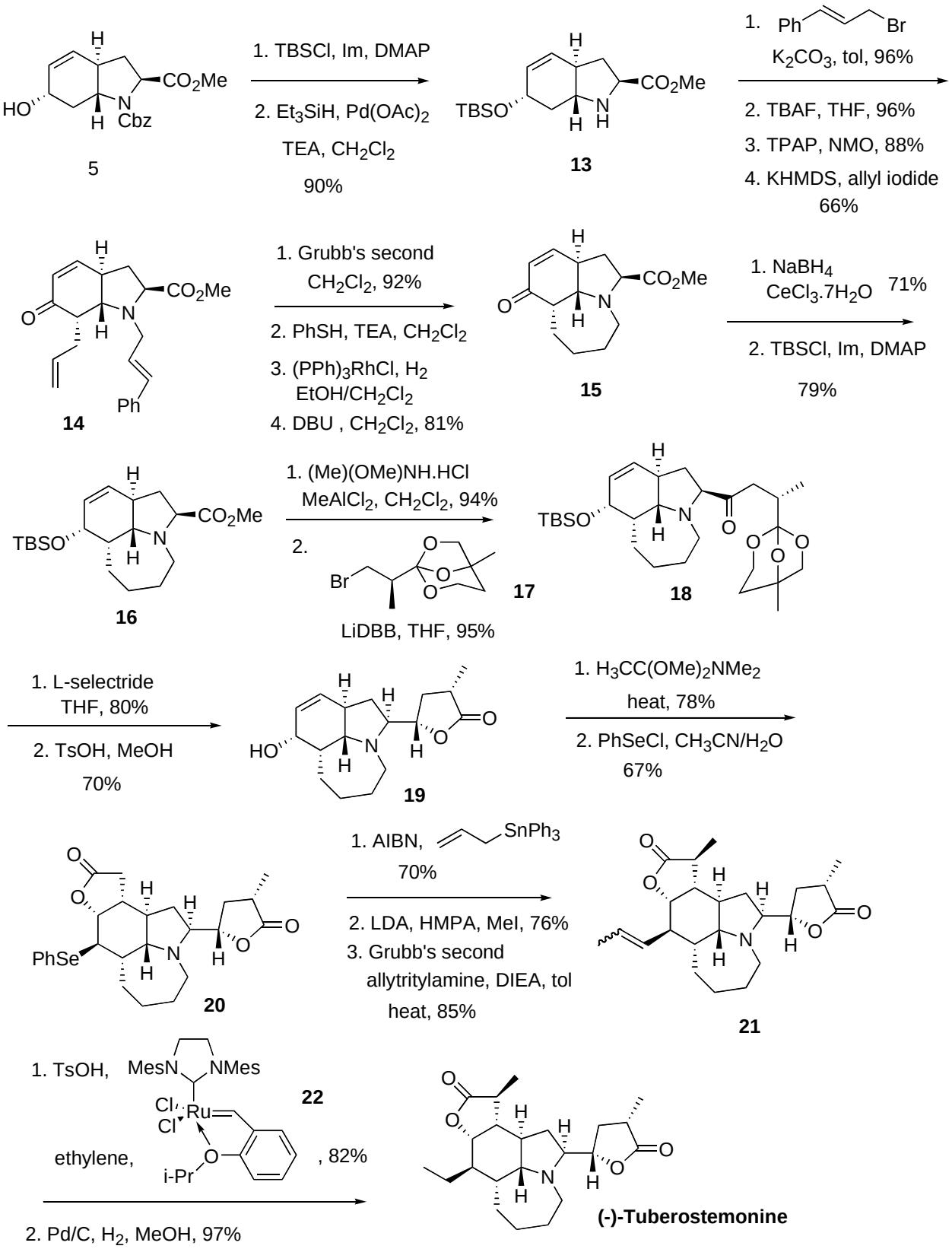
Scheme 31. Synthesis of hydroindole 1[12]

Taking advantage of the novel preparation of hydroindole **1**, Wipf, Kim and Goldstein reported the first asymmetric total synthesis of (–)-stenine in 1995 (Scheme 32).[76(b)] This synthesis began with the benzoylation and Luche reduction of hydroindole **1** to give equatorial alcohol **4** in 89%. Reduction of the π-allylpalladium complex derived from allylic benzoate **4** at the more hindered tertiary carbon was accomplished in 68% yield by the use of catalytic *tris*(dibenzylideneacetone)-dipalladium (0) chloroform complex, triethyl phosphine and triethylammonium formate, after considerable optimization of the reaction conditions. Oxidation of allylic alcohol **5** with TPAP regenerated the enone, which was deprotonated with KHMDS and reacted with triflate to give enone **6** in 46% yield. Luche reduction of enone **6** was followed by Eschenmoser-Claisen rearrangement to provide **7** in 77% yield. Functional group manipulations at the terminal alkene of **7** and pyrrolidine ring of **8** resulted in **9**. Iodolactonization of **9** under pH 5.5 conditions, followed by Keck allylation gave lactone **10** in 77% yield. Methylation of lactone **10** occurred selectively in 87% yield from the sterically more accessible face, and subsequent conversion of the allyl to a vinyl group by a Johnson-Lemieux oxidation, reduction and Grieco-elimination sequence provided tricyclic **11**. Closure of the azepine, the last remaining ring of the tetracyclic stenine, was initiated by desilylation of **11** and oxidation of the primary alcohol to the acid by sequential treatment with Dess-Martin periodinane and sodium chlorite. Without purification, the resulting acid was directly hydrogenated and cyclized with FDDP to give amide **12**. Conversion of the amide **12** to the thioamide with Lawesson's reagent and desulfirization with Raney nickel finally provided (–)-stenine. Through this elegant total synthesis, they not only realized the first aymmetric route to (–)-stenine, but also showed the potential for pyrrolidine alkaloid synthesis offered by the ready availability of hydroindole **1**.



Scheme 32. Total synthesis of (–)-stenine[2(c)]

Wipf, Rector and Takahashi reported the first asymmetric total synthesis of (–)-tuberostemonine in 2002, utilizing hydroindole **1** as a starting material (Scheme 33).[83] The synthesis began with an improvement of the π-allylpalladium reaction for allyl alcohol **5**. Silylation of the secondary alcohol, followed by carbamate deprotection, gave amine **13** in 90% yield. Cinnamylation of the amine **13**, desilylation, TPAP oxidation and a stereoselective allylic alkylation sequence provided enone **14**, which was converted to the tricyclic compound by a key ring closing metathesis reaction with Grubb's second-generation catalyst. The resulting double bond in tricyclic compound was removed via a high-yielding, three-step sequence to give tricyclic **15** after transient protection of the enone double bond by conjugate addition-β-elimination of thiophenol. Ester **16** was obtained as a single diastereomer after Luche reduction and TBDMS protection. In preparation for the introduction of the right-side butyrolactone, addition of the Weinreb amide, derived from ester **12**, to a solution of the lithium anion formed from bromo ortho ester **17** and LiDBB provided ketone **18** in excellent yield. The carbonyl group was subsequently reduced to give the alcohol in a ~7:1 diasteremeric ratio. Exposure of this mixture of alcohol to TsOH in methanol removed both ortho-ester and silyl enol ether protecting groups and also catalyzed cyclization, affording the desired lactone **19**. Claisen rearrangement, followed by selenolactonization provided **20**, which was converted to **21** by Keck-allylation, α-methylation and isomerization. Cross-metathesis of **21** in the presence of ethane and Ru catalyst **22** and TsOH, followed by a catalytic hydrogenation over Pd on carbon completed the first total synthesis of (–)-tuberostemonine.

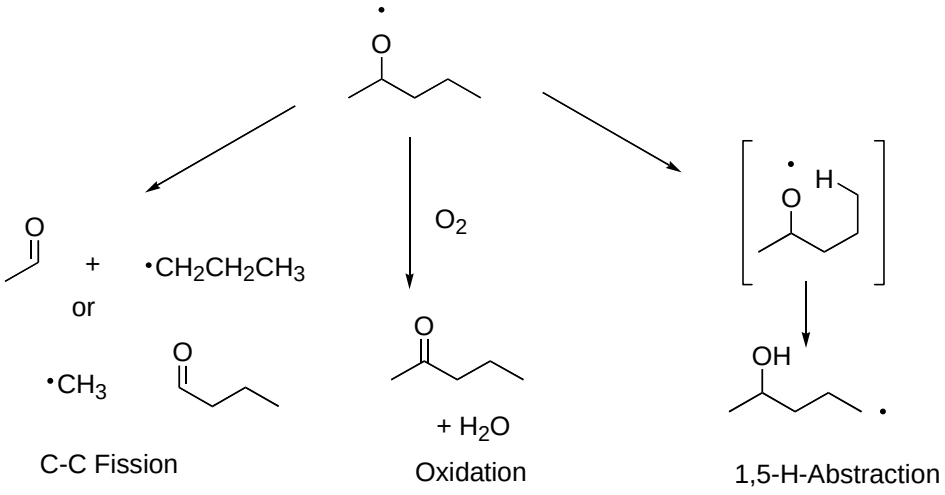


Scheme 33. Total synthesis of (–)-tuberostemonine[9]

2.1.3. Alkoxy Radical Fragmentations

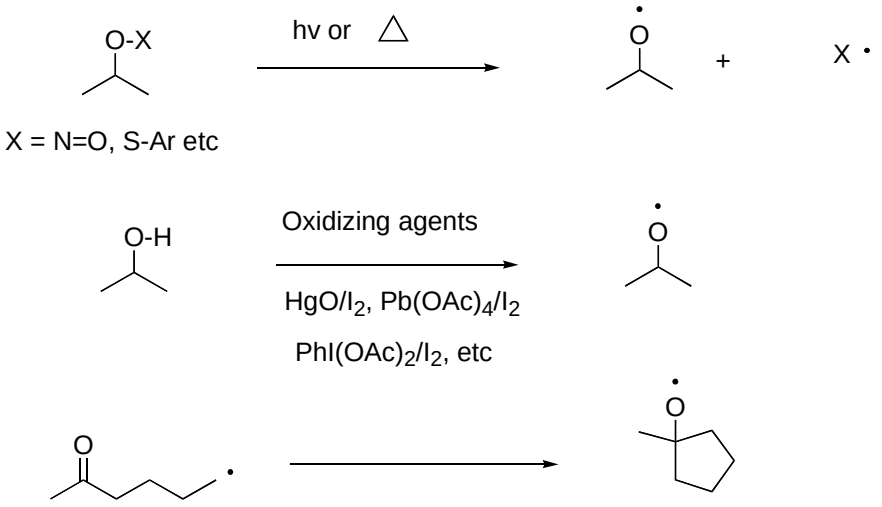
Free radical reactions have become increasingly important in organic synthesis in the last two decades.[87] Especially carbon-centered radicals are now well studied and widely used.[87] In contrast, use of oxygen-centered radicals in organic synthesis is still somewhat limited because of a relative neglect of this field in comparison with carbon-centered radicals.[88]

Alkoxy radicals can react with oxygen, isomerize, or undergo C-C fission as illustrated in Scheme 1.[88] In general, alkoxy radicals will cleave to give a ketone (or aldehyde) and the most stable possible alkyl radical.[88]



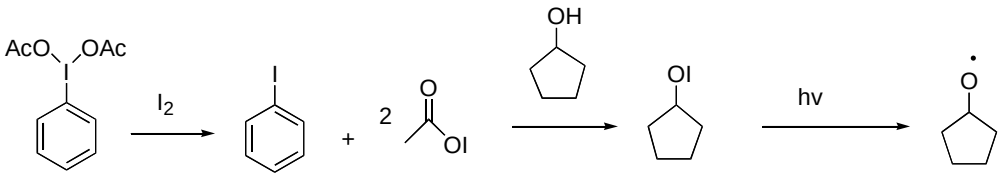
Scheme 34. Reactions of alkoxy radicals[88]

Alkoxy radicals have been generated by various methods (Scheme 35).[88,89] They can be generated by homolytic cleavage of O-X bonds under photolytic or thermal conditions.[89] A famous example of this process is the Barton reaction.[90] Alkoxy radicals can also be generated by oxidative cleavage of O-H bonds.[88] Another method for generating alkoxy radicals is radical transfer to ketone (or aldehyde) functional groups from carbon-centered radicals.[91]



Scheme 35. Methods for generation of alkoxy radicals

Suárez and co-workers introduced photoactivated iodobenzene diacetate /iodine (Suárez reagent), a reagent that reliably converts hydroxy-containing substrates (alcohols, carboxylic acids, carbohydrates, lactols) into products derived from intermediate oxygen-centered free radicals.[92] Unlike many other reagent combinations,[88,89] conversions using this reagent do not, so far, appear to be complicated by consumption of first-formed products. These reactions, for alcohols, are assumed to involve intermediate hypohalites (Scheme 36).[93]



Scheme 36. Generation of alkoxy radicals by the Suárez reagent[92]

The oxidative cleavage of alkoxy radicals attached to fused bicyclic systems may result in the formation of medium-sized rings. For example, the oxidative fragmentation of hydroindole **1** may lead to either the formation of a 9-membered ring via cleavage of the C3a-C7a bond or the formation of a pyrrolidine ring via cleavage of the C3a-C4 bond (Figure 27). We envisioned that the formation of a 9-membered ring from hydroindole **1** could be utilized in the total synthesis of tuberostemonone,[94] whereas the formation of pyrrolidine ring could be utilized in the total synthesis of parvistemonine.[95]

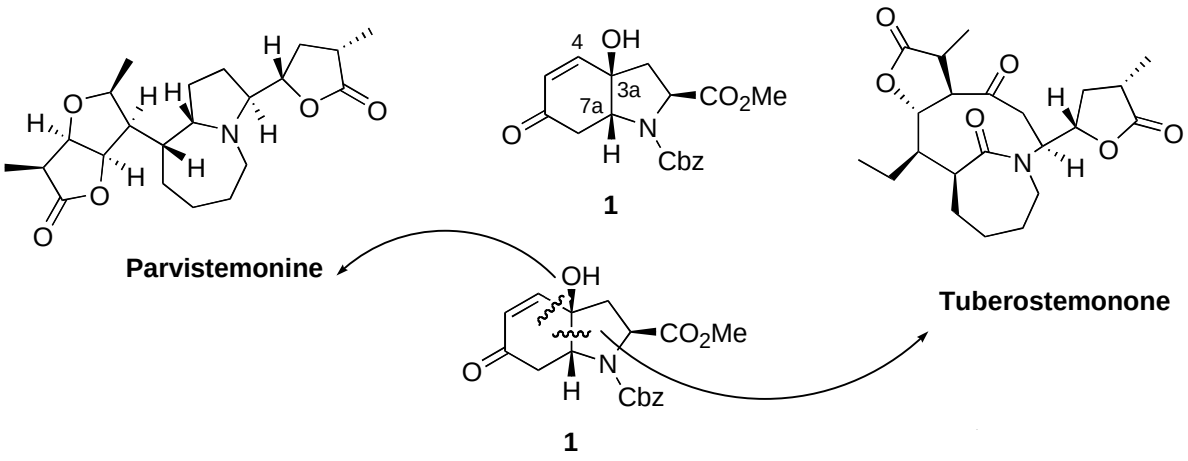
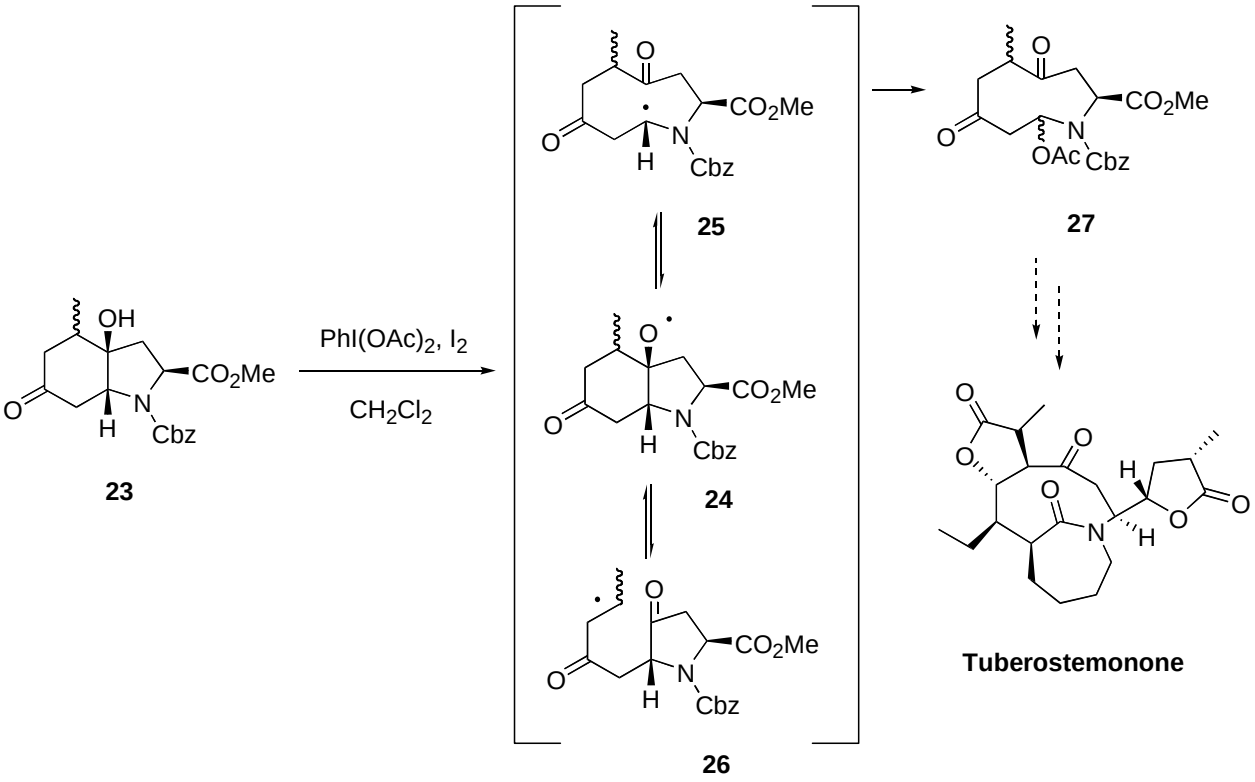


Figure 27. Oxidative cleavage of hydroindole 1

In this context, new methodology for the ring expansion of 4-hydroxyindoles such as **23** to azanonanes was recently reported by our group in an effort toward the total synthesis of tuberostemonone (Scheme 37).[94] We reported that treatment of **23** with iodine and iodobenzene diacetate (Suárez conditions) resulted in the formation of azonane **27** presumably via intermediate **25**, where the radical is stabilized by the adjacent nitrogen atom.

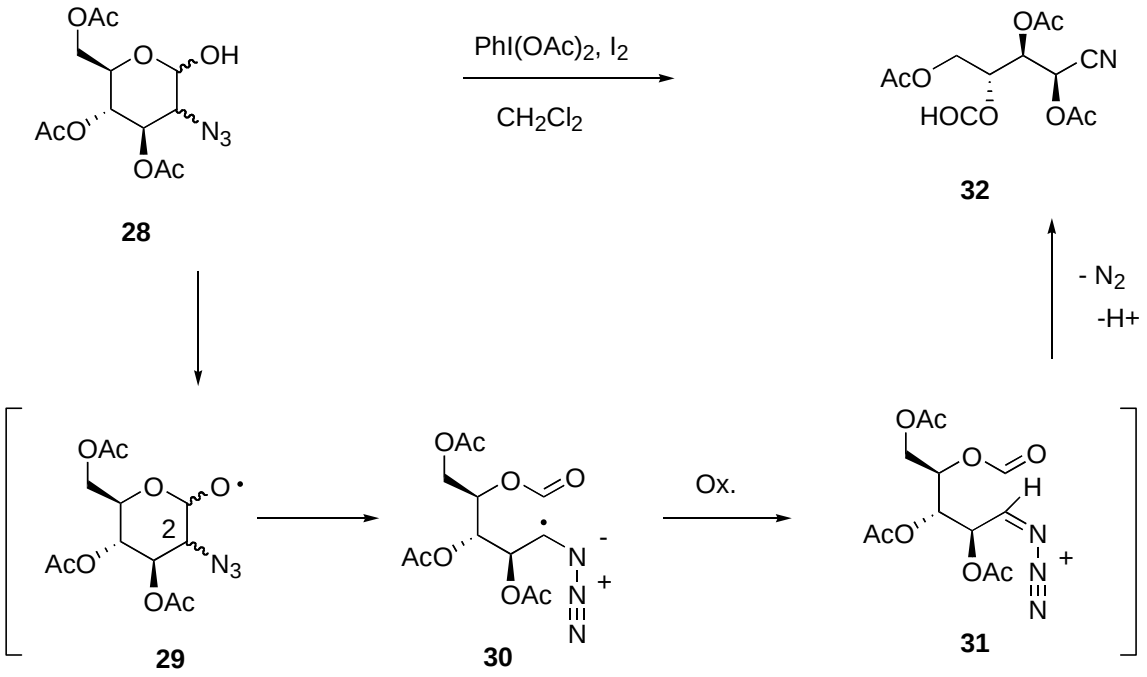


Scheme 37. The ring expansion of 4-hydroxyhydroindole **23**

We need to direct the oxidative cleavage to afford products arising from C3-C4 bond fragmentation of 4-hydroxyindole **1** for a synthesis of parvistemonine (Figure 27). However, such a cleavage in a hydroindole system proved to be difficult without a proper directing group because of the radical stabilization effect of the nitrogen atom in 4-hydroxyindole **1**, which facilitates cleavage of the C3a-C7a bond. Thus, we tried to develop a strategy for specific C3-C4 bond fragmentation of 4-hydroxyindole **1,** overcoming the radical stabilization effect of the nitrogen atom.

The Suárez group had reported a new protocol for the synthesis of nitriles by β-fragmentation of alkoxy radicals derived from β-hydroxy azides in the presence of (diacetoxyiodo)benzene (DIB) and iodine.[96] In particular, this reagent was applied to the

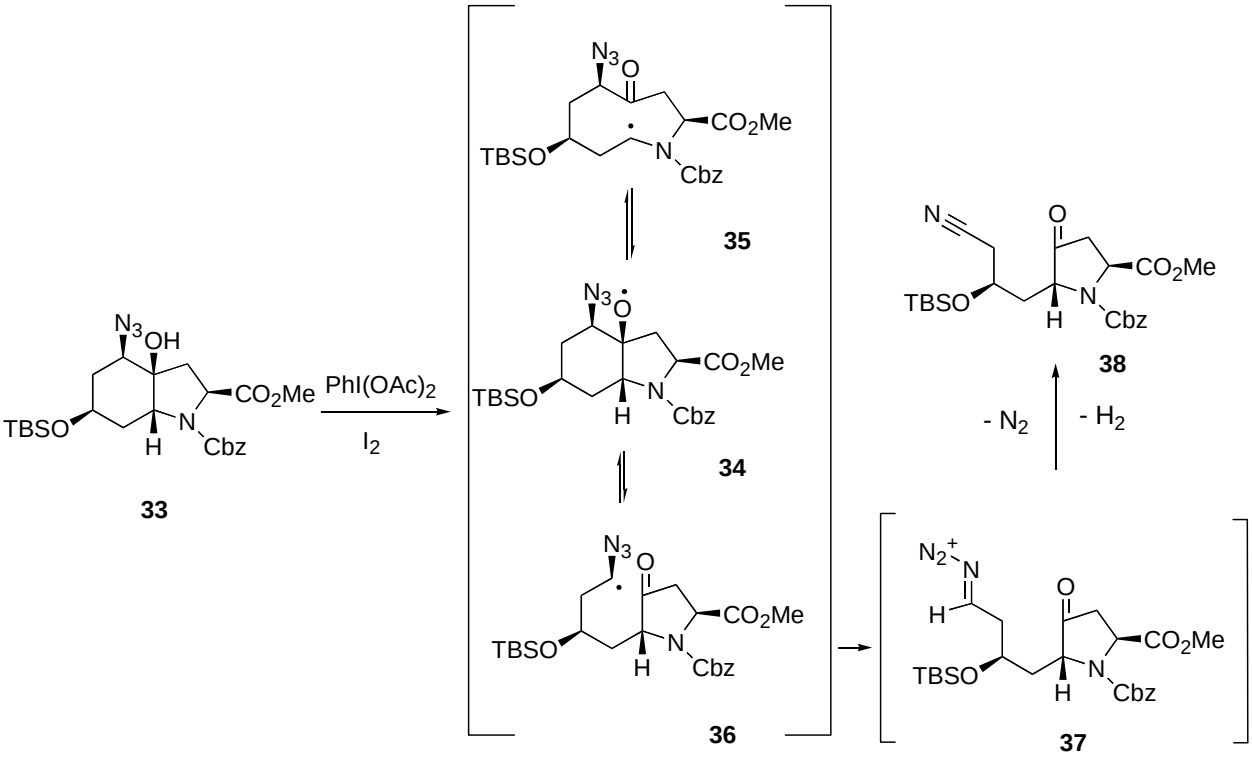
synthesis of chiral nitriles by the β-fragmentation of anomeric alkoxy radicals from 2-azido-2-deoxysugars as shown in Scheme 38. For example, azidosugar **28** was treated with Suarez reagent in dichloromethane solution to provide nitrile **32**. The proposed mechanism deserves some more comment. The C(2) radical initially formed must be oxidized by the reagent to a carbocation in order for the nitrile group to be formed after loss of molecular nitrogen.[97]



Scheme 38. Radical cleavage of a β-hydroxy azide

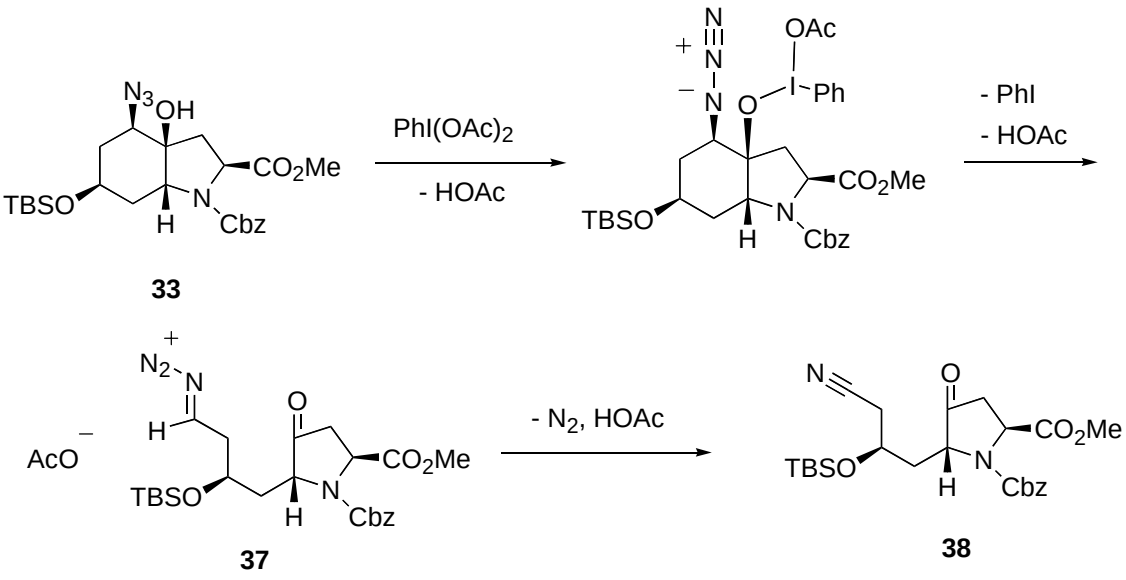
Based on this result, we hypothesized that the C(3a)-C(4) cleavage of the hydroindole framework would be feasible via an azido fragmentation reaction. Treatment of hydroindole **33** with $PhI(OAc)_2/I_2$ led indeed to oxidative fragmentation of the β-hydroxy azide moiety and resulted in the exclusive formation of keto nitrile **38** via radical cleavage of the lateral C-C bond (Scheme 39).[95] The formation of **38** may be explained by an oxidative fragmentation as proposed by the Suárez group. Although the transannular cleavage intermediate **35** and the lateral C-C

bond cleavage intermediate **36** may both be accessible from the initial alkoxy radical **34**, rapid and irreversible oxidation of **36** to **37** followed by elimination of N_2 provided ketonitrile **38**.



Scheme 39. Radical cleavage of a β-hydroxy azide[21]

However, ionic mechanisms cannot be excluded as alternatives and Scheme 40 shows one possible example for an ionic mechanism.

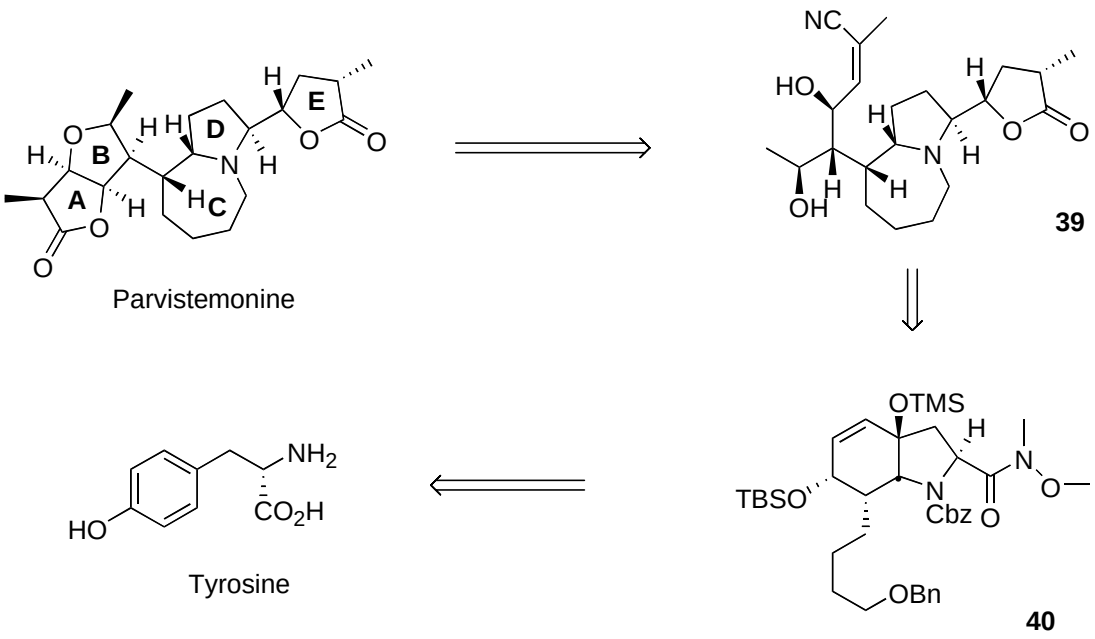


Scheme 40. An alternative ionic mechanism

2.2. Strategy and Goals

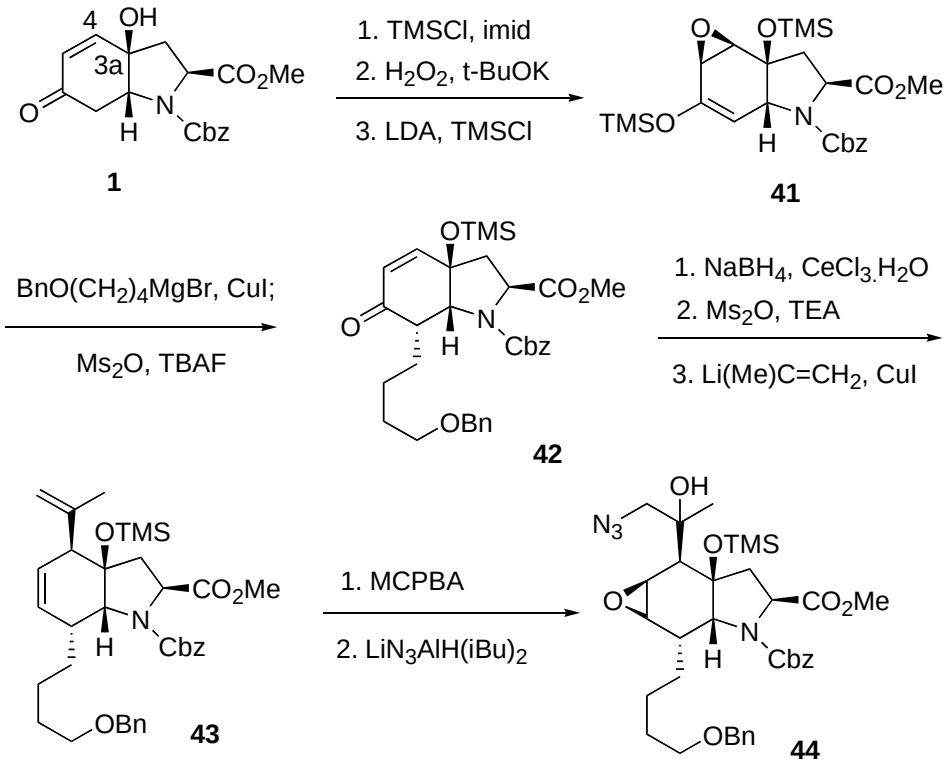
2.2.1. Initial Synthetic Scheme for Parvistemonine

Scheme 41 outlines briefly our retrosynthetic approach toward parvistemonine. In this scheme, the key reaction is the application of the azido alcohol fragmentation that we have recently reported[95] and which is discussed in the previous chapter. Starting from L-tyrosine via bicyclic **40,** we will obtain the fragmentation product **39**. Intramolecular Michael addition to the α,β-unsaturated nitrile function of **39**, followed by acid-mediated cyclization of the remaining secondary alcohol into the nitrile group and hydrolysis of the resulting imidate should furnish the novel **A/B**-ring system of the target molecule. The natural configuration of the **A/B**-ring system appears to be thermodynamically favored based upon our modeling studies.[98] Therefore, two of the five stereocenters in the **A/B**-ring will rely on equilibrating conditions.



Scheme 41. Retrosynthetic analysis of parvistemonine

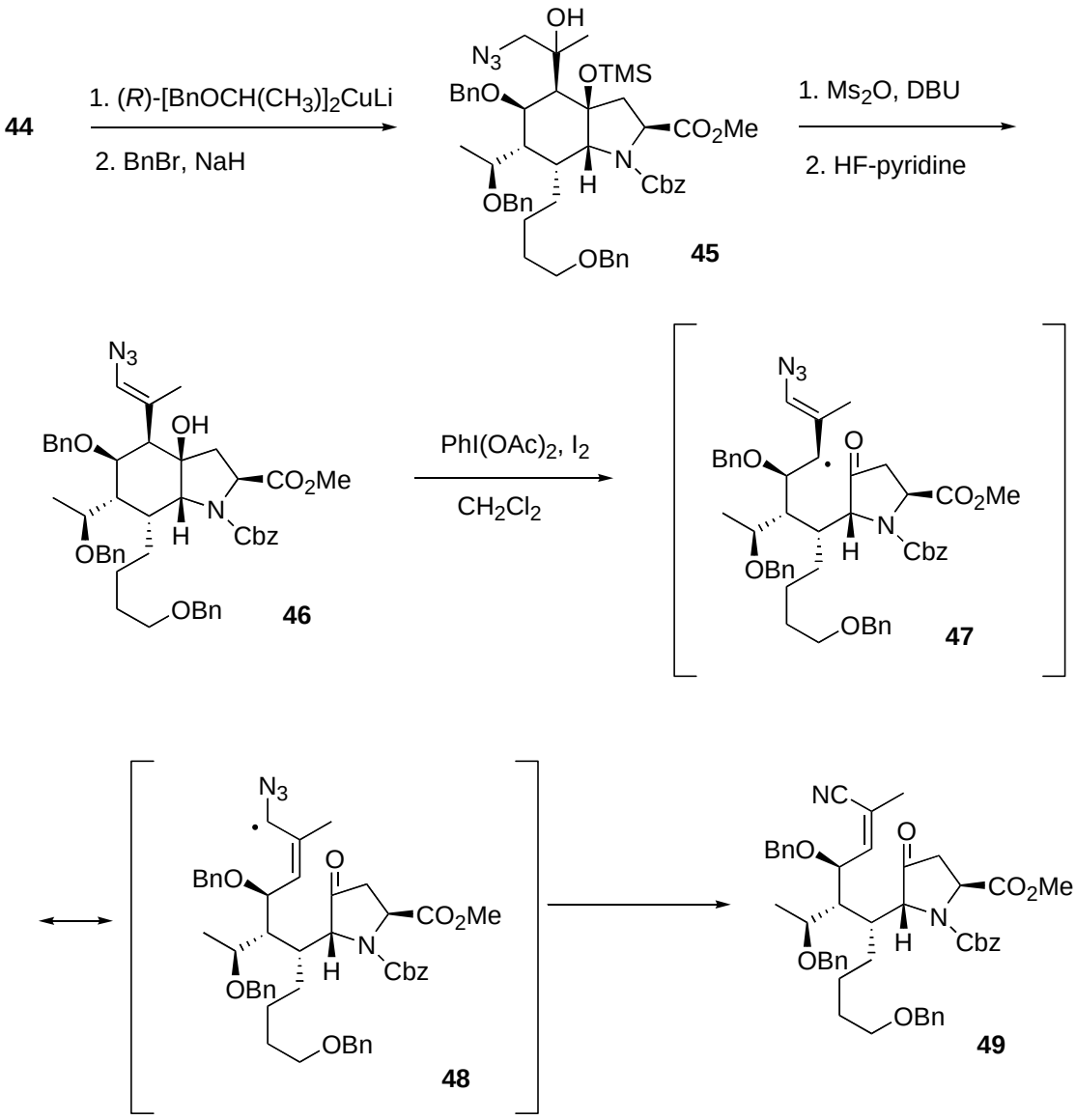
Our synthesis will commence with **1**[86] (Scheme 42). First, protection of the hydroxy group of **1** with TMSCl, followed by epoxidation and TMS enol ether formation will provide **41**. Treatment of **41** with a Grignard reagent and catalytic CuI will give the secondary alcohol resulting from an anti-selective S_N2' substitution[99] and mesylation and elimination will regenerate the enone functionality in **42**. Luche reduction of **42**, followed by mesylation and a second S_N2'-substitution with a vinyl cuprate reagent should furnish diene **43**. Bis-epoxidation of **43** with MCPBA, followed by azidolysis with lithium azidohydridoisobutylaluminate[100] will provide azido alcohol **44**. In this sequence, epoxidation should occur mostly from the β-face of the bicycle (the stereoselectivity of the concomitant epoxidation of the side chain alkene is not important for the synthesis) and azide will preferentially open the terminally unsubstituted epoxide.



Scheme 42. Planned total synthesis of parvistemonine

Next, the addition of (*R*)-[$BnOCH(CH_3)]_2CuLi$[101] to epoxide **44** and benzylation of the resulting alcohol will give **45** (Scheme 43). Although it is difficult to predict what the regioselectivity of the addition step will be, inspection of models allows rationalization for either regioisomeric an attack based on the fact that the six-membered ring of the bicycle should be in a boat conformation. The major isomer is believed to be formed by an attack distant to the tertiary alcohol due to electrostatic repulsions.[102] In case the incorrect regioisomer is favored, we will attempt dihydroxylation of the endocyclic alkene, selective triflation of the sterically more accessible C(5) alcohol and a direct S_N2 displacement. Preparation of fully functionalized **46** sets the stage for the crucial fragmentation step. Since the nitrile side chain in the model study[95] fell two carbons short of what is needed for parvistemonine, we will attempt a novel vinylogous azido alcohol fragmentation. Vinyl azide **46** will be generated by mesylation/elimination[103] and

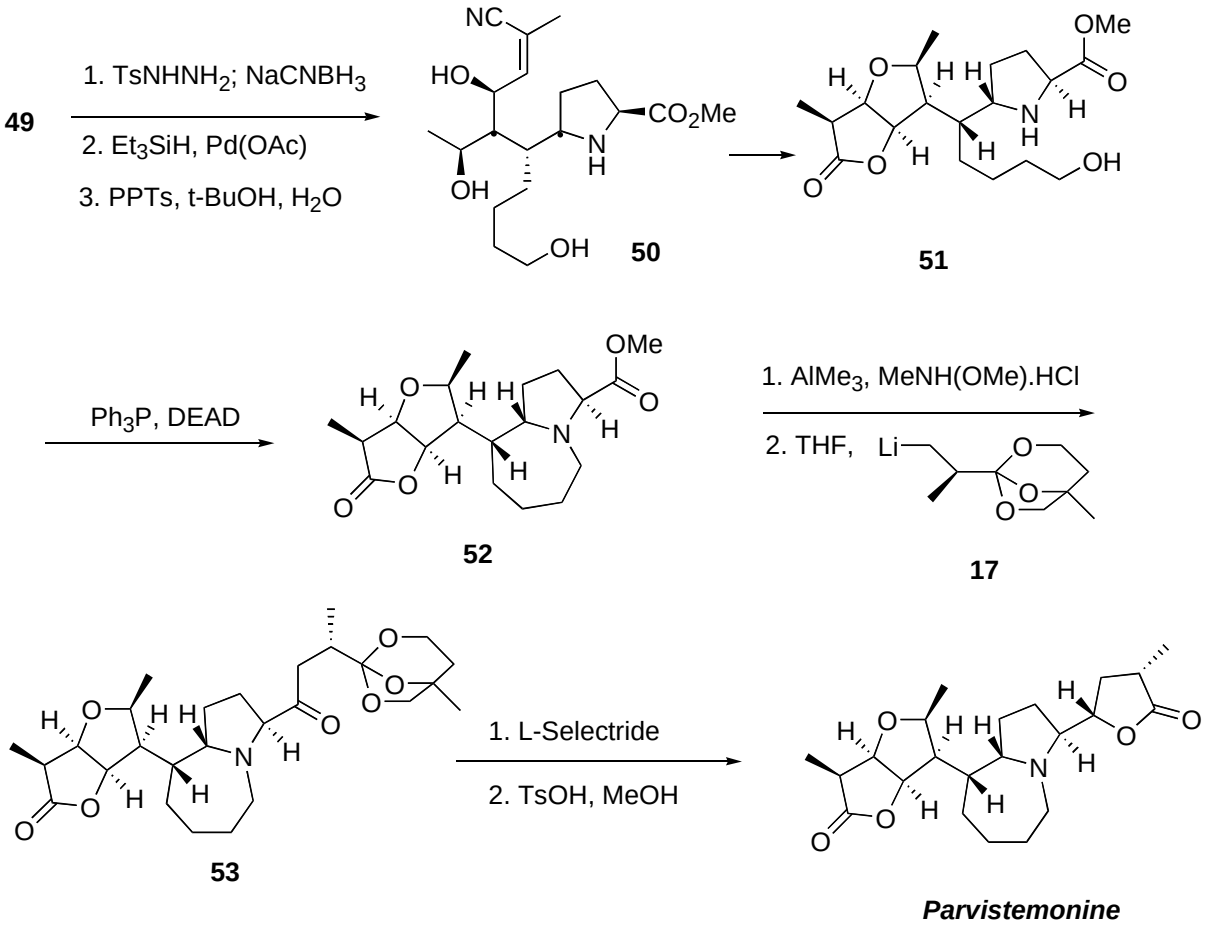
TMS-ether deprotection of **45**. The α,β-unsaturated nitrile **49** will be obtained via **47** and **48** by treatment of **46** with hypervalent iodine reagent and iodine.



Scheme 43. Planned total synthesis of parvistemonine

Relatively mild tosyl hydrazone reduction[104] of **49**, and selective removal of the benzyl protective groups in the presence of the alkene with $Pd(OAc)_2/Et_3SiH$[105] will generate triol **50**

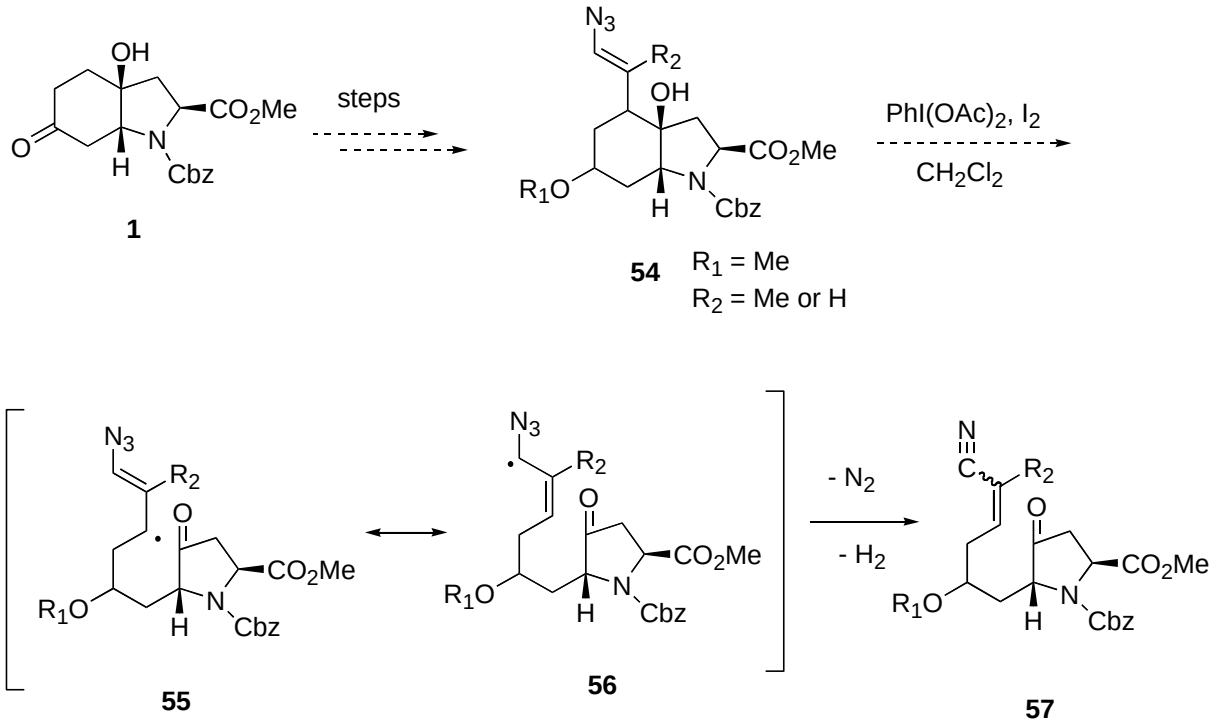
which is expected to close via intramolecular Michael and nitrile additions followed by hydrolysis of the intermediate imidate to the desired tetrahydrofuranyl tetrahydrofuran **51** (Scheme 44).[106] Azepine ring closure of **51** will provide the advanced intermediate **52**. Treatment of **52** by the standard sequence with organolithium reagent **53** that we have used for tuberostemonine and tuberostemonone preparations will lead to the remaining ring. The selective conversion of the methyl ester moiety in **53** to the hydroxamate as well as the subsequent reaction with the organolithium reagent in the presence of a lactone might stir some controversy. However, we believe that the steric shielding and the electronic deactivation around the lactone are sufficient to protect it from these transformations.



Scheme 44. Planned total synthesis of parvistemonine

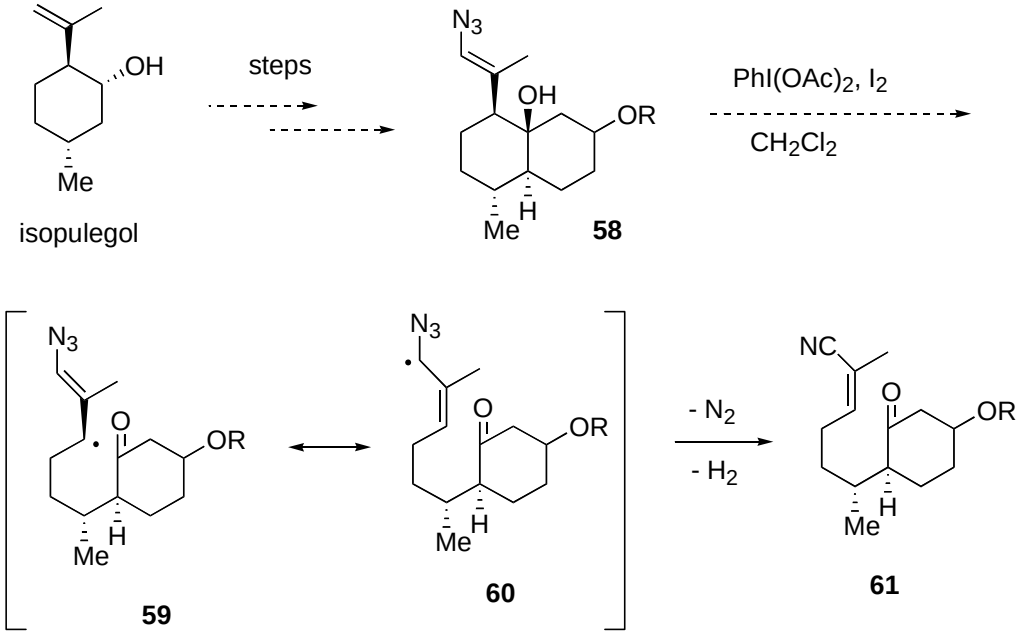
2.2.2. Vinylogous Alkoxy Azido Radical Fragmentation Reaction

The proposed synthetic scheme for parvistemonine requires a vinylogous alkoxy azido radical fragmentation reaction as a key step. Though alkoxy azido fragmentation reactions were reported as discussed earlier, the vinylogous version of this reaction is novel. Thus, before embarking on this preparation of the fully functionalized system, we decided to study the vinylogous azido alcohol fragmentation in a simplified model system to check the feasibility of this reaction. Our initial strategy was to synthesize hydroxy vinyl azide **54** from hydroindole **1** as a substrate for the fragmentation. We were going to try the vinylogous azido alcohol fragmentation of **54** with $PhI(OAc)_2/I_2$ to hopefully generate the desired α,β-unsaturated nitrile **57** ().



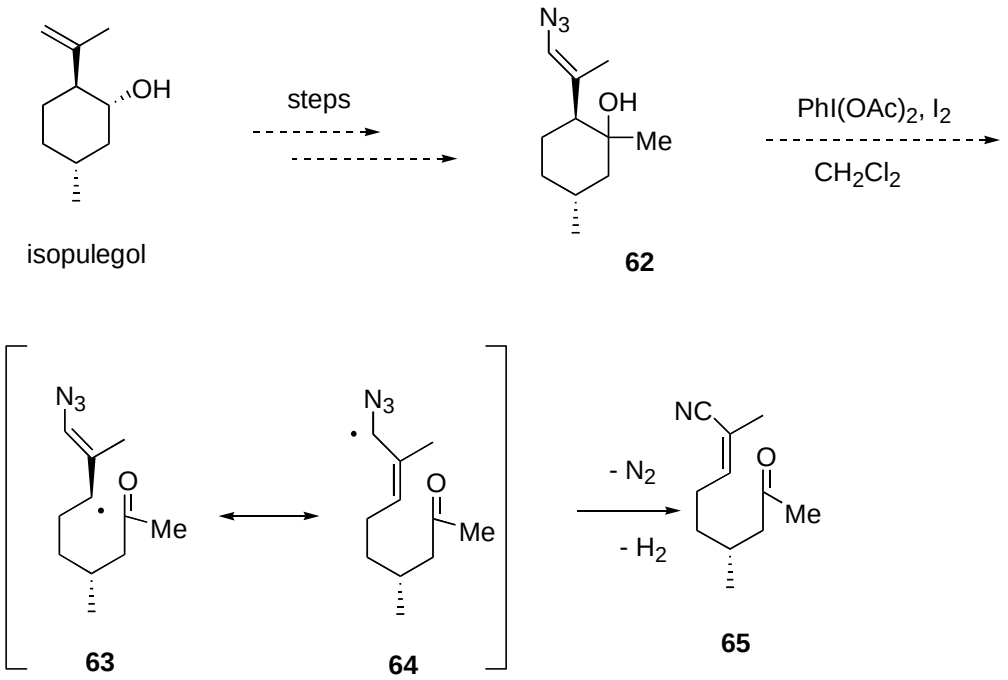
Scheme 45. Model study for fragmentation

Although **54** was chosen as the first substrate for a model study, the synthesis of **54** was still challenging because of the introduction of the isopropenyl group and the subsequent manipulations toward the vinyl azide. Therefore, compound **58** was also selected as a second substrate (Scheme 46). It is advantageous to use **58** as a substrate for the fragmentation because isopulegol, the starting material for **58**, has an isopropenyl group already located in the right position next to the alcohol group.



Scheme 46. Simplified model study for fragmentation

We also envisioned that it would be worthwhile to pursue an even more readily available substrate because we could test the feasibility of the fragmentation reaction more quickly. In addition, the synthetic methods for this study could be used in the second model system. Therefore, we decided to synthesize **62** starting from isopulegol and test the vinylogous alkoxy azido fragmentation (Scheme 46).



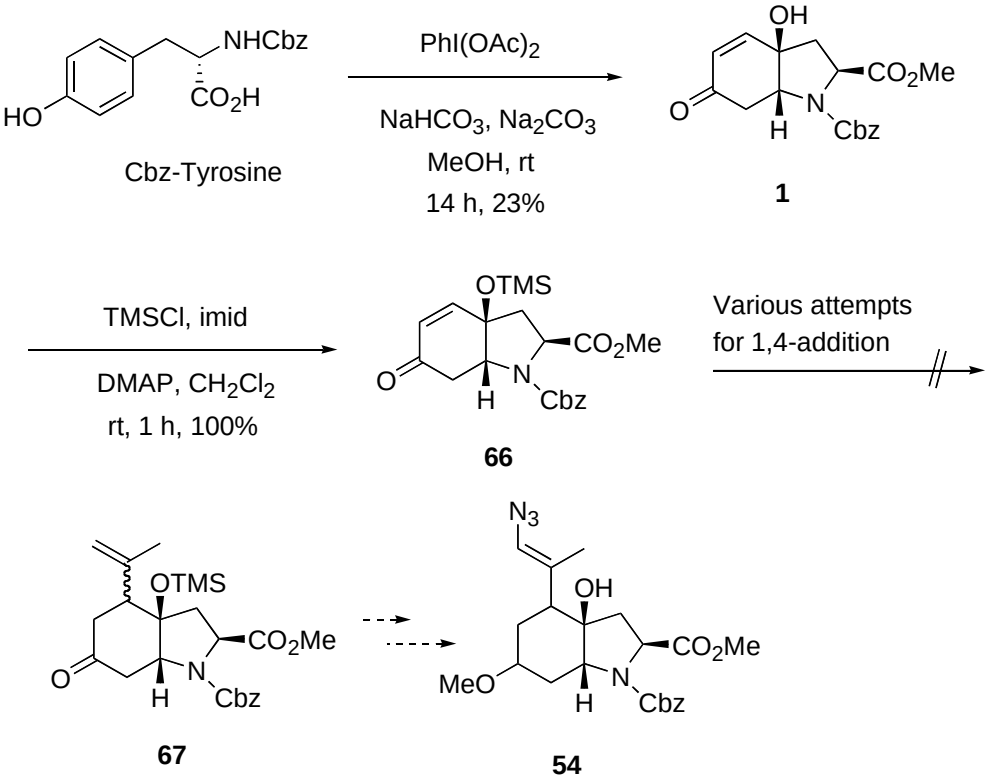
Scheme 47. Third model study for fragmentation

These model studies might not solve all outstanding issues even if we succeeded in obtaining the desired products via fragmentation reactions. First of all, we cannot pursue any further elaboration of the resulting α,β-unsaturated nitriles. Next, we cannot be absolutely sure of the success of a fragmentation in the total synthesis of parvistemonine because radical fragmentation reactions are usually very substrate dependent.[107] Therefore, the applicability of this reaction toward the total synthesis of parvistemonine was still going to remain questionable. In spite of these problems, model studies can be justified because of the novelty of the vinylogous azido alcohol fragmentation for generating α,β-unsaturated nitriles in an unprecedented manner.

2.3. Results and Discussion

2.3.1. Fragmentation Model Studies

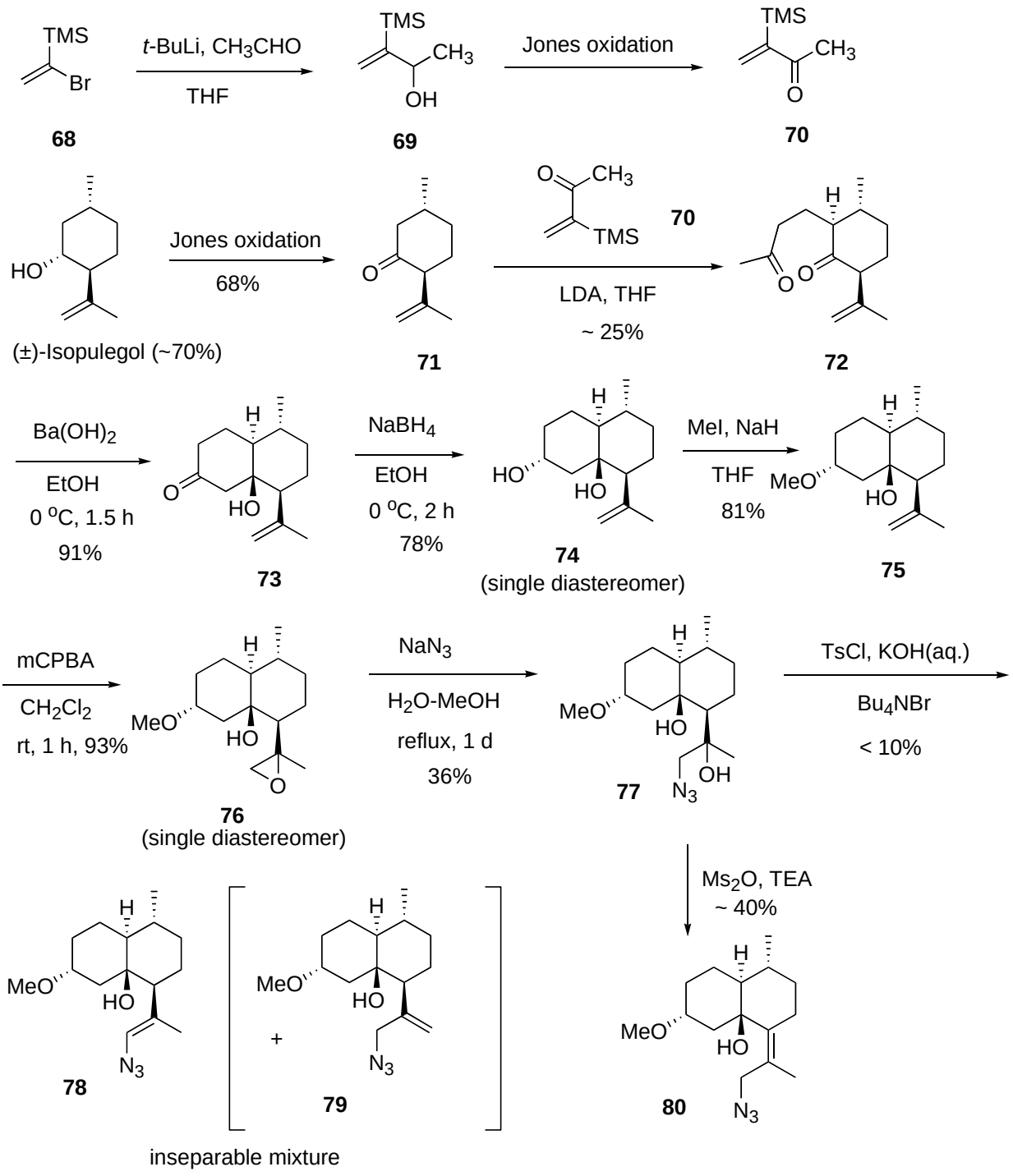
As discussed in Section 2.2, we initially wanted to synthesize hydroxy vinyl azide **54** for a model study of the vinylogous alkoxy azido fragmentation. Exposure of Cbz-tyrosine to $PhI(OAc)_2$ in the presence of sodium bicarbonate and sodium carbonate gave **1** in low to moderate yield (Scheme 47). This reaction worked more successfully on small scale, but poorly on large scale (> 10 g). Nonetheless, alcohol **3** was protected as a TMS-ether with TMSCl to give **66**. Unfortunately, many attempts for a 1,4-addition of the isopropenyl group to **66** did not give the desired product **67**.



Scheme 48. Attempted synthesis of the first model system

While we were not quite sure why we were unable to obtain the desired 1,4-addition product at this point, we decided to proceed to the second model study and revisit this first model system later. We found subsequently that the use of a free hydroxy group in hydroindole **1** was critical for the success of the conjugated reaction. For the second model study, we selected **77** as the target substrate for the fragmentation reaction and we thought that **78** would be readily prepared from the known compound **72**[108] (Scheme 48). For the synthesis of **78**, we first prepared ketone **70** according to literature procedures.[109] Then, isopulegol (technical, ~70%) was subjected to Jones oxidation and the resulting ketone **71** was reacted with **70** in the presence of LDA to give **72**. Treatment of **72** with $Ba(OH)_2$ at 0 ^oC provided **73**. The structure of **73** was confirmed by comparison of NMR data with the literature.[108] Reduction of **73** with $NaBH_4$ in EtOH gave diol **74** as a single diastereomer. Though the stereochemistry of the secondary alcohol of **74** was not important, it was tentatively assigned as α based on the previous reports and NMR analysis.[110] The secondary alcohol group in **74** was then selectively methylated with excess MeI to give methyl ether **75**. Epoxidation of **75** with MCPBA provided **76** as a single diastereomer in good yield (the stereochemistry was not determined). The epoxide was subjected to azidolysis with NaN_3 in the presence of NH_4Cl to give hydroxy azide **77** along with a regioisomer, which was generated by attack of azide at the more hindered carbon. Other conditions for azidolysis with various catalysts proved to be unpractical.[111] In addition, after considerable attempts for dehydration, we found that only trace amounts of the desired vinyl azide **78** as an inseparable mixture with other isomers could be obtained from the reaction of **77** with TsCl in the presence of KOH. In most other cases, the undesired alkene **80** was obtained as the major isomer. These results may be explained by insufficient acidity of the α-position of the

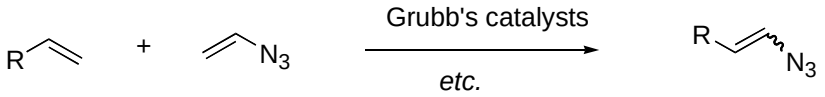
azide, the thermodynamic instability of the desired vinyl azide or steric effects. In other to avoid these problems, we decided to change the strategy and generate the vinyl azide at an early stage.



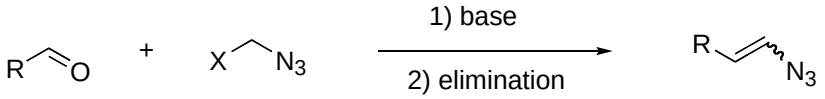
Scheme 49. Attempted preparation of the second model system

Though we had considered several possible literature transformations,[111] we could only test some reactions for the synthesis of the vinyl azide due to the potential danger in the use of low boiling azides (Scheme 50).[112]

1) Cross-Metathesis Reaction

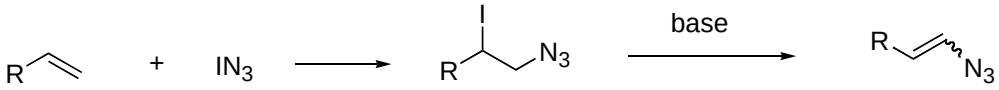


2) Wittig Type (or Peterson or Julia) Reaction



(X = PPh_3, $P(O)(OR)_2$, SiR_3, SO_2R)

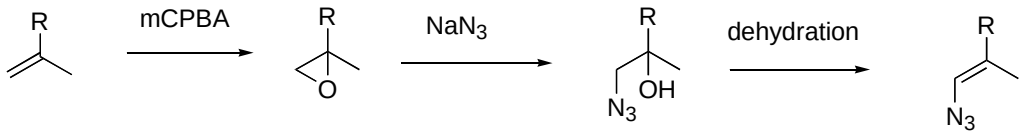
3) IN_3 reaction[38]



Scheme 50. Some possible transformations for the synthesis of vinyl azides

Two routes were examined for the synthesis of the vinyl azide (Scheme 51). One method was to use the same protocol as in the second model study to synthesize a vinyl azide in at a relatively early stage and to separate the desired vinyl azide from other regioisomers. This approach was thought to be only feasible if the generation of vinyl azide would be preferred due to reduced steric hindrance and the separation would be easy. An alternative method was to use a Peterson-type olefination in order to achieve much better regioselectivity, while a relatively long reaction sequence would be required.

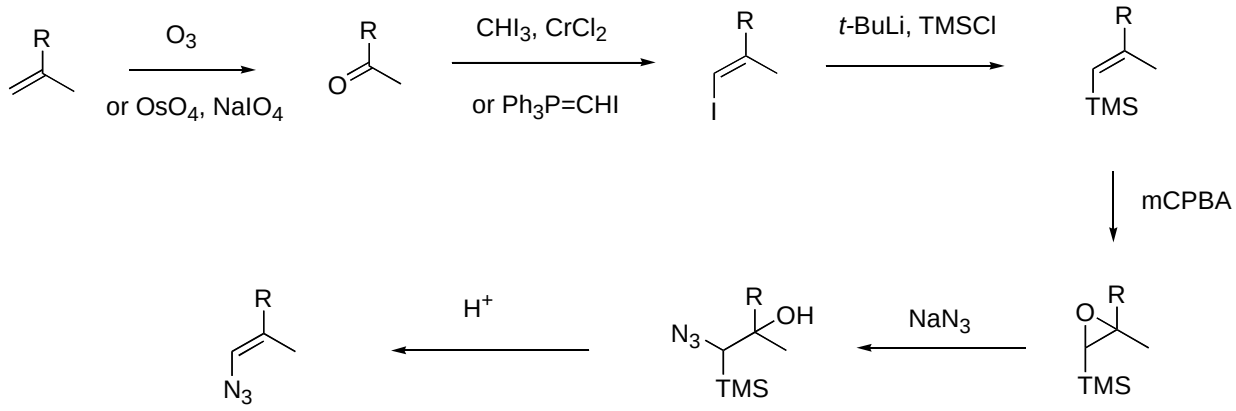
1) Hydroxy Azide



advantage: common and known method

problem: regioselectivity of dehydration step

2) Peterson-Type Olefination



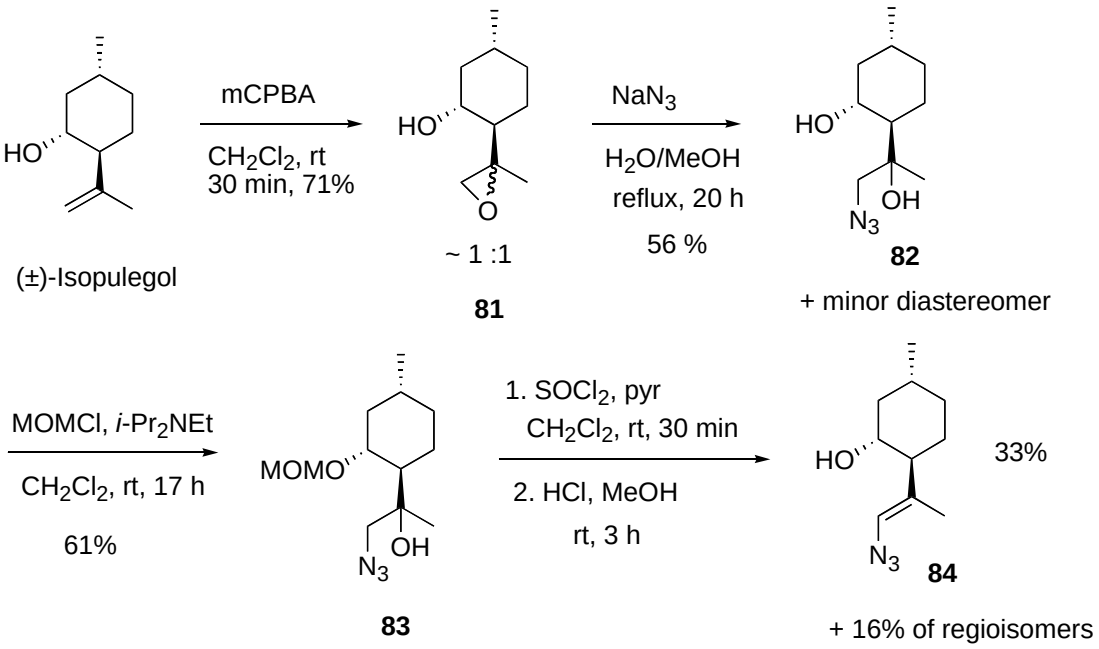
advantage: easy control of regioselectivity

problem: a long reaction sequence

Scheme 51. Alternative methods for vinyl azide preparation

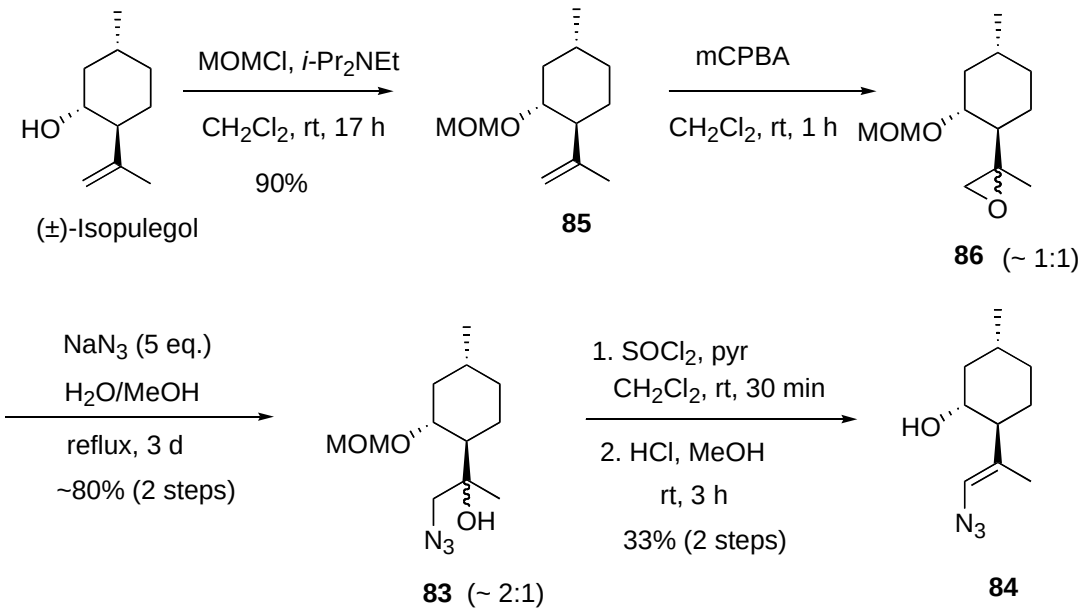
After significant experimentation pursuing these two routes, we could identify a suitable method to generate the desired hydroxy vinyl azide in a satisfactory sequence (Scheme 52). Treatment of (±)-isopulegol with MCPBA gave epoxide **81** as ~1:1 mixture of diastereomers in good yield. Epoxide **81** was then subjected to azidolysis with NaN_3 to give azide **82**, which could be isolated as a predominantly single isomer along with a trace of a minor isomer. Since the yield was moderate, one of the two diastereomers of epoxide **81** might have been less reactive or decomposed preferentially. Selective protection of the secondary hydroxy group in azido alcohol **82** as the MOM ether with MOMCl gave **83**. Treatment of **83** with $SOCl_2$ and pyridine[114]

followed by treatment with concentrated HCl gave the desired hydroxy vinyl azide **84** along with other regioisomers. Fortunately, in this case, the separation of **88** was possible by chromatography on SiO_2.



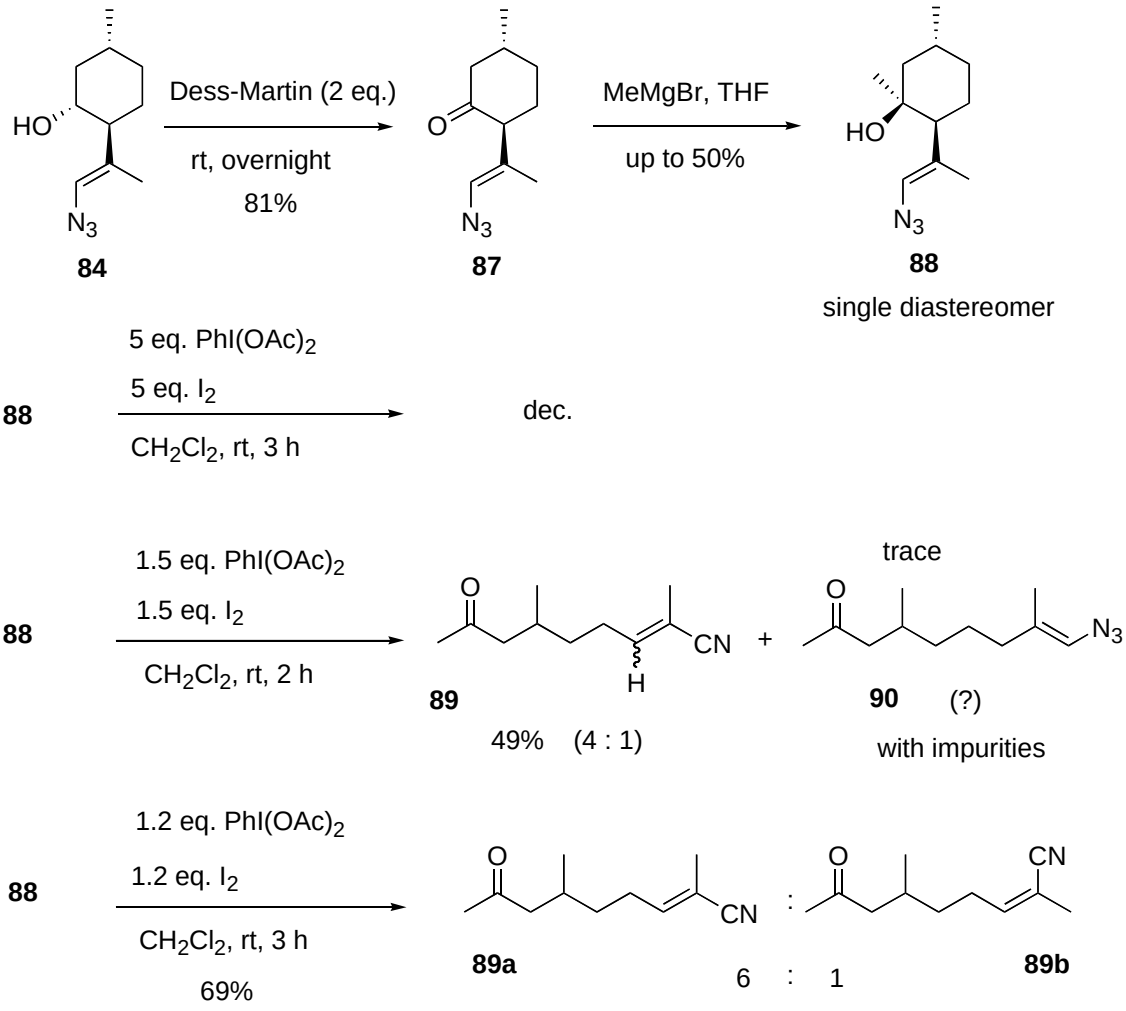
Scheme 52. Synthesis of hydroxy vinyl azide **84**

Alternatively, vinyl azide **84** was synthesized according to Scheme 53. In this route, isopulegol was first protected with MOMCl to give MOM ether **85**. Then, MOM-protected isopulegol **85** was transformed into epoxide **86** (~1:1 diastereomeric ratio) by epoxidation with MCPBA. Azidolysis of **86** with NaN_3 gave **83** which also underwent dehydration and deprotection as described previously. Compared with the previous route described in Scheme 52, this route was better because overall yield of this route was 23%, whereas that of the previous route was 8%.



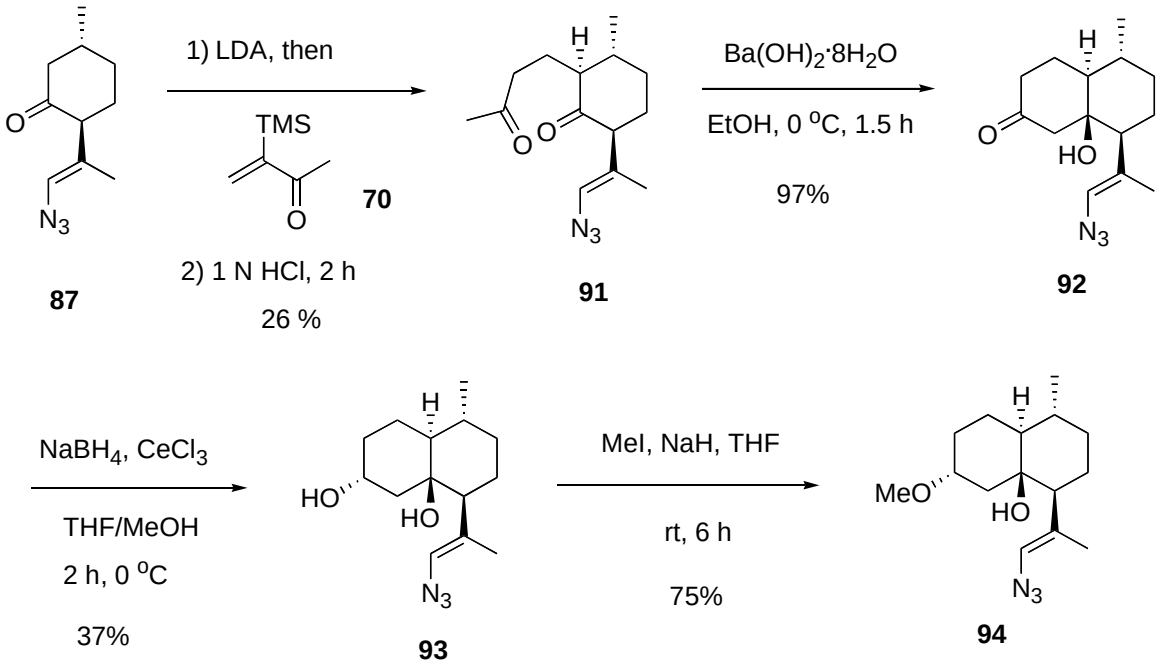
Scheme 53. Alternative route for the synthesis of hydroxy vinyl azide **84**

With the desired hydroxy vinyl azide **84** in hand, we wanted to synthesize the tertiary alcohol substrate **88** to test the fragmentation reaction (Scheme 54). First, Dess-Martin reaction of **84** gave **87** in 81% yield and Grignard reaction of **87** with MeMgBr gave **88** in good diastereoselectivity, presumably due to preferential α-attack of the Grignard reagent.[114] Now, the stage was set for attempting the first vinylogous azido alcohol fragmentation. The initial attempt for this reaction was made using excess $PhI(OAc)_2$ and iodine, but failed to generate the desired product **89**. A second attempt was made using 1.5 equiv. of $PhI(OAc)_2$ and 1.5 equiv. of iodine and gave the desired product **89** in 49% yield. The third attempt used 1.5 equiv. of $PhI(OAc)_2$ and 1.5 equiv. of iodine and gave the desired product **89** in 69% yield. Further separation and NMR analysis showed that **71** was obtained as a 6:1 *E/Z* mixture, and the double bond geometry was determined by the comparison of the ^1H NMR spectrum with a closely related compound.[115]



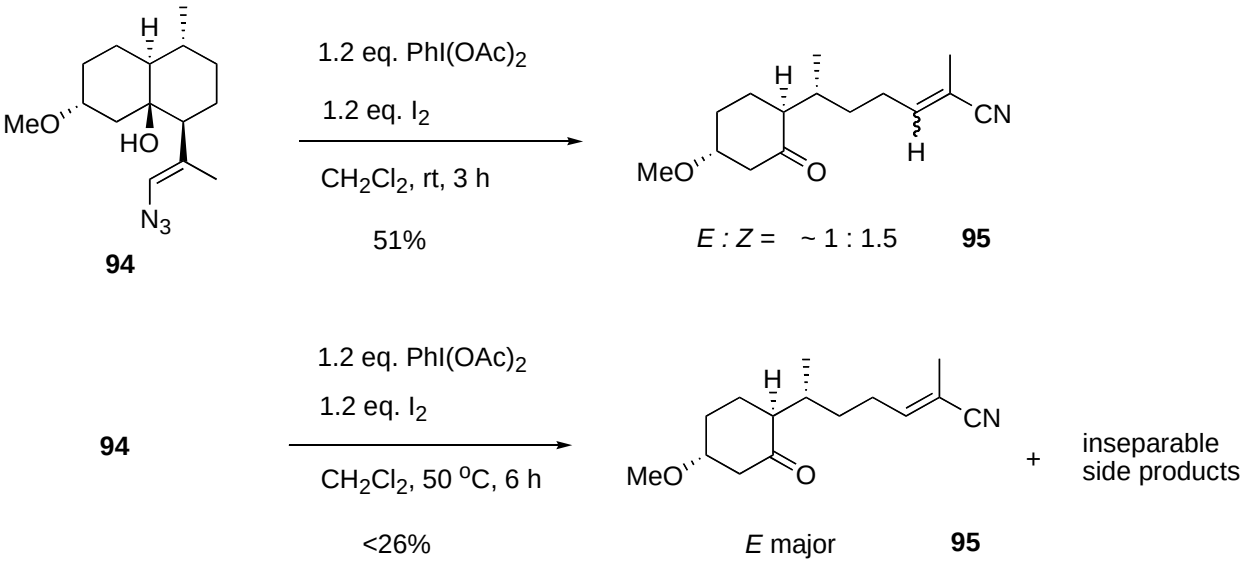
Scheme 54. The first successful fragmentation reactions

Encouraged by these results, we moved to a bicyclic system to test the generality of this novel fragmentation process. Treatment of **87** with **70** in the presence of LDA, followed by treatment with 1N HCl gave diketone **91** (Scheme 55). Diketone **91** was then cyclized to give bicyclic **92** by an aldol type reaction with $Ba(OH)_2$. Reduction of **92** with $NaBH_4$ and $CeCl_3$ furnished diol **93** and the secondary alcohol of **93** was selectively methylated with MeI in the presence of NaH to give the desired product **94**.



Scheme 55. Synthesis of bicyclic hydroxy vinyl azide **94**

Exposure of **94** to Suárez conditions (1.2 equiv. of $PhI(OAc)_2$ and 1.2 equiv. of iodine at room temperature for 3 h) gave the desired fragmented product in 51% yield (Scheme 56). In this case, two *E/Z* isomers were formed in almost equal amounts. The configuration of the vinyl azide seemed to lack control. Therefore, another procedure with 1.2 equiv. of $PhI(OAc)_2$ and 1.2 equiv. of iodine under elevated reaction temperature and longer reaction time was used and showed improved selectivity for the *E*-isomer but produced a lower yield along with inseparable side products. Based on these results, we might conclude that the *E/Z*-selectivity of the fragmentation is controlled by thermodynamic factors and an isomerization process during the fragmentation leads to the more stable *E*-configuration of the α,β-unsaturated nitrile.



Scheme 56. Further fragmentation reactions

The mechanism of our fragmentation reactions can be proposed as shown in Figure 28 based on the previous reports.[95,96] However, the actual mechanism for the fragmentation is still unclear and ionic mechanisms for these conversions cannot be excluded as discussed in Section 2.1.3.

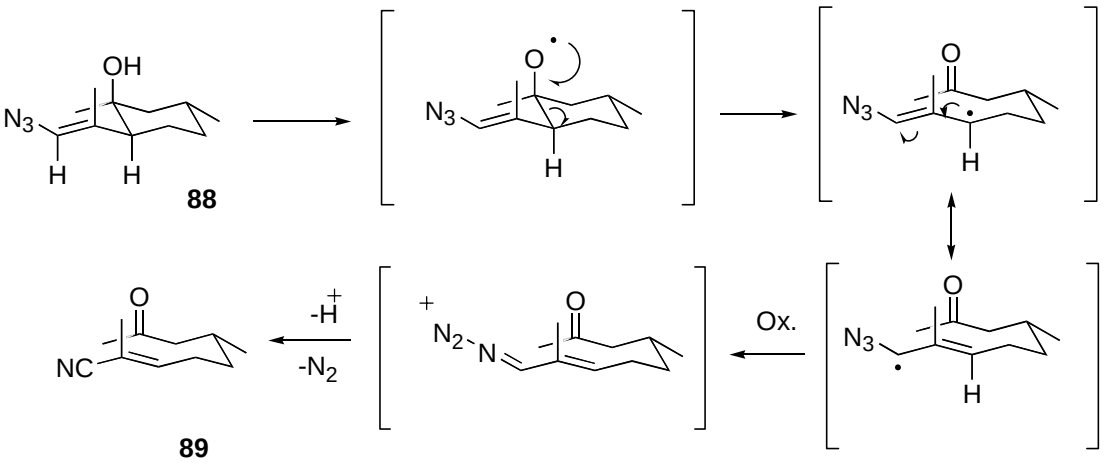
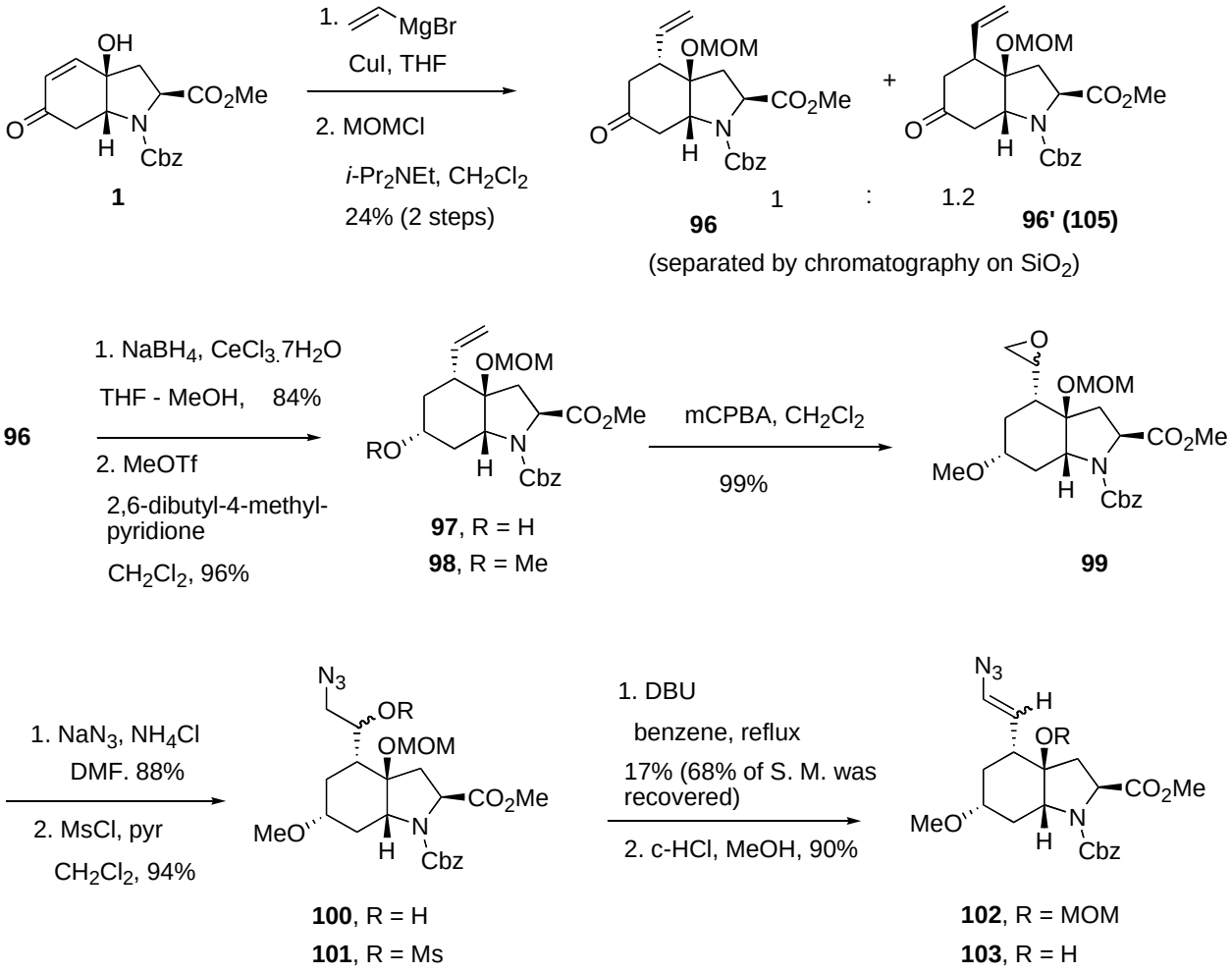


Figure 28. Proposed mechanism of fragmentation reactions of **88**

2.3.2. Fragmentation Reactions in Hydroindole Systems

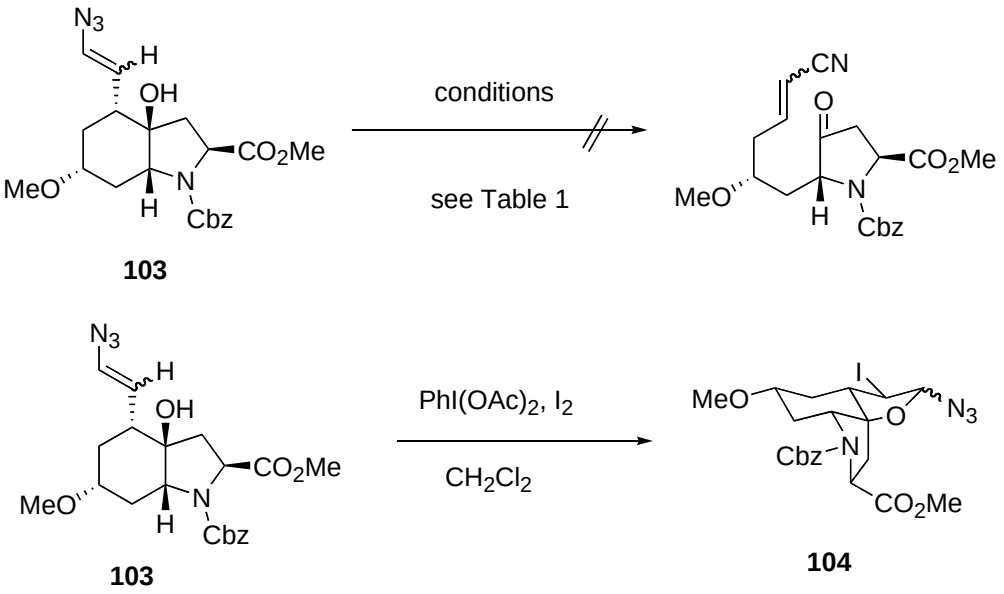
After accomplishing two model studies successfully, we decided to revisit hydroindole systems. To this end, we synthesized hydroxy vinyl azide **103** from common intermediate **1** in several steps (Scheme 57).



Scheme 57. Synthesis of hydroxy vinyl azide **103**

The 1,4-conjugate addition reaction of hydroindole **1** with vinyl magnesium bromide in the presence of copper iodide provided a 1:1.2 mixture of diastereomers in 40% yield. This time, the

1,4-conjugate addition of the vinyl group was achieved by using a free hydroxy group instead of using the TMS-protected alcohol. The addition product was reacted with MOMCl to give separable diastereomers, and purification by chromatography on Si_2O provided pure ketone **96**.[117] Ketone **96** was reduced with $NaBH_4$ to furnish alcohol **97**, which was O-methylated to give **98**. Epoxidation of **98**, followed by the azidolysis of **99** gave azido alcohol **100**, which was reacted with methane sulfonyl chloride to give mesylate **101**. Elimination of mesylate **101** turned out to be a very sluggish reaction, so only small amounts of vinyl azide **102** could be obtained by the reaction of **101** with DBU in benzene under reflux conditions. Since more vigorous reaction conditions led to rapid decomposition of **101**, we repeated the elimination reaction under the same conditions several times to get sufficient material. Vinyl azide **102** was converted to the desired hydroxy vinyl azide **103** by the removal of the MOM group of **102** with HCl. With the desired vinyl azide **103** in hand, we tried the fragmentation reaction under several reaction conditions. However, we could not obtain products of a vinylogous azido alcohol fragmentation (Scheme 58). In most cases, we just isolated the undesired product **104** derived from the iodoetherification of hydroxy vinyl azide substrates or starting material (Table 10).



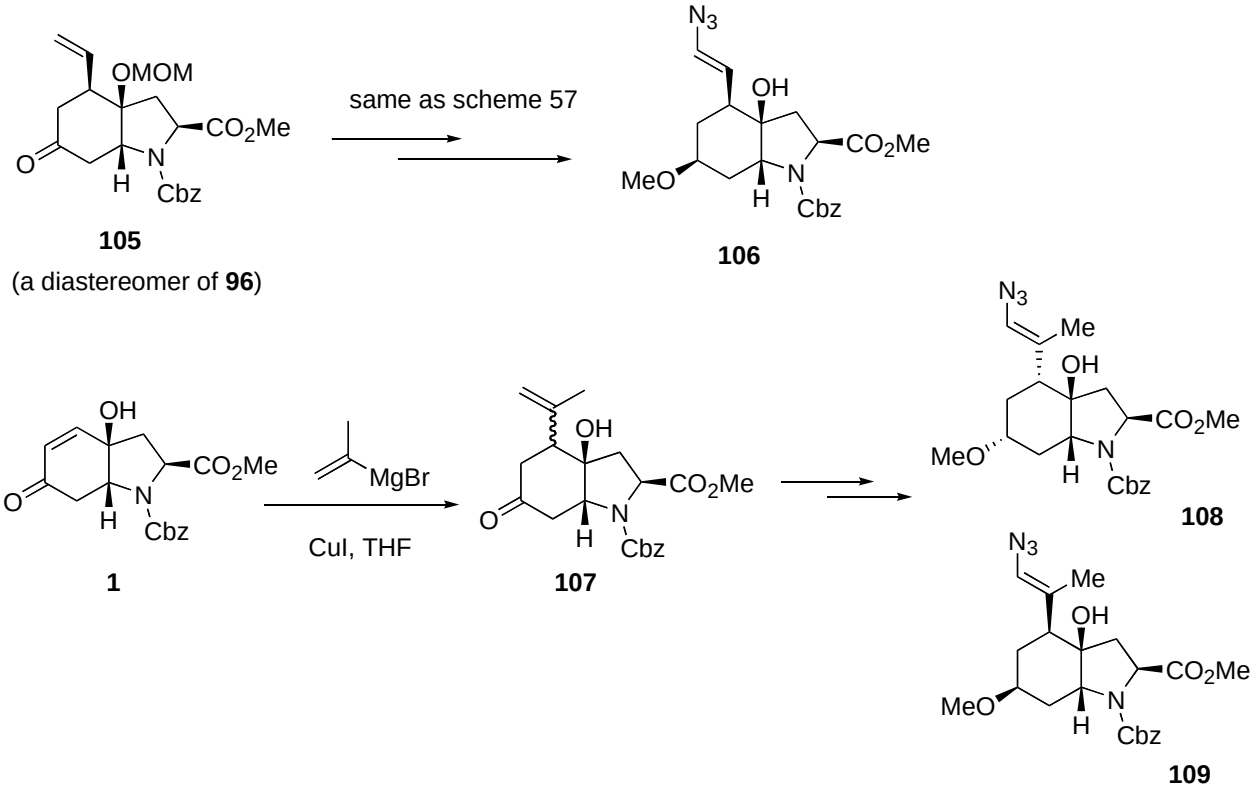
Scheme 58. Attempts for fragmentation of **103**

Table 10. Attempted conditions for fragmentation of **103.**

Entry	Reagents	Temperature	Solvent	Results
1	$PhI(OAc)_2$ (1.2 equiv.) I_2 (1.2 equiv.)	Room temp.	CH_2Cl_2 (0.03 M)	**104** (77%)
2 [a]	$PhI(OAc)_2$ (1.2 equiv.) I_2 (1 equiv.)	Room temp.	CH_2Cl_2 (0.04 M)	**104** (57%)
3	I_2 (1.2 equiv.)	Room temp.	CH_2Cl_2 (0.03 M)	**104** [b]
4	$PhI(OAc)_2$ (1.2 equiv.) I_2 (1 equiv.), AcOH	Room temp.	CH_2Cl_2 (0.04 M)	**104** (71%)
5	$PhI(OAc)_2$ (2 equiv.)	Room temp.	CH_2Cl_2 (0.02 M)	No reaction (S. M.)
6	$Pb(OAc)_4$ (2 eqiuv.)	Room temp.	CH_2Cl_2 (0.03 M)	No reaction (S. M.)
7	$Pb(OAc)_4$ (2 eqiuv.)	Reflux	CH_2Cl_2 (0.02 M)	No reaction (S. M.)
8	$PhI(OAc)_2$ (2 equiv.) ICl (1 equiv.)	Room temp.	CH_2Cl_2 (0.04 M)	**104** (53%)

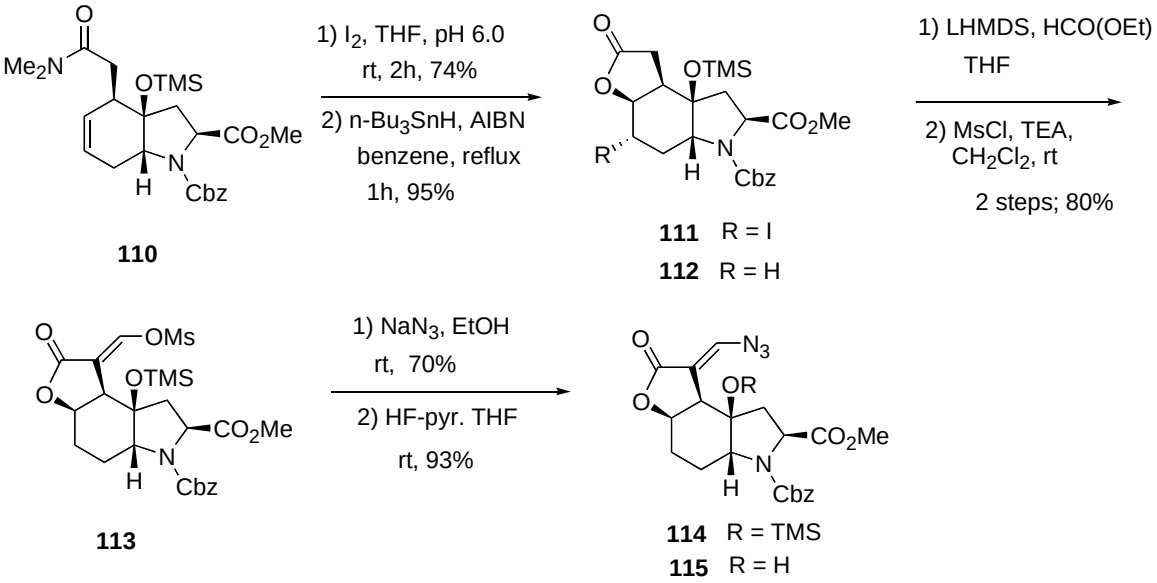
[a.] Reagents were mixed and stirred for 30 min before addition of substrate.
[b.] Yield was not determined.

In the hope that small changes in the structure of substrate would result in a dramatic effect on the fragmentation reaction, we decided to synthesize additional hydroindole substrates using similar chemistry to the synthesis of **103** (Scheme 59). First, we synthesized hydroxy vinyl azide **106** in several steps starting from **105**, a diastereomer of **96**, using the same sequence as described in the synthesis of **103**. Then, hydroxy vinyl azides **108** and **109** were similarly prepared from **107**, which was the product of the 1,4-addition of **1** with isopropenyl magnesium bromide under Kharash conditions. However, to our great disappointment, we could not obtain any desired product from the reaction of hydroxy vinyl azides **106**, **108** and **109** with iodine/iodobenzene diacetate or other reagents. Mostly, the major products formed were derived from iodo-etherification as shown in Scheme 58.



Scheme 59. Synthesis of other hydroxy vinyl azides in the hydroindole system

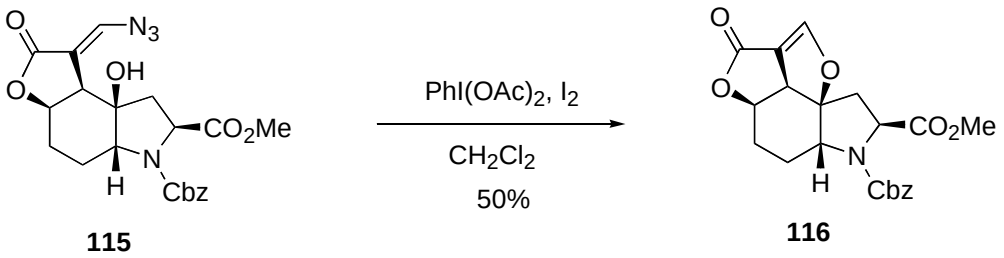
Based on these observations, we prepared another hydroxy vinyl azide substrate, which was thought to avoid the iodo-etherification reaction due to the decreased reactivity of the vinyl functionality. Hydroxy vinyl azide **115** was obtained in several steps from the known amide **110**[94] (Scheme 60). Iodolactonization of **110**, followed by reduction of iodide **111** with *n*-Bu_3SnH provided lactone **112**, which was converted to vinyl mesylate **113** by formylation and subsequent mesylation.[118] Displacement with azide gave vinyl azide **114**,[119] and deprotection of the TMS group of **114** afforded the desired substrate **115**.



Scheme 60. Synthesis of hydroxy vinyl azide **115**

Initially, we envisioned that the conjugation of the double bond by the lactone functionality in **115** and the resulting conformational change might prohibit the iodo-etherification of **115**, but we were also concerned about the possibility of a conjugate addition-elimination reaction. Indeed, treatment of **115** with $PhI(OAc)_2$ and I_2 provided the addition-

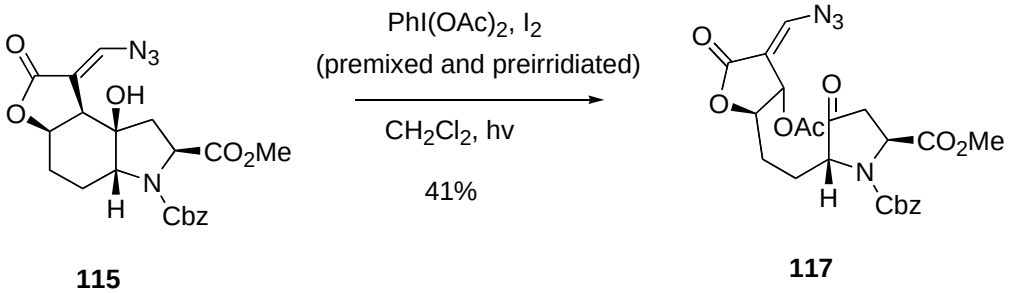
elimination product **116** as a major product along with inseparable by-products (Scheme 61). It is possible that iodine acted as catalyst for this addition-elimination reaction.



115 **116**

Scheme 61. Addition-elimination reaction of **115**

However, the reaction of **115** with pre-mixed and pre-irradiated $PhI(OAc)_2$ and I_2 afforded the fragmented product **117** presumably via prompt quenching of the radical intermediate with the acetoxy radical (Scheme 62). Even though we obtained the fragmented product **117** with the correct C,C-bond cleavage, further manipulation of **117** seemed to be difficult because of the presence of several sensitive functionalities. Therefore, we chose another substrate for the desired fragmentation, which could allow further conversions.



115 **117**

Scheme 62. A regioselective oxidative fragmentation of **115**

2.3.3. Alternative Regioselective Fragmentation Reactions

The β-effect of silicon[120] involves the stabilization of a positive charge β to silicon by overlap of the carbon-silicon σ-bond with the vacant p-orbital of the adjacent carbocation as shown in Figure 29.[121] This effect has been widely utilized in organic synthesis.

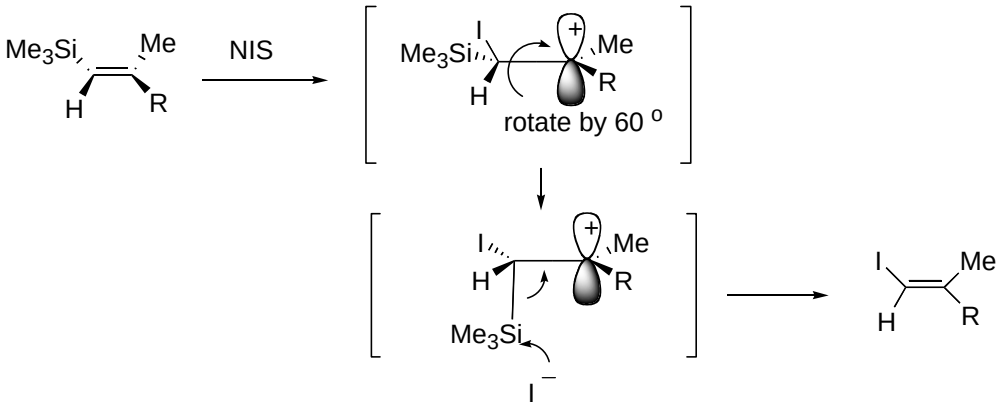
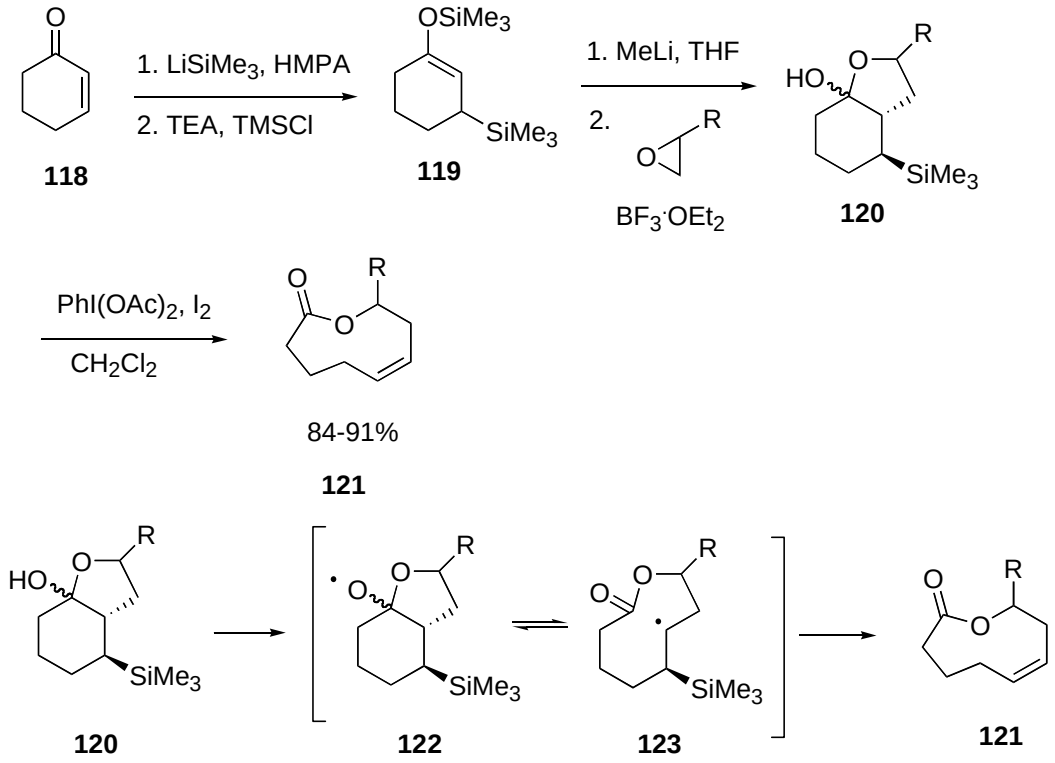


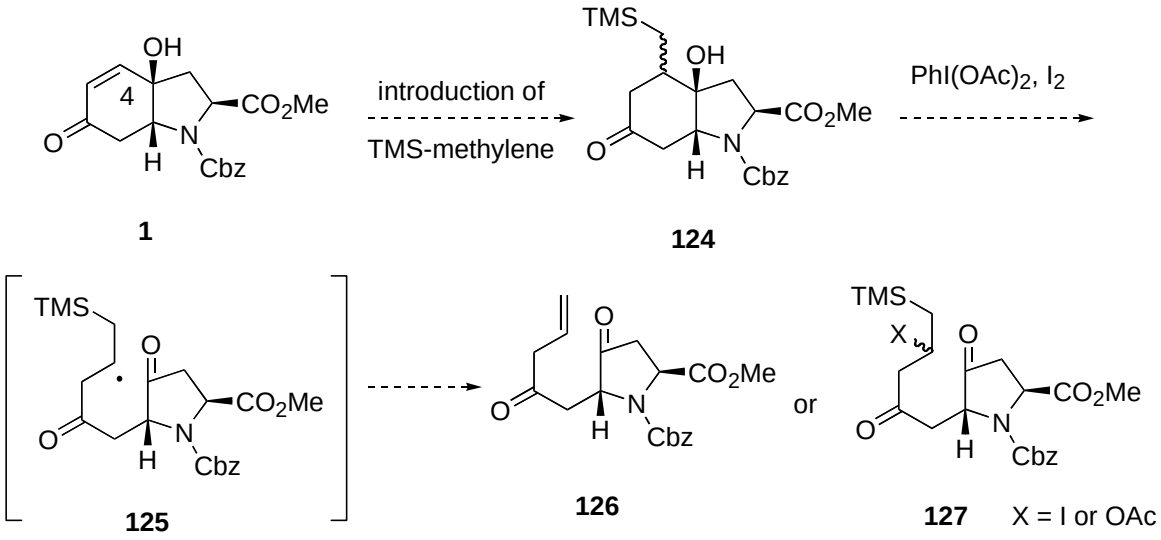
Figure 29. β-Effect of silicon in the iododesilylation[121]

We envisioned that a radical β to silicon might be stabilized by an adjacent silicon atom in a similar way. Recently, the Posner group utilized this β-effect of silicon in the ring expansion of n-sized conjugated cycloalkenones into homoallylic n+3 lactones as shown in Scheme 63.[122] They prepared γ-lactols **120** by nucleophilic 1,4-addition of $LiSiMe_3$ to 2-cyclohexenone **118**, followed by mild and rapid α-alkylation of the corresponding cycloalkanone enolates using diverse epoxides and $BF_3 \bullet OEt_2$. Treatment of **120** with $PhI(OAc)_2$ and I_2 provided lactone **121** presumably via radical intermediates **122** and **123**. In this case, the formation of **120** can be attributed to the β-effect of silicon.



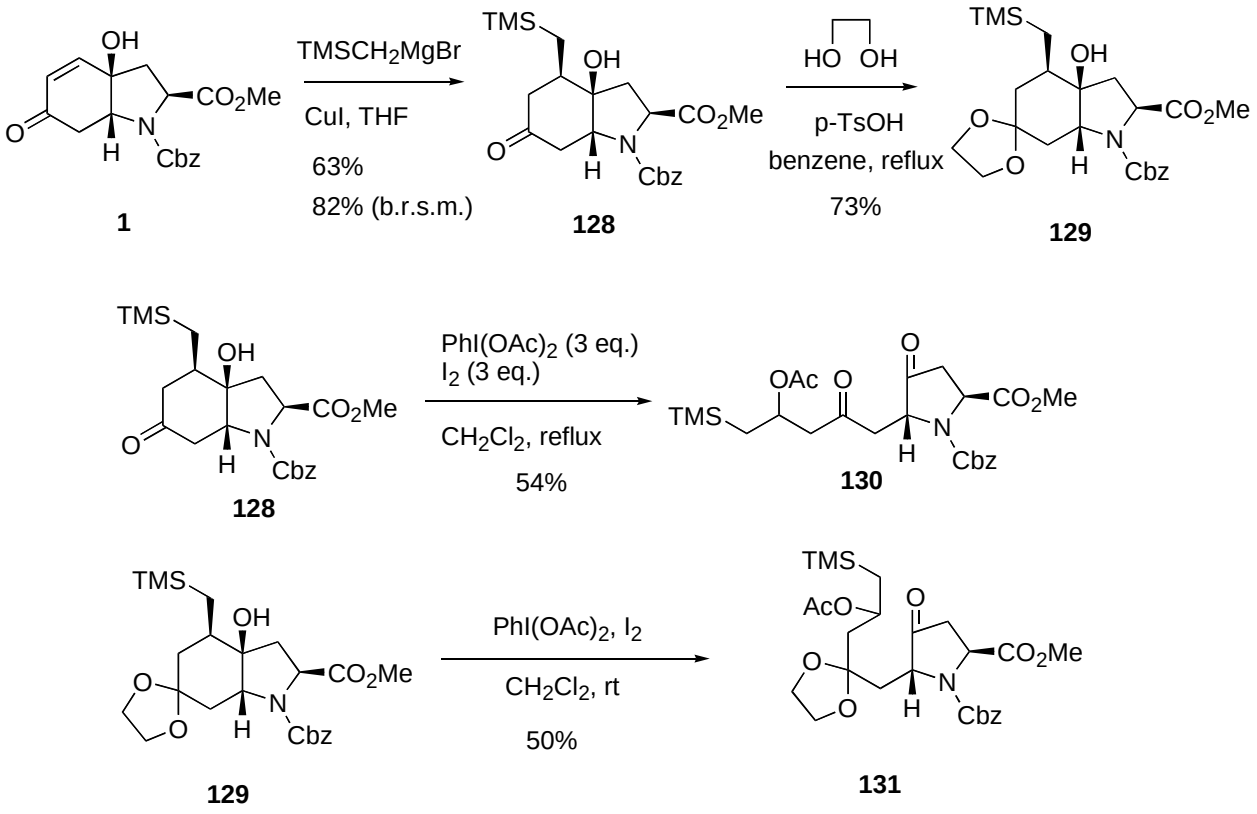
Scheme 63. Ring expansion of cycloalkenones into lactones by fragmentation[122]

Thus, we envisioned that the introduction of a TMS-methylene functional group at C(4) of hydroindole **1** might induce a directing effect to stabilize the radical intermediate **125**, presumably due to the β-effect of silicon, and result in the formation of the desired pyrrolidinones **126** or **127** as shown in Scheme 64.



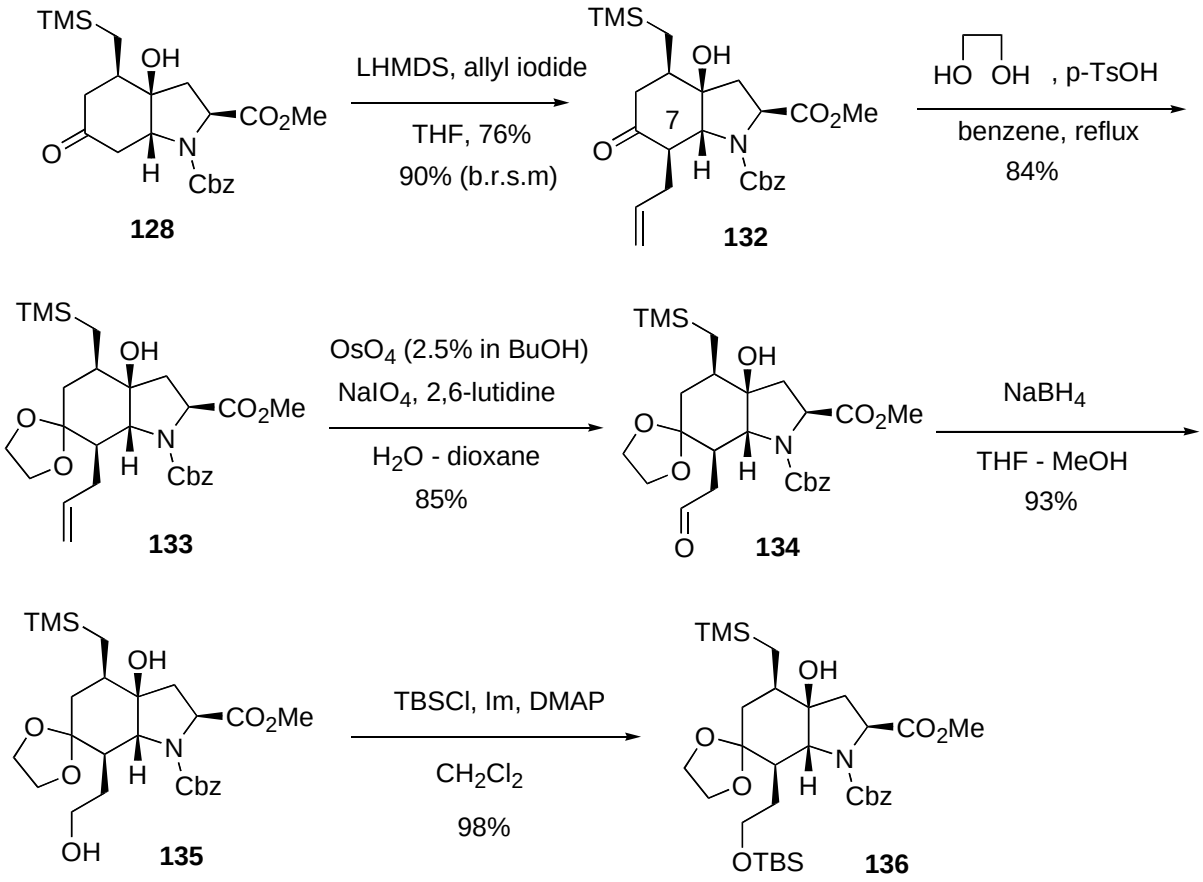
Scheme 64. β-Effect of silicon in the fragmentation of hydroindole **124**

With this concept in mind, we synthesized silane **128** by the stereoselective conjugate addition of hydroindole **1** with $TMSCH_2MgBr$ under Kharash conditions (Scheme 65).[123] Acetal **129** was also synthesized by the treatment of **128** with ethylene glycol under mild acidic conditions. Fragmentation of compounds **128** and **129** with iodine and iodobenzenediacetate led indeed to the desired pyrrolidinones **130** and **131**.[124]



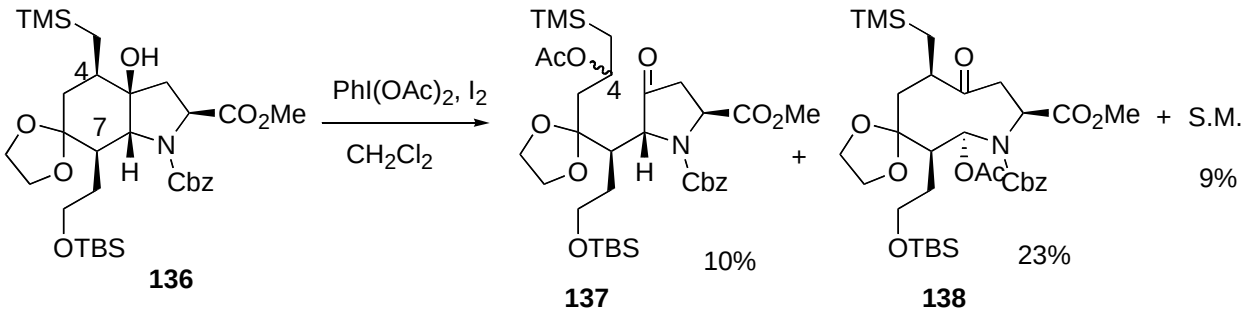
Scheme 65. Regioselective oxidative fragmentation of **128** and **129**

After the successful regioselective fragmentation of **128** and **129**, we prepared a more highly substituted substrate with a TMS-methlyene side chain to probe the generality of the reaction. Especially, we wanted to investigate the effect of an additional side chain at C(7) in the fragmentation reaction. For this purpose, we synthesized alcohol **136** from **128** in 5 steps (Scheme 66). Ketone **128** was deprotonated with LHMDS and reacted with allyl iodide to give **132** as a single diastereomer[125] in 76% yield (90% based on recovered starting material). Compound **132** was acetalized with ethylene glycol in 84% yield, and **133** was subjected to a Johnson-Lemieux-reaction[126] to provide aldehyde **134** in 85% yield. This aldehyde was reduced to the primary alcohol **135**, which was protected with TBSCl to provide **136** in 98% yield.



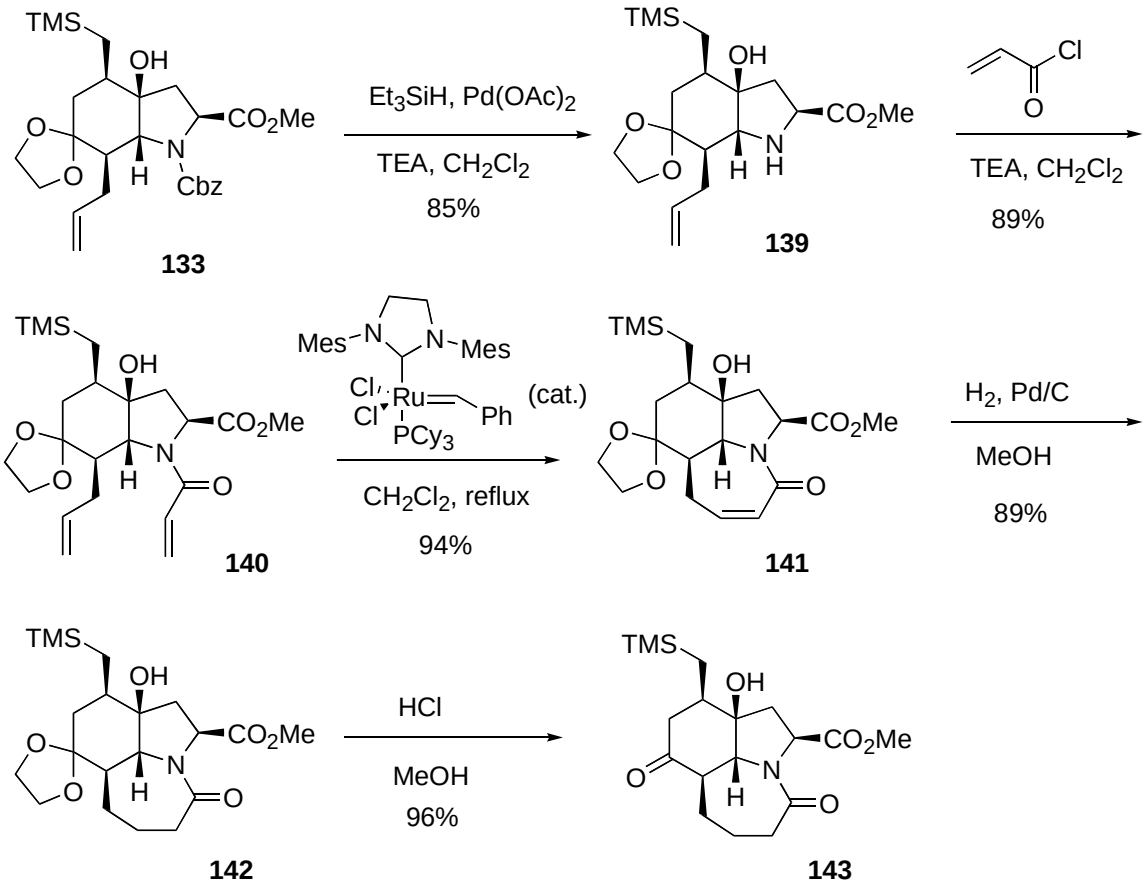
Scheme 66. Preparation of **136**

With the desired substrate **136** in hand, we tried the fragmentation reaction of **136** with iodine and iodobenzene-diacetate (Scheme 67). Interestingly but unfortunately, we obtained the internally fragmented product **138**[127] as a major product in 23% yield along with the desired product **137**[128] in 10% and starting material in 9% yield. Though we are not sure about the reasons for the reactivity difference between **129** and **136**, this result suggested that the introduction of an alkyl chain at the C(7a) position could affect the fragmentation reaction.



Scheme 67. Fragmentation reaction of **136**

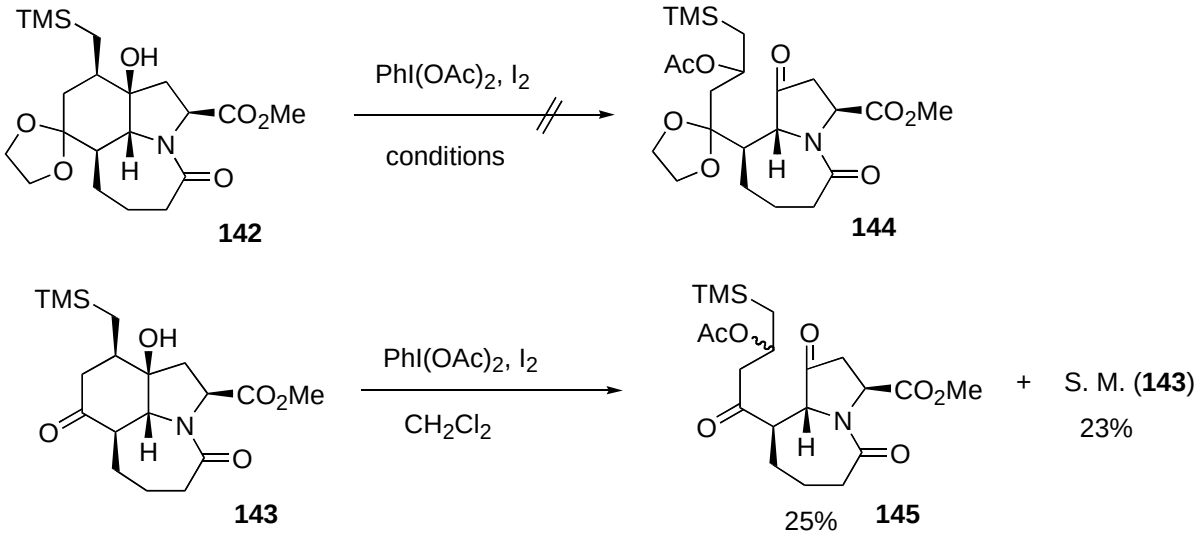
The result of the fragmentation reaction of **136** inspired the preparation of another substrate, which could avoid the undesired regioselectivity in the fragmentation. We envisioned that in tricyclic ring compounds access of the acetoxy group to the C(7a) position would be prevented by severe steric hindrance, thus overcoming the radical stabilizing effect at C(7a) by the additional side chain. In this context, we synthesized the tricycles **142** and **143** in several steps from **133**, which was described in the synthesis of **136** (Scheme 68). The Cbz group of aceetal **133** was selectively removed to give amine **139** in 85% in the presence of the terminal alkene using the conditions[105] from the synthesis of (–)-tuberostemonine.[83] The free secondary amine of **139** was acylated with acryloyl chloride to provide diene **140**, which was subjected to ring closing metathesis with the second generation Grubb's catalyst[129] to give tricyclic **141** in an excellent 94% yield. The hydrogenation of **141** reduced the internal double bond to furnish **142** in 89% yield and deacetalization of **142** provided **143** in 96% yield.



Scheme 68. Synthesis of tricyclic compounds **142** and **143**

With the desired tricyclic compounds **142** and **143** in hand, we explored the fragmentation reactions using iodine and iodobenzene diacetate (Scheme 69). We observed that tricyclic **142** was stable under the standard reaction conditions (using 3 equiv. of iodine and 3 equiv. of iodobenzene diacetate at ambient temperature in dichloromethane solution), and most of the starting material was recovered after 1-day reaction time. Trials under more vigorous conditions such as reflux in toluene or dichloroethane solution led to extensive decomposition of **142** instead of controlled fragmentation. The tricyclic ketone **143**, in contrast, provided the desired fragmented product **145**[130] in 25% yield. It is noteworthy that there was no evidence for the formation of the undesired internally fragmented product during this reaction consistent with

our original strategy. After some attempts to optimize the fragmentation of **143**, we realized that the low yield of this reaction resulted from the instability of the product **145**. Although the reaction yield was not satisfactory, we did succeed in obtaining the desired product in the fragmentation reaction of the tricyclic derivative. Hence, we hope that this reaction can be applied in the synthesis of parvistemonine or other pyrrolidine alkaloids.



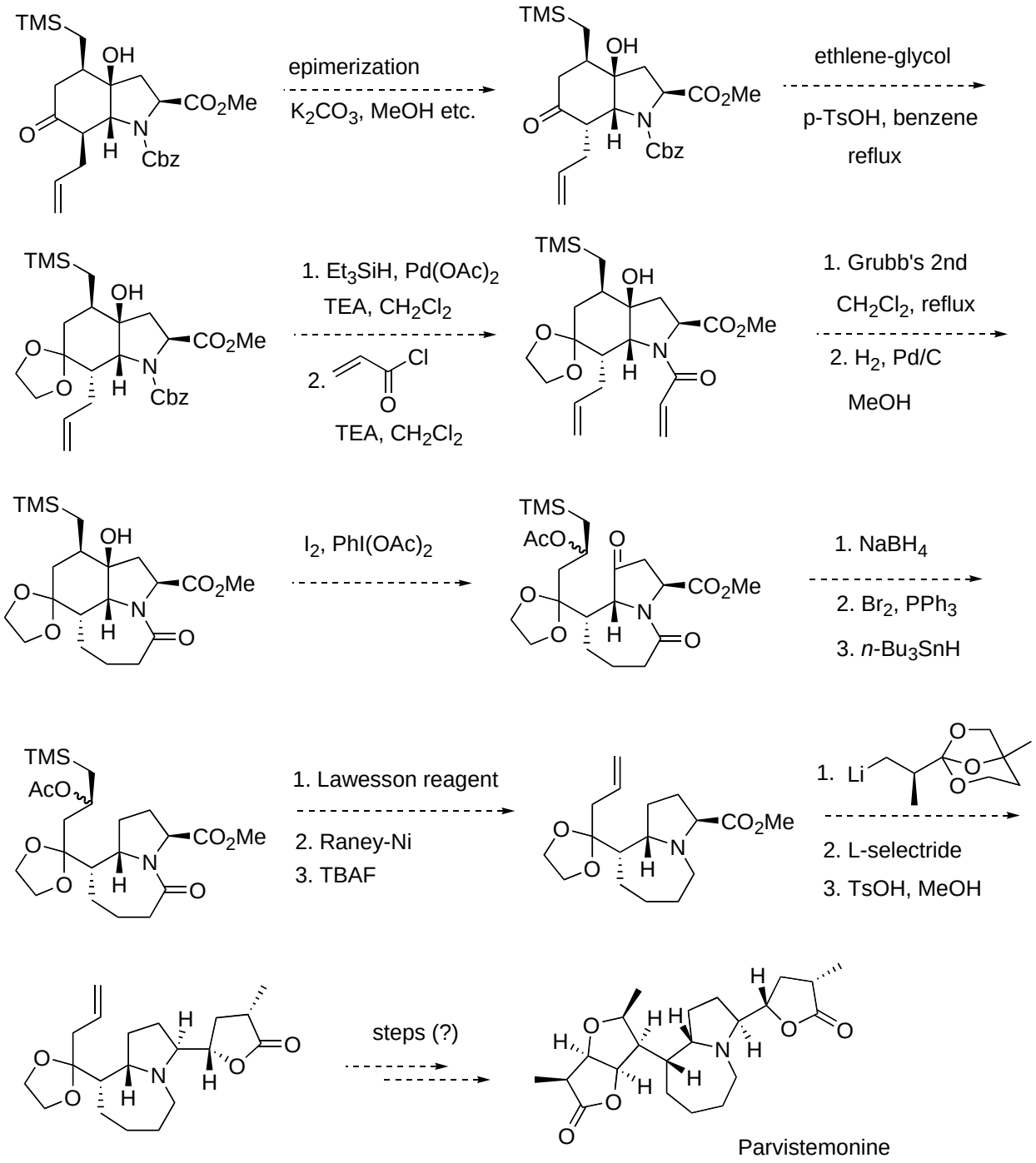
Scheme 69. Fragmentation reactions of tricyclic compounds **142** and **143**

2.4. Conclusion

Two model studies for a novel vinylogous azido alkoxy radical fragmentation reaction were successfully completed as described in Section 2.3.1. Although these model studies were still limited in terms of generality and applicability, they established the feasibility of the vinylogous azido alkoxy radical fragmentation reaction. This new fragmentation reaction is of fundamental mechanistic interest and also provides a new approach for the preparation of acrylamides, which are versatile intermediates in organic synthesis.

Attempts for a vinylogous azido alkoxy radical fragmentation in hydroindole systems were not successful mainly due to competing side reactions such as iodo-etherification and conjugate addition-elimination as stated in Section 2.3.2. Though it is not entirely clear why these side reactions were preferred over the desired fragmentations in hydroindoles, our findings illustrate that fragmentation reactions are highly substrate dependent. Thus, it is very difficult to make general predictions.

The introduction of a TMS-methylene group at the C(3) position in hydroindole systems directed the fragmentation to give the desired bond cleavage products, even though undesired side reactions or low reactivity was a problem. Since fragmentation reactions are very substrate-dependent, it is not yet clear if this fragmentation approach is feasible for the total synthesis of parvistemonine. However, the results in Section 2.3.3 are promising and we hope that this approach will bear fruit in the near future. Scheme 70 shows one possible approach to parvistemonine using the TMS-methylene group fragmentation strategy.



Scheme 70. A possible scheme for the completion of the synthesis of parvistemonine

2.5. Experimental Section

General Methods. All moisture-sensitive reactions were performed under an atmosphere of dry nitrogen and all glassware was dried in an oven prior to use. THF and ether were dried by distillation over Na/benzophenone and CH_2Cl_2 was dried by distillation over CaH_2 or filtered through a solvent filtration system. Pure isopulegol was obtained by chromatography on SiO_2 of technical grade isopulegol from Acros. Unless otherwise stated, all commercially available materials were used without purification. IR spectra were recorded neat using NaCl cells. NMR spectra were obtained at 300MHz/75MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless noted otherwise. High and low resolution mass spectra were determined by introduction with a direct insertion probe into a VG-70-70 HF spectrometer operating in the electron ionization (EI) mode.

(2*S*,3a*R*,7a*R*)-3a-Hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (1). Prepared according to literature procedures:[86] ^1H NMR (mixture of rotamers) δ 7.45-7.20 (m, 5 H), 6.84, 6.80 (2d, 1 H, *J* = 10.3 Hz), 6.03, 6.02 (2d, 1 H, *J* = 10.4 Hz), 5.23, 5.11 and 5.11, 5.02 (2AB, 2 H, *J* = 12.1 Hz), 4.60-4.40 (m, 2 H), 3.87, 3.57 (2s, 3 H), 3.33, 3.12 (2dd, 1 H, *J* = 16.4, 6.0 Hz), 2.70-2.50 (m, 1 H), 2.4-2.1 (m, 2 H).

(2*S*,3a*R*,7a*R*)-6-Oxo-3a-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (66). Prepared according to literature procedures:[94] ^1H NMR (mixture of rotamers) δ 7.40-7.30 (m, 5 H), 6.76, 6.74 (2d, 1 H, *J* = 10.3 Hz), 6.03, 6.00 (2d, 1 H, *J* = 10.4 Hz), 5.23, 5.18 and 5.19, 5.08 (2AB, 2 H, J = 12.2 Hz), 4.66-4.35 (m, 2 H), 3.74, 3.59 (2s, 3 H), 3.33, 3.12 (2dd, 1 H, *J* = 16.4, 6.0 Hz), 2.55-2.26 (m, 3 H), 0.13, 0.11 (2s, 9 H).

3-Trimethylsilanylbut-3-en-2-ol (69). Prepared according to literature procedures:[109] ^{1}H NMR δ 5.81 (dd, 1 H, *J* = 2.4, 1.5 Hz), 5.39 (dd, 1 H, *J* = 2.4, 1.0 Hz), 4.49 (q, 1 H, *J* = 6.0 Hz), 1.45 (br, 1 H, -OH), 1.30 (d, 3 H, *J* = 6.5 Hz), 0.15 (s, 9 H).

3-Trimethylsilanylbut-3-en-2-one (70). Prepared according to literature procedures:[109] ^{1}H NMR δ 6.50 (d, 1 H, *J* = 1.0 Hz), 6.17 (d, 1 H, *J* = 1.0 Hz), 2.29 (s, 3 H), 0.15 (s, 9 H).

(2*S,3*R**,6*S**)-6-Isopropenyl-3-methyl-2-(3-oxobutyl)-cyclohexanone (72).** Prepared according to literature procedures:[108] ^{1}H NMR δ 4.89 (s, 1 H), 4.66 (s, 1 H), 2.97 (dd, 1 H, *J* = 13.0, 5.1 Hz), 2.63-2.50 (m, 1 H), 2.40-2.25 (m, 1 H), 2.09 (s, 3 H), 2.06-1.53 (m, 8 H), 1.72 (s, 3 H), 1.06 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 211.3, 209.2, 143.5, 112.6, 58.4, 56.6, 41.3, 40.0, 34.5, 31.7, 29.9, 21.6, 20.7, 20.2.

(4a*S,5*R**,8*S**,8a*S**)-8a-Hydroxy-8-isopropenyl-5-methyloctahydronaphthalen-2-one (73).** Prepared according to a literature procedure:[108] ^{1}H NMR δ 4.90 (s, 1 H), 4.73 (s, 1 H), 2.45-2.20 (m, 4 H), 2.11-2.02 (m, 2 H), 1.88-1.62 (m, 3 H), 1.76 (s, 3 H), 1.60-1.15 (m, 4 H), 0.92 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 211.1, 146.9, 113.2, 75.9, 54.7, 53.4, 50.0, 41.3, 35.4, 32.0, 27.5, 25.9, 25.1, 20.3.

(2*R,4a*S**,5*R**,8*S**,8a*S**)-8-Isopropenyl-5-methyloctahydronaphthalene-2,8a-diol (74).** A solution of **73** (18 mg, 0.080 mmol) in EtOH (1 mL) was treated with $NaBH_4$ (5.0 mg, 0.13 mmol) and stirred for 2 h at 0 ^oC. The reaction mixture was quenched with saturated NH_4Cl solution, diluted with EtOAc (25mL) and washed with brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give **74** (14 mg, 78%) as a white solid: Mp 105-106 ^oC (CH_2Cl_2); IR (neat) 3430, 2943, 2927, 2863, 2844, 1620, 1454 cm^{-1}; ^{1}H NMR δ 4.90 (s, 1 H), 4.75 (s, 1 H), 3.97-3.86 (m, 1 H), 2.10-1.90 (m, 3 H), 1.82 (s, 3 H), 1.80-1.72 (m, 3 H),

1.50-1.31 (m, 4 H), 1.30-1.00 (m, 4 H), 0.88 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 148.1, 112.3, 73.4, 67.8, 54.7, 50.7, 46.9, 35.8, 35.7, 31.6, 27.4, 25.2, 23.8, 20.3; MS (EI) *m/z* (relative intensity) 224 (M^+, 5), 206 (24), 188 (18), 123 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1780.

(1*R,4*S**,4a*S**,6*R**,8a*S**)-4-Isopropenyl-6-methoxy-1-methyloctahydronaphthalen-4a-ol (75).** A solution of **74** (15 mg, 0.067 mmol) in THF (1 mL) was treated with NaH (60% in mineral oil, 6.0 mg, 0.15 mmol) and MeI (10 μL, 0.16 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, quenched with saturated aqueous NH_4Cl solution, diluted with EtOAc (50 mL) and washed with of brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give **75** (13 mg, 81%) as a white solid: Mp 100-102 ^{o}C; IR (neat) 3536, 2951, 2921, 2878, 1635, 1456, 1369 cm^{-1}; ^{1}H NMR δ 4.90 (s, 1 H), 4.75 (s, 1 H), 3.48-3.40 (m, 1 H), 3.34 (s, 3 H), 2.20-1.90 (m, 3 H), 1.82 (s, 3 H), 1.82-1.65 (m, 3 H), 1.50-1.35 (m, 3 H), 1.40-1.20 (m, 1 H), 1.18-1.02 (m, 3 H), 0.88 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 148.2, 112.3, 76.5, 73.2, 56.0, 54.7, 51.0, 43.7, 35.7, 31.8, 31.7, 27.5, 25.3, 23.7, 20.3; MS (EI) *m/z* (relative intensity) 238 (M^+, 6), 220 (18), 188 (22), 123 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1934.

(1*R,4*S**,4a*S**,6*R**,8a*R**)-6-Methoxy-1-methyl-4-(2-methyloxiranyl)-octahydronaphthalen-4a-ol (76).** A solution of **75** (14 mg, 0.060 mmol) in CH_2Cl_2 (1 mL) was treated with mCPBA (~70%, 40 mg, ~0.16 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (25 mL) and saturated aqueous $Na_2S_2O_3$ solution (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography

on SiO_2 (Hexanes/EtOAc, 5:1) to give **76** (14 mg, 93%) as a white solid: Mp 92-96 °C; IR (neat) 3505, 2953, 2924, 2851, 1444, 1371, 1093 cm^{-1}; ^1H NMR δ 3.57-3.49 (m, 1 H), 3.39 (s, 3 H), 2.67 (d, 1 H, *J* = 4.5 Hz), 2.62 (d, 1 H, *J* = 4.5 Hz), 2.47-2.43 (m, 1 H), 2.25-2.15 (m, 1 H), 2.03 (bs, 1 H, OH), 1.76-1.60 (m, 4 H), 1.38 (s, 3 H), 1.35-1.00 (m, 7 H), 0.81 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 76.0, 73.8, 59.4, 55.9, 55.1, 51.7, 51.1, 43.0, 35.2, 31.5 (2C), 24.5, 23.0, 22.2, 20.0; MS (EI) *m/z* (relative intensity) 254 (M^+, <1), 236 (6), 205 (12), 123 (25), 108 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1882.

(1*R,4*S**,4a*S**,6*R**,8a*S**)-4-(2-Azido-1-hydroxy-1-methylethyl)-6-methoxy-1-methyloctahydronaphthalen-4a-ol (77).** A solution of **76** (156 mg, 0.610 mmol) in MeOH (5 mL) and H_2O (2 mL) was treated with NaN_3 (397mg, 6.11 mmol) and NH_4Cl (326 mg, 6.09 mmol) at room temperature. The reaction mixture was heated at reflux for 1 d at 90 °C, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (30 mL) and washed with H_2O (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give a regioisomer (45 mg, 25%) and **77** (65 mg, 36%) as a white solid: Mp 102-106 °C; IR (neat) 3404, 2925, 2862, 2109, 1451, 1380, 1296, 1157, 1089 cm^{-1}; ^1H NMR δ 3.57 (d, 1 H, *J* = 12.0 Hz), 3.52-3.42 (m, 1 H), 3.37 (s, 3 H), 3.32 (d, 1 H, *J* = 12.0 Hz), 2.90-2.80 (m, 1 H), 2.20-2.10 (m, 1 H), 1.90-1.45 (m, 6 H), 1.40 (s, 3 H), 1.30-1.00 (m, 5 H), 0.87 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 76.5, 76.3, 75.8, 60.6, 55.8, 53.4, 51.6, 44.5, 35.7, 31.5, 31.3, 29.3, 23.6, 23.5, 20.3; MS (EI) *m/z* (relative intensity) 297 (M^+, <1), 275 (<1), 108 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{27}N_3O_3$ 297.2052, found 297.2050.

(1*R,4a*S**,6*R**,8a*R**)-4-(2-Azido-1-methylethylidene)-6-methoxy-1-methyloctahydronaphthalen-4a-ol. (80).** A solution of **77** (17 mg, 0.057 mmol) in CH_2Cl_2 (1

mL) was treated with Ms_2O (50 mg, 0.28 mmol) and TEA (0.040 mL, 0.28 mmol). The reaction mixture was stirred for 1 h at room temperature and directly purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give undesired **80** (7.0 mg, 40%) as the major product: ^{1}H NMR δ 3.8-3.7 (m, 1 H), 3.55 (d, 1 H, *J* = 12.5 Hz), 3.43 (d, 1 H, *J* = 12.4 Hz), 3.39 (s, 3 H), 3.32 (d, 1 H, *J* = 12.0 Hz), 2.25-2.12 (m, 1 H), 1.9-0.9 (m, 11 H), 1.75 (s, 3 H), 0.89 (d, 3 H, *J* = 6.5 Hz).

(1*R,2*S**,5*R**)-5-Methyl-2-(2-methyloxiranyl)-cyclohexanol (81).** A solution of pure (±)-isopulegol (1.5 g, 10 mmol) in CH_2Cl_2 (20 mL) was treated with mCPBA (~70 %, 3.4 g, ~ 14 mmol). The reaction mixture was stirred for 1 h at room temperature, diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ solution (50 mL×2) and saturated aqueous $Na_2S_2O_3$ solution (50 mL×2). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes /EtOAc, 2:1) to give **81** (1.2 g, 71 %) as a colorless oil (~1:1 diastereomeric ratio): IR (neat) 3428, 2918, 2863, 1642, 1457 cm^{-1}; ^{1}H NMR δ 3.63 (dt, 0.5 H, *J* = 4.4, 10.4 Hz), 3.40 (bs, 0.5 H, -OH), 3.24 (dt, 0.5 H, *J* = 4.2, 10.4 Hz), 2.90 (bs, 0.5 H, -OH), 2.85 (d, 0.5 H, *J* = 4.1 Hz), 2.61 (d, 0.5 H, *J* = 4.2 Hz), 2.53 (d, 0.5 H, *J* = 4.7 Hz), 2.48 (d, 0.5 H, *J* = 4.7 Hz), 2.00-1.75 (m, 2 H), 1.70-1.50 (m, 2 H), 1.49-0.99 (m, 3 H), 1.30 (s, 1.5 H), 1.26 (s, 1.5 H), 0.98-0.90 (m, 1 H), 0.87 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 71.3, 70.5, 60.2, 59.2, 52.8, 52.6, 51.2, 49.3, 43.6, 43.0, 33.9, 31.2, 31.0, 27.7, 27.6, 22.1, 20.5, 17.0; MS (EI) *m/z* (relative intensity) 152 ($[M–H_2O]^+$, 40), 123 (40), 109 (33), 95 (48), 84 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ (M–H_2O) 152.1201, found 152.1198.

(1*R,2*S**,5*R**)-2-(2-Azido-1-hydroxy-1-methylethyl)-5-methylcyclohexanol (82).** A solution of **63** (850 mg, 4.99 mmol) in H_2O (5 mL) and MeOH (15 mL) was treated with NaN_3 (1.6 g, 25 mmol) at room temperature. The reaction mixture was heated at reflux for 20 h, cooled to room temperature, diluted with EtOAc (50 mL) and washed with H_2O (25 mL). The organic

layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes /EtOAc, 2:1) to give **82** (560 mg, 56%) as a pale brown oil containing a trace of a minor diastereomer. Major diastereomer: IR (neat) 3296, 2912, 2866, 2094, 1595 cm^{-1}; ^1H NMR δ 5.18 (br, 1 H, -OH), 4.63 (br, 1 H, -OH), 3.69 (dt, 1 H, *J* = 4.2, 10.4 Hz), 3.19 (d, 1 H, *J* = 12.7 Hz), 3.08 (d, 1 H, *J* = 12.6 Hz), 1.95-1.80 (m, 1 H), 1.70-1.30 (m, 3 H), 1.12 (s, 3 H), 1.20-0.95 (m, 3 H), 0.85 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 77.0, 72.1, 59.4, 48.2, 44.6, 34.1, 31.2, 26.4, 22.0, 20.7; MS (EI) *m/z* (relative intensity) 214 ($[M+H]^+$, 2), 157 (90), 139 (95), 95 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{20}N_3O_2$ (M+H) 214.1556, found 214.1554.

(1*R,2*S**,5*R**)-2-(2-Azido-1-hydroxy-1-methyl-ethyl)-1-(2-methoxymethoxy)-5-methyl-cyclohexanol (83).** A solution of **82** (280 mg, 1.31 mmol) in CH_2Cl_2 (10 mL) was treated with MOMCl (0.20 mL, 2.6 mmol) and *i*-$PrNEt_2$ (0.45 mL, 2.6 mmol) at 0 °C. The reaction mixture was stirred for 17 h at room temperature and diluted with CH_2Cl_2 (50 mL). The solution was washed with brine (25 mL) and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes /EtOAc, 5:1) to give **83** (200 mg, 61%) as a colorless oil: IR (neat) 3469, 2952, 2927, 2096, 1463 cm^{-1}; ^1H NMR δ 5.04 (bs, 1 H, -OH), 4.89 (d, 1 H, *J* = 7.1 Hz), 4.64 (d, 1 H, *J* = 7.1 Hz), 3.77 (dt, 1 H, *J* = 4.0, 10.6 Hz), 3.45 (s, 3 H), 3.25 (d, 1 H, *J* = 12.6 Hz), 3.03 (d, 1 H, *J* = 12.6 Hz), 2.25-2.15 (m, 1 H), 1.90-1.80 (m, 1 H), 1.75-1.55 (m, 2 H), 1.50-1.30 (m, 1 H), 1.18 (s, 3 H), 1.20-1.00 (m, 3 H), 0.96 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 94.3, 78.7, 76.4, 59.2, 56.7, 47.5, 40.4, 34.1, 31.2, 26.8, 22.1, 21.1; MS (EI) *m/z* (relative intensity) 258 ($[M+H]^+$, 8), 212 (12); HRMS (EI) *m/z* calcd for $C_{12}H_{24}N_3O_3$ (M+H) 258.1818, found 258.1806.

(1*R,2*S**,5*R**)-2-(2-Azido-1-methylvinyl)-5-methylcyclohexanol (84).** A solution of **83** (1.3 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was treated with pyridine (2.0 mL, 25 mmol) and $SOCl_2$ (0.90 mL, 13 mmol) at 0 ^oC. The reaction mixture was stirred for 30 min at room temperature and diluted with CH_2Cl_2 (50 mL). The solution was washed with brine (25 mL) and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was diluted with MeOH (10 mL) and treated with concentrated HCl (2 mL). The reaction was stirred for 3 h and concentrated. The residue was diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes /EtOAc, 10:1) to give **84** (0.32 g, 33%) as a colorless oil: IR (neat) 3379, 2925, 2862, 2103, 1655, 1452, 1273, 1025 cm^{-1}; ^1H NMR δ 6.08 (s, 1 H), 3.43 (dt, 1 H, *J* = 3.8, 10.1 Hz), 2.05-1.90 (m, 1 H), 1.93 (bs, 1 H, -OH), 1.80-1.25 (m, 6 H), 1.55 (s, 3 H), 0.98-0.94 (m, 1 H), 0.90 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 128.3, 122.7, 70.1, 52.0, 43.1, 34.2, 31.5, 29.6, 22.2, 11.3; MS (EI) *m/z* (relative intensity) 195 (M^+, 5), 169 (7), 96 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{17}N_3O$ 195.1372, found 195.1363.

(1*S,2*R**,4*R**)-1-Isopropenyl-2-methoxymethoxy-4-methylcyclohexane (85).** A solution of pure isopulegol (7.1 g, 46 mmol) in CH_2Cl_2 (100 mL) was treated with MOMCl (5.2 mL, 69 mmol) and *i*-$PrNEt_2$ (12 mL, 69 mmol) at 0 ^oC. The reaction mixture was stirred for 16 h at room temperature and diluted with CH_2Cl_2 (200 mL). The solution was washed with brine (200 mL) and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **85** (8.2 g, 90%) as a colorless oil: IR (neat) 3077, 2923, 1651, 1461, 1382, 1212, 1156, 1105, 1034, 915 cm^{-1}; ^1H NMR δ 4.76 (s, 1 H), 4.75 (s, 1 H), 4.68 (d, 1 H, *J* = 7.0 Hz), 4.51 (d, 1 H, *J* = 7.0 Hz), 3.44 (dt, 1 H, *J* = 4.3, 10.6 Hz), 3.30 (s, 3 H), 2.10-1.90 (m, 2 H), 1.70 (s, 3 H), 1.65-1.20 (m, 5 H), 0.99-0.95 (m, 1 H), 0.87 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 147.7, 111.4, 95.0,

77.4, 55.3, 52.0, 41.4, 34.3, 31.6, 30.9, 22.3, 19.8; MS (EI) *m/z* (relative intensity) 198 (M^+, 2.5), 183 (3), 167 (63), 123 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{22}O_2$ 198.1620, found 198.1616.

(1*R,2*R**,4*R**)-1-Methyloxirane-2-methoxymethoxy-4-methylcyclohexane (86).** A solution of **85** (9.60 g, 48.4 mmol) in CH_2Cl_2 (100 mL) was treated with mCPBA (~70 %, 16.7 g, ~67.7 mmol). The reaction mixture was stirred for 1 h at room temperature, diluted with EtOAC (500 mL) and washed with saturated aqueous $NaHCO_3$ solution (125 mL×2) and saturated aqueous $Na_2S_2O_3$ solution (125 mL×2). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **86** (9.60 g, 93%) as a colorless oil (~1:1 diastereomeric ratio): IR (neat) 3036,2915, 2826, 1448, 1386, 1222, 1154, 1108, 1046 cm^{-1}; ^1H NMR δ 4.69 (d, 0.5 H, *J* = 7.0 Hz), 4.61 (d, 0.5 H, *J* = 7.0 Hz), 4.50 (d, 0.5 H, *J*= 6.9 Hz), 4.42 (d, 0.5 H, J = 6.7 Hz), 3.47-3.30 (m, 1 H), 3.30 (s, 1.5 H), 3.22 (s, 1.5 H), 2.60-2.58 (m, 0.5 H), 2.55-2.51 (m, 0.5 H), 2.40-2.30 (m, 1 H), 2.05-1.90 (m, 1 H), 1.80-1.70 (m, 0.5 H), 1.60-1.45 (m, 1.5 H), 1.40-1.20 (m, 2 H), 1.20 (s, 1.5 H), 1.12 (s, 1.5 H), 1.20-0.80 (m, 2 H), 0.79 (d, 3 H, J = 6.6 Hz); ^{13}C NMR δ 94.6, 94.5, 76.7, 58.1, 57.5, 56.4, 55.6, 55.4, 51.5, 50.6, 49.6, 40.8, 40.7, 33.9, 33.7, 31.3, 31.2, 28.0, 26.3, 22.1, 17.8, 16.3; MS (EI) *m/z* (relative intensity) 214 (M^+, <1), 183 (20), 169 (93); HRMS (EI) *m/z* calcd for $C_{12}H_{22}O_3$ 214.1569 , found 214.1564.

(2*S,5*R**)-2-(2-Azido-1-methylvinyl)-5-methylcyclohexanone (87).** A solution of **84** (0.87 g, 4.5 mmol) in CH_2Cl_2 (25 mL) was treated with Dess-Martin periodinane (3.2 g, 9.0 mmol). The reaction mixture was stirred for 20 h at room temperature, diluted with EtOAC (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give

87 (0.70 g, 81%) as a pale yellow oil: IR (neat) 2952, 2922, 2860, 2106, 1719, 1655, 1463, 1380, 1284 cm^{-1}; ^1H NMR δ 5.97 (s, 1 H), 2.87 (dd, 1 H, *J* = 12.8, 5.0 Hz), 2.43-2.37 (m, 1 H), 2.06 – 1.72 (m, 5 H), 1.61 (s, 3 H), 1.49-1.35 (m, 1 H), 1.03 (d, 3 H, *J* = 6.1 Hz); ^{13}C NMR δ 209.8, 125.9, 123.1, 56.0, 50.5, 35.2, 33.9, 31.2, 22.4, 13.9; MS (EI) *m/z* (relative intensity) 193 (M^+, 1), 94 (65), 84 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{15}N_3O$ 193.1215, found 193.1224.

(1*S,2*S**,4*R**)-2-(2-Azido-1-methyl-vinyl)-1,5-dimethyl-cyclohexanol (88).** A solution of **87** (120 mg, 0.621 mmol) in THF (5 mL) was treated with MeMgBr (3.0 M in THF, 0.31 mL, 0.93 mmol) at 0 °C under an N_2 atmosphere. The reaction mixture was stirred for 3 h at 0 °C, quenched with saturated aqueous NH_4Cl solution (5 mL), diluted with EtOAc (25 mL) and washed with water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 10:1) to give **70** (65 mg, 50%) as a pale yellow oil: IR (neat) 3492, 2950, 2920, 2865, 2103, 1647, 1449, 1384, 1290 cm^{-1}; ^1H NMR δ 6.05 (s, 1 H), 1.81-1.71 (m, 4 H), 1.70 (s, 3 H), 1.65-1.62 (m, 1 H), 1.46-1.40 (m, 1 H), 1.14 (s, 3 H), 1.08-1.00 (m, 2 H), 0.89 (d, 3 H, *J* = 6.2 Hz); ^{13}C NMR δ 129.8, 122.5, 71.9, 52.2, 49.4, 35.0, 29.8, 28.0, 27.7, 22.3, 15.9; MS (EI) *m/z* (relative intensity) 209 (M^+, 8), 161 (40), 146 (70), 108 (80), 96 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{19}N_3O$ 209.1528, found 209.1532.

2,6-Dimethyl-8-oxonon-2-enenitrile (89). A solution of **88** (63 mg, 0.30 mmol) in CH_2Cl_2 (10 mL) was treated with $PhI(OAc)_2$ (0.12 g, 0.36 mmol) and I_2 (91 mg, 0.36 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, diluted with EtOAC (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous $Na_2S_2O_3$ solution (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (Hexanes/EtOAc,

5:1) to give **89** (37 mg, 69%) as a pale yellow oil (~6:1, *E/Z* isomers). Major isomer: IR (neat) 2959, 2922, 2873, 2214, 1704, 1637, 1432, 1460, 1368, 1161 cm^{-1}; ^1H NMR δ 6.31 (dt, 1 H, *J* = 7.5, 1.3 Hz), 2.40 (dd, 1 H, J = 16.5, 6.1 Hz), 2.28 (dd, 1 H, *J* = 16.5, 7.3 Hz), 2.2-2.1 (m, 2 H), 2.13 (s, 3 H), 2.10-1.95 (m, 1 H), 1.85 (s, 3 H), 1.50-1.35 (m, 1 H), 1.30-1.20 (m, 1 H), 0.91 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 208.3, 148.1, 120.7, 109.4, 50.9, 35.1, 30.7, 28.8, 26.2, 19.6, 14.9; MS (EI) *m/z* (relative intensity) 179 (M^+, 6), 164 (10), 122 (90), 95 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1315.

(2*S,3*R**,6*S**)-6-(2-Azido-1-methylvinyl)-3-methyl-2-(3-oxobutyl)-cyclohexanone (91).** According to the procedure described for the synthesis of **72, 91** (350 mg, 26%) was prepared from **87** (1.0 g, 5.2 mmol) and **70** (1.1 g, 7.7 mmol) as a pale yellow oil: IR (neat) 2952, 2931, 2866, 2100, 1707, 1652, 1441, 1364, 1281 cm^{-1}; ^1H NMR δ 5.95 (s, 1 H), 2.92 (dd, 1 H, *J* = 13.0, 5.1 Hz), 2.6-2.5 (m, 1H), 2.45-2.30 (m, 1 H), 2.11 (s, 3 H), 2.15-1.50 (m, 8 H), 1.60 (s, 3 H), 1.08 (d, 3 H, *J* = 5.8 Hz); ^{13}C NMR δ 211.1, 209.2, 125.9, 122.9, 56.7, 56.6, 41.3, 39.8, 34.5, 31.6, 30.0, 20.7, 20.2, 14.2; MS (EI) *m/z* (relative intensity) 235 ($[M–N_2]^+$, 21), 201 (40), 158 (65), 109 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{21}NO$ (M–N_2) 2351572, found 235.1561.

(4a*S,5*R**,8*S**,8a*S**)-8a-Hydroxy-8-(2-azido-1-methylvinyl)-5-methyl-octahydronaphthalene-2-one (92).** According to the procedure described for the synthesis of **73, 92** (340 mg, 97%) was prepared from **91** (350 mg, 1.33 mmol) as a pale yellow oil: IR (neat) 3472, 2956, 2931, 2872, 2103, 1722, 1642, 1287 cm^{-1}; ^1H NMR δ 6.02 (s, 1 H), 2.50-2.20 (m, 3 H), 2.15-1.75 (m, 6 H), 1.65 (s, 3 H), 1.60-1.10 (m, 4 H), 0.94 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 210.9, 128.3, 123.8, 76.9, 54.1, 53.3, 50.5, 41.4, 35.5, 32.2, 27.4, 26.0, 20.3, 16.3; MS (EI) *m/z* (relative intensity) 263 (M^+, 0.5), 235 (2); HRMS (EI) m/z calcd for $C_{14}H_{21}N_3O_2$ 263.1634, found 263.1642.

(2*R,4a*S**,5*R**,8*S**,8a*S**)-8-(2-Azido-1-methylvinyl)-5-methyloctahydro-naphthalene-2,8a-diol (93).** $CeCl_3 \bullet 7H_2O$ (300 mg, 0.805 mmol) was added to a solution of **92** (190 mg, 0.722 mmol) in THF (5 mL) and MeOH (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min, cooled to 0 ^oC, reacted with $NaBH_4$ (30 mg, 0.79 mmol), stirred for 30 min, diluted with EtOAc (25 mL) and washed with brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give **93** (70 mg, 37%) as a pale yellow solid: Mp 107-111 °C (CH_2Cl_2); IR (neat) 3394, 2928, 2872, 2106, 1652, 1454, 1380, 1284 cm^{-1}; ^1H NMR δ 6.02 (s, 1 H), 3.95-3.85 (m, 1 H), 2.05-1.92 (m, 2H), 1.88-1.70 (m, 4 H), 1.67 (s, 3 H), 1.60 (br, 1 H, -OH), 1.45-1.30 (m, 2 H), 1.30 (m, 3 H), 1.15-1.00 (m, 2 H), 0.88 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 129.2, 122.7, 74.2, 67.6, 53.8, 50.7, 46.3, 35.5, 35.4, 31.6, 26.9, 23.6, 20.1, 15.8; MS (EI) *m/z* (relative intensity) 265 (M^+, 0.5), 237 (2), 219 (40), 123 (40), 96 (100); HRMS (EI) m/z calcd for $C_{14}H_{23}N_3O_2$ 265.1790, found 263.1801.

(1*R,4*S**,4a*S**,6*R**,8a*S**)-4-(2-Azido-1-methylvinyl)-6-methoxy-1-methyloctahydronaphthalen-4a-ol (94).** A solution of **93** (62 mg, 0.23 mmol) in THF (5 mL) was treated with 60% NaH (96 mg, 1.2 mmol) and MeI (0.15 mL, 1.2 mmol). The reaction mixture was stirred for 6 h at room temperature and quenched with saturated aqueous NH_4Cl solution (5 mL), diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give **94** (48 mg, 75%) as a pale yellow solid: Mp 106-109 °C; IR (neat) 3487, 2928, 2869, 2100, 1648, 1448, 1380, 1290, 1101 cm^{-1}; ^1H NMR δ 6.00 (s, 1 H), 3.45-3.35 (m, 1 H), 3.34 (s, 3 H), 2.20-2.10 (m, 1 H), 2.01 (ddd, 1 H, *J* = 13.0, 4.2, 2.2 Hz), 1.86-1.70 (m, 4 H), 1.66 (s, 3 H), 1.45-0.97 (m, 7 H), 0.88 (d, 3 H, *J* = 6.4 Hz); ^{13}C

NMR δ 129.1, 122.7, 76.2, 74.0, 56.0, 53.8, 51.0, 43.3, 35.4, 31.6 (2C), 27.0, 23.4, 20.1, 15.8; MS (EI) *m/z* (relative intensity) 279 (M^+, 2), 251 (3), 236 (2), 123 (75), 96 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{25}N_3O_2$ 279.1947, found 279.1942.

6-{(1*S,4*R**)-4-Methoxy-2-oxo-cyclohexyl)}-2-methyl-hept-2-enenitrile (95).** To a solution of **94** (42 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was added $PhI(OAc)_2$ (58 mg, 0.18 mmol) and I_2 (46 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, diluted with EtOAc (25 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (Hexanes/EA, 10:1) to give **95** (19 mg, 51%) as a pale yellow oil (~1:1.5, *E/Z* mixture): IR (neat) 2925, 2878, 2217, 1713, 1456, 1373, 1237, 1101 cm^{-1}; ^1H NMR δ 6.33 (t, 0.4 H, *J* = 7.3 Hz), 6.14 (t, 0.6 H, *J* = 7.5 Hz), 3.50-3.35 (m, 1 H), 3.35 (s, 3 H), 2.80 (dd, 1 H, *J* = 13.2, 2.7 Hz), 2.40-1.95 (m, 6 H), 1.92 (s, 1.8 H), 1.86 (s, 1.2 H), 1.70-1.55 (m, 2 H), 1.50-1.20 (m, 3 H), 0.87 (d, 1.8 H, *J* = 6.5 Hz), 0.86 (d, 1.2 H, *J* = 6.5 Hz); ^{13}C NMR δ 209.6, 209.4, 148.2, 120.8, 118.2, 109.5, 78.9, 56.2, 54.5, 54.2, 48.2, 33.8, 35.6, 30.7, 29.5, 30.3, 22.4, 22.2, 20.1, 15.9, 14.9; MS (EI) *m/z* (relative intensity) 249 (M^+, <1), 234 (1), 217 (1), 96 (90); HRMS (EI) m/z calcd for $C_{15}H_{23}NO_2$ 249.1729, found 249.1732.

(2*S*,3a*R*,4*R*,7a*R*)-3a-Methoxymethoxy-6-oxo-4-vinyl-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (96). To a solution of hydroindole **1** (1.43 g, 4.14 mmol) and CuI (237 mg, 1.24 mmol) in THF (40 mL) was added vinylmagnesium bromide (1.0 M in THF, 8.3 mL) at –20 °C. The reaction mixture was warmed to room temperature for 3 h, quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude

residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give conjugate addition product (700 mg, 45%) as a white foam. The conjugate addition product (700 mg, 1.87 mmol) was then dissolved in CH_2Cl_2 (10 mL) and treated with MOMCl (0.43 mL, 5.7 mmol) and diisopropylethyl amine (0.99 mL, 5.7 mmol) at room temperature. The reaction mixture was stirred for 5 d at room temperature, diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **96** (195 mg, 25%) as a white foam and its diastereomer **105** (225 mg, 29%) along with 263 mg of recovered starting material. **96**: $[\alpha]_D$ −15.0 (*c* 1.0, CH_2Cl_2); IR (neat) 2955, 2904, 1752, 1711, 1414, 1347, 1219, 1025 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.00-5.80 (m, 1 H), 5.25-4.95 (m, 4 H), 4.80-4.65 (m, 2 H), 4.65-4.35 (m, 2 H), 3.70, 3.55 (2s, 3 H), 3.36, 3.35 (2s, 3 H), 3.30-3.10 (m, 1 H), 3.00-2.70 (m, 2 H), 2.60-2.20 (m. 4 H); ^1H NMR (DMSO-d_6 at 373 °K) δ 7.50-7.30 (m, 5 H), 6.10-5.90 (m, 1 H), 5.30-5.15 (m, 4 H), 4.90-4.75 (m, 2 H), 4.65-4.50 (m, 2 H), 3.70 (s, 3 H), 3.40 (s, 3 H), 3.45-3.30 (m, 1 H), 3.10-2.95 (m, 1 H), 2.85-2.65 (m, 2 H), 2.65-2.35 (m, 2 H), 2.18 (d, 1 H, *J* = 14.3 Hz); ^{13}C NMR (mixture of rotamers) δ 207.7, 206.9, 172.0, 171.3, 154.7, 154.6, 136.2, 135.5, 128.7, 128.5, 128.3, 128.2, 117.5, 117.4, 91.8, 91.6, 85.6, 85.1, 67.7, 67.3, 60.9, 60.0, 58.0, 57.8, 56.5, 52.4, 52.2, 44.7, 43.2, 41.6, 41.1, 36.2, 35.1; MS (EI) *m/z* (relative intensity) 355 ($[M- C_2H_6O_2]^+$, 0.25), 252 (15), 91 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{21}NO_5$ ($M-C_2H_6O_2$) 355.1420, found 355.1424.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-6-Hydroxy-3a-methoxymethoxy-4-vinyl-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (97). A solution of 96 (720 mg, 1.72 mmol) in THF-MeOH (1:1, 20 mL) was treated with $CeCl_3 \bullet 7H_2O$ (640 mg, 1.72 mmol) and $NaBH_4$ (196 mg, 5.11 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, diluted

with EtOAc (150 mL) and washed with brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:2) to give **97** (606 mg, 84%) as a white foam: $[\alpha]_D$ −19.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3411, 2955, 1762, 1685, 1634, 1414, 1347, 1199, 1020 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.05-5.95 (m, 1 H), 5.25-5.00 (m, 4 H), 4.79, 4.77 (2d, 1 H, *J* = 17.7 Hz), 4.60, 4.58 (2d, 1 H, *J* = 17.7 Hz) 4.43, 4.37 (2d, 1 H, *J* = 9.7 Hz), 4.40-4.25 (m, 1 H), 3.80-3.60 (m, 1 H), 3.69, 3.56 (2s, 3 H), 3.37, 3.35 (2s, 3 H), 2.90-2.30 (m, 4 H), 2.15-1.90 (m, 2 H), 1.40-1.20 (m, 1 H), 1.15-1.10 (m, 1 H); ^1H NMR (DMSO-d6, 373 °K) δ 7.50-7.30 (m, 5 H), 6.02-5.90 (m, 1 H), 5.25-5.05 (m, 4 H), 4.75 (d, 1 H, *J* = 6.9 Hz), 4.64 (d, 1 H, *J* = 6.9 Hz) 4.45 (d, 1 H, *J* = 10.0 Hz), 4.33 (bs, 1 H, -O*H*), 4.27 (dd, 1 H, *J* = 10.5, 4.3 Hz), 3.70-3.55 (m, 1 H), 3.62 (s, 3 H), 3.33 (s, 3 H), 2.90-2.70 (m, 1 H), 2.65-2.40 (m, 2 H), 2.00-1.80 (m, 2 H), 1.35 (dd, 1 H, *J* = 24.2, 12.1 Hz), 1.14 (dd, 1 H, J = 23.1, 11.8 Hz); ^{13}C NMR (mixture of rotamers) δ 171.9, 171.3, 154.7, 154.3, 137.0, 136.8, 136.6, 136.5, 128.6, 128.5, 128.2, 128.0, 116.1, 116.0, 91.2, 85.3, 84.5, 67.3, 67.2, 66.6, 66.4, 58.6, 58.5, 56.9, 56.8 , 56.4, 56.3, 52.2, 52.0, 40.7, 40.6, 39.8, 39.3, 36.9, 36.5, 36.2, 35.0; MS (EI) *m/z* (relative intensity) 419 (M^+, 0.01), 387 (0.1), 357 (8), 254 (7), 224 (8), 91 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{29}NO_7$ 419.1944, found 419.1938.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-6-Methoxy-3a-methoxymethoxy-4-vinyl-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (98). A solution of **97** (434 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) was treated with MeOTf (0.35 mL, 3.1 mmol) and 2,6-dibutyl-4-dimethyl-pyridine (637 mg, 3.10 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, diluted with EtOAc (50 mL) and washed with brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was

purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **98** (430 mg, 96%) as a white foam: $[\alpha]_D$ −7.8 (*c* 1.0, CH_2Cl_2); IR (neat) 2950, 2822, 1762, 1705, 1403, 1358, 1209, 1086 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.05-5.95 (m, 1 H), 5.25-5.00 (m, 4 H), 4.81, 4.78 (2d, 1 H, *J* = 17.5 Hz), 4.60, 4.56 (2d, 1 H, *J* = 17.5 Hz) 4.43, 4.37 (2d, 1 H, *J* = 9.7 Hz), 4.40-4.25 (m, 1 H), 3.69, 3.56 (2s, 3 H), 3.37, 3.36 (2s, 3 H), 3.34, 3.28 (2s, 3 H), 3.30-3.10 (m, 1 H), 3.00-2.55 (m, 2 H), 2.45-2.30 (m. 1 H), 2.15-2.00 (m, 2 H), 1.35-1.20 (m, 1 H), 1.10-0.90 (m, 1 H); ^1H NMR (DMSO-d6, 373 °K) δ 7.50-7.30 (m, 5 H), 6.05-5.90 (m, 1 H), 5.30-5.05 (m, 4 H), 4.77 (d, 1 H, *J* = 7.0 Hz), 4.66 (d, 1 H, *J* = 6.8 Hz) 4.46 (d, 1 H, *J* = 9.9 Hz), 4.27 (dd, 1 H, *J* = 10.8, 6.3 Hz), 3.70-3.50 (m, 1 H), 3.62 (s, 3 H), 3.34 (s, 3 H), 3.29 (s, 3 H), 2.85-2.70 (m, 1 H), 2.65-2.40 (m, 2 H), 2.05-1.85 (m, 2 H), 1.31 (dd, 1 H, *J* = 23.5, 11.9 Hz), 1.14 (dd, 1 H, J = 23.5, 11.9 Hz); ^{13}C NMR (mixture of rotamers) δ 171.9, 171.3, 154.6, 154.2, 137.0, 136.8, 136.7, 136.6, 128.6, 128.5, 128.2, 128.0, 116.0, 115.9, 91.3, 85.5, 84.6, 75.3, 67.3, 67.0, 58.5, 58.4, 56.9, 56.8, 56.4, 56. 3, 56.2, 52.2, 52.0, 40.8, 40.7, 36.5, 36.2, 35.5, 35.0, 33.8, 33.4; MS (EI) *m/z* (relative intensity) 433 (M^+, 0.1), 371 (0.2), 236 (12), 146 (5), 91 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{31}NO_7$ 433.2100, found 433.2121.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-6-Methoxy-3a-methoxymethoxy-4-oxiranyl-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (99). A solution of **98** (505 mg, 1.16 mmol) in CH_2Cl_2 (11 mL) was treated with mCPBA (70%, 1.15 g, 4.66 mmol) at room temperature. The reaction mixture was stirred for 18 h at room temperature, diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (2×50 mL) and saturated aqueous $Na_2S_2O_3$ solution (2×50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give **99** (518 mg, 99%, ~1:1 inseparable mixture of diastereomers) as a white foam: $[\alpha]_D$ −24.1 (*c* 1.0, CH_2Cl_2); IR (neat) 2950, 1759, 1703, 1407, 1347, 1207, 1084,

1025 cm^{-1}; ^1H NMR (mixture of rotamers and diastereomers) δ 7.45-7.25 (m, 5 H), 5.30-5.00 (m, 2 H), 4.85-4.70 (m, 1 H), 4.70-4.20 (m, 3 H), 3.70, 3.57 (2s, 3 H), 3.39, 3.37, 3.34, 3.33 (4s, 3 H), 3.30, 3.24 (2s, 3 H), 3.20-3.05 (m, 2 H), 2.95-2.00 (m, 6 H), 1.95-1.80 (m, 1 H), 1.20-0.80 (m, 2 H); ^1H NMR (DMSO-d6, 373 °K, mixture of diastereomers) δ 7.50-7.30 (m, 5 H), 5.25-5.05 (m, 2 H), 4.85-4.65 (m, 2 H), 4.60-4.45 (m, 1 H), 4.40-4.20 (m, 1 H), 3.64 (s, 3 H), 3.36, 3.34 (2s, 3 H), 3.27 (s, 3 H), 3.15-3.00 (m, 1 H), 2.80-2.50 (m, 5 H), 2.35-2.05 (m, 2 H), 2.00-1.80 (m, 1 H), 1.50-1.05 (m, 2 H); ^{13}C NMR (mixture of rotamers and diastereomers) δ 171.8, 171.1, 154.6, 154.1, 136.5 (1C), 128.6, 128.5, 128.2, 128.1, 128.0 (5C), 91.5, 91.4 (1C), 85.2, 84.8, 84.4, 83.9 (1C), 75.1 (1C), 67.6, 67.3, 67.2 (1C), 58.7, 58.5, 58.4 (1C), 57.1, 57.0 (1C), 56.4 (1C), 56.3, 55.8 (1C), 52.2, 52.0 (1C), 51.7 (1C), 45.0, 44.8, 44.0 (1C), 39.0, 38.8, 38.4 (1C), 36.7, 36.3 (1C), 35.7, 35.5, 35.3, 35.1 (1C), 29.7, 29.4, 29.3 (1C); MS (EI) *m/z* (relative intensity) 390 ($[M–CO_2CH_3]^+$, 1.2), 346 (1.6), 328 (1.3), 300 (45), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{28}NO_6$ ($M–CO_2CH_3$) 390.1917, found 390.1926.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-4-(2-Azido-1-hydroxy-ethyl)-6-methoxy-3a-methoxymethoxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (100). A solution of **99** (510 mg, 1.13 mmol) in DMF (5.5 mL) was treated with NaN_3 (735 mg, 11.3 mmol) and NH_4Cl (604 mg, 11.3 mmol) at room temperature. The reaction mixture was heated at reflux for 18 h, cooled to room temperature, diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (2×50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **100** (490 mg, 88%, ~1:1 mixture of diastereomers) as a white foam: $[\alpha]_D$ −14.0 (*c* 0.5, CH_2Cl_2); IR (neat) 3460, 2951, 2827, 2101 (N_3), 1759, 1704 cm^{-1}; ^1H NMR (mixture of rotamers and diastereomers) δ 7.45-7.25 (m, 5 H), 5.30-5.00 (m, 2 H), 5.00-4.75 (m, 1 H), 4.60-

4.30 (m, 3 H), 4.25-4.10 (m, 1 H), 3.90-3.10 (m, 3 H), 3.71, 3.70, 3.59, 3.57 (4s, 3 H), 3.47, 3.27, 3.26 (3s, 3 H), 3.33, 3.32 (2s, 3 H), 2.95-2.20 (m, 4 H), 2.10-1.80 (m, 2 H), 1.55-1.35, 1.10-0.80 (m, 2 H); ^{13}C NMR (mixture of rotamers and diastereomers) δ 172.2, 171.6, 171.5, 170.9, 154.5, 154.3, 154.0, 136.6, 136.5, 136.3, 128.6-127.8, 92.0, 91.1, 86.8, 85.8, 85.3, 84.5, 75.6, 74.7, 74.6, 73.8, 73.7, 67.6, 67.4, 67.3, 67.1, 58.7, 58.5, 58.0, 57.8, 57.1, 57.0, 56.4, 56.2, 54.3, 54.2, 52.3, 52.1, 40.3, 40.2, 40.0, 37.0, 36.3, 36.0, 35.8, 35.4, 35.0, 34.9, 32.0, 31.7, 28.1, 27.9; MS (EI) *m/z* (relative intensity) 402 ([M–C_7H_7]$^+$, 0.5), 371 (1.5), 344 (5), 300 (7.5), 91 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{26}N_4O_8$ (M–C_7H_7) 402.1750, found 402.1749.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-4-(2-Azido-1-methanesulfonyloxy-ethyl)-6-methoxy-3a-methoxymethoxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (101). A solution of **100** (485 mg, 0.985 mmol) in CH_2Cl_2 (5 mL) was treated with MsCl (564 mg, 4.92 mmol) and pyridine (0.80 mL, 9.9 mmol) at room temperature. The reaction mixture was stirred for 2 d at room temperature, diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **101** (531 mg, 94%, ~1:1 mixture of diastereomers) as a white foam: $[\alpha]_D$ –28.7 (*c* 1.0, CH_2Cl_2); IR (neat) 2951, 2107 (N_3), 1759, 1701, 1413 cm^{-1}; ^{1}H NMR (mixture of rotamers and diastereomers) δ 7.45-7.25 (m, 5 H), 5.30-4.90 (m, 3 H), 4.85-4.70 (m, 1 H), 4.70-4.15 (m, 3 H), 3.90-3.10 (m, 3 H), 3.72, 3.71, 3.59, 3.58 (4s, 3 H), 3.36, 3.34 (2s, 3 H), 3.33, 3.27, 3.26 (3s, 3 H), 3.11 (s, 3 H), 3.00-2.00 (m, 5 H), 1.50-1.20 (m, 1 H), 1.10-0.90 (m, 1 H); ^{13}C NMR (mixture of rotamers and diastereomers) δ 171.6, 171.5, 170.9, 154.3, 154.1, 154.0, 136.5, 128.6, 128.5, 128.2, 128.0, 127.9, 91.6, 91.3, 84.5, 84.2, 83.8, 83.3, 82.1, 81.6, 75.2, 75.0, 67.4, 67.3, 58,9, 58.5, 57.2, 57.0,

56.6, 56.4, 53.9, 53.6, 53.4, 52.3, 52.1, 41.1, 40.9, 40.4, 40.1, 39.5, 39.1, 37.2, 36.2, 36.0, 35.8, 35.3, 35.2, 34.6, 31.7, 31.0, 29.4, 29.0.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-4-(2-Azidovinyl)-6-methoxy-3a-methoxymethoxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (102). A solution of **101** (0.29 g, 0.51 mmol) in benzene (10 mL) was treated with DBU (0.38 mL, 2.5 mmol) at room temperature. The reaction mixture was heated at reflux for 20 h, cooled to room temperature, diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **102** (42 mg, 17%, ~2:1 *E/Z* mixture of isomers) as a white foam and 198 mg of recovered **101** (68%). **102**: ^{1}H NMR (mixture of rotamers and *E/Z* isomers) δ 7.45-7.25 (m, 5 H), 6.24 (d, 0.33 H, *J* = 7.5 Hz), 5.94 (d, 0.67 H, *J* = 13.7 Hz), 5.43 (dd, 0.67 H, *J* = 13.7,7.0 Hz), 5.30-5.00 (m, 2 H), 4.90-4.20 (m, 4.33 H), 3.40-3.05 (m, 1 H), 3.72, 3.58 (2s, 3 H), 3.37, 3.34 (2s, 3 H), 3.27 (s, 3 H), 3.00-2.30 (m, 3 H), 2.20-1.90 (m, 2 H), 1.30-1.10 (m, 1 H), 1.05-0.80 (m, 1 H); ^{13}C NMR (mixture of rotamers and *E/Z* isomers) δ 171.8, 171.2, 154.7, 154.5, 154.1, 136.7, 136.6, 136.5, 128.6-128.0 (6C), 118.7, 118.6, 91.5, 91.3, 85.6, 85.1, 84.8, 84.1, 75.1, 75.0, 67.4, 67.2, 58.2, 58.1, 56.7, 56.4, 56.3, 56.2, 52.2, 52.1, 38.5, 36.4, 36.2, 35.5, 35.0, 34.8, 34.3.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-4-(2-Azidovinyl)-6-methoxy-3a-hydroxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (103). A solution of **102** (92 mg, 0.19 mmol) in MeOH (2 mL) was treated with concentrated HCl (0.2 mL) at 0 °C. The reaction mixture was stirred for 2 h, diluted with EtOAc (20 mL) and washed with H_2O (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **103** (75 mg, 90%, ~2:1 *E/Z* mixture) as a

white foam: ^{13}C NMR (mixture of rotamers and *E/Z* isomers) δ 175.6, 175.4, 175.2, 175.0, 154.7, 153.7, 136.3, 136.1, 136.0, 128.7-127.9 (6C), 118.7, 118.6, 118.5, 118.4, 80.2, 80.1, 79.3, 79.2, 75.3, 67.6, 65.4, 65.2, 57.1, 56.4, 56.3, 53.3, 53.2, 52.9, 52.8, 41.2, 41.1, 36.3, 35.3, 34.2, 33.7. Further separation by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) provided pure *E* and *Z* isomer. **(*E*)-isomer**: ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.00 (d, 1 H, *J* = 13.4 Hz), 5.39, 5.37 (2dd, 1 H, J = 13.6, 7.4 Hz), 5.35-4.98 (m, 2 H), 4.57 (s, 1 H, -O*H*), 4.40-4.30 (m, 1 H), 3.92, 3.87 (2dd, 1 H, *J* = 11.6, 6.3 Hz), 3.84-3.54 (s, 3 H), 3.36, 3.32 (2s, 3 H), 3.40-3.20 (m, 1 H), 2.80-2.30 (m, 3 H), 2.15-2.00 (m, 1 H), 1.85-1.70 (m, 1 H), 1.35-1.15 (m, 1 H), 1.10-0.85 (m, 1 H); **(*Z*)-isomer**: ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.30 (d, 1 H, *J* = 7.5 Hz), 5.25-4.98 (m, 2 H), 4.80-4.65 (m, 1 H), 4.45-4.30 (m, 1 H), 4.14 (s, 1 H, -O*H*), 3.92, 3.87 (2dd, 1 H, *J* = 11.5, 6.1 Hz), 3.81, 3.53 (2s, 3 H), 3.36, 3.32 (2s, 3 H), 3.40-3.20 (m, 1 H), 3.10-2.90 (m, 1 H), 2.80-2.40 (m, 2 H), 2.05-1.95 (m, 1 H), 1.87, 1.83 (2d, 1 H, *J* = 5.3 Hz), 1.35-1.15 (m, 1 H), 1.10-0.85 (m, 1 H).

2-Azido-3-iodo-5-methoxyoctahydro-1-oxa-7-aza-cyclopenta[*d*]indene-7,8-dicarboxylic acid 7-benzyl ester 8-methyl ester (104). To a solution of **103** (~2:1 *E/Z* mixture of isomers, 75 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was added iodobenzene diacetate (67 mg, 0.21 mmol) and iodine (53 mg, 0.21 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **104** (75 mg, 77%, ~3:1 mixture of diastereomers) as a white foam. Further separation by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) provided pure major diastereomer: IR (neat) 2950, 2107 (N_3), 1758, 1704,

1414, 1351, 1210, 1094 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 5.72 (d, 1 H, *J* = 6.1 Hz), 5.30-5.00 (m, 2 H), 4.59, 4.52 (2d, 1 H, *J* = 9.5 Hz), 4.10, 4.00 (2dd, 1 H, *J* = 9.1, 6.7 Hz), 3.81, 3.65 (2s, 3 H), 3.65-3.55 (m, 1 H), 3.45-3.30 (m, 1 H), 3.34, 3.28 (2s, 3 H), 2.80-2.45 (m, 2 H), 2.45-2.30 (m, 1 H), 2.28-1.90 (m, 2 H), 1.35-1.10 (m, 2 H); ^{13}C NMR (mixture of rotamers) δ 171.9, 171.4, 154.3, 153.9, 136.4, 128.7-128.1, 100.4, 88.7, 87.9, 67.6, 67.3, 60.7, 60.3, 57.8, 56.8, 56.6, 52.9, 52.7, 50.8, 36.6, 35.2, 34.1, 32.8, 28.8, 28.3, 23.1; MS (EI) *m/z* (relative intensity) 557 ($[M+1]^+$, 0.2), 497 (15), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{26}N_4O_6I$ (M+H) 557.0897, found 557.0924.

(2*S*,3a*R*,4*R*,7a*R*)-3a-Methoxymethoxy-6-oxo-4-vinyl-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (105). Obtained as a diastereomer in the synthesis of **96. 105**: $[\alpha]_D$ –46.6 (*c* 1.0, CH_2Cl_2); IR (neat) 3062, 2955, 1747, 1705, 1639, 1414, 1342, 1214, 1020 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.00-5.80 (m, 1 H), 5.25-4.90 (m, 4 H), 4.80-4.65 (m, 2 H), 4.40-4.25 (m, 2 H), 3.70, 3.44 (2s, 3 H), 3.32 (s, 3 H), 3.05-2.85, 2.75-2.50 (m, 4 H), 2.45-2.20 (m. 3 H); ^1H NMR (DMSO-d_6 at 373 °K) δ 7.50-7.30 (m, 5 H), 6.10-5.95 (m, 1 H), 5.35-5.10 (m, 4 H), 4.85-4.70 (m, 2 H), 4.57 (dd, 1 H, *J* = 8.5, 5.3 Hz), 4.35 (dd, 1 H, *J* = 7.0, 6.8 Hz) 3.69 (s, 3 H), 3.38 (s, 3 H), 3.45-3.30 (m, 1 H), 3.10-2.80 (m, 2 H), 2.70-2.50 (m, 3 H), 2.50-2.30 (m, 2 H); ^{13}C NMR (mixture of rotamers) δ 208.5, 208.3, 172.4, 171.0, 155.1, 154.4, 136.0, 135.9, 135.7, 128.7, 128.6, 128.5, 128.3, 128.0, 118.4, 91.8, 83.3, 82.2, 67.9, 67.3, 61.4, 60.5, 58.4, 58.2, 56.2, 52.5, 52.3, 46.2, 45.8, 42.8, 41.2, 41.0, 35.1, 34.9; MS (EI) *m/z* (relative intensity) 417 (M^+, 3), 386 (15), 355 (42), 312 (33), 252 (67), 91 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{21}NO_5$ ($M-O_2C_2H_6$) 386.1604, found 386.1617.

(2*S*,3a*R*,4*S*,6*S*,7a*R*)-4-(2-Azido-vinyl)-6-methoxy-3a-hydroxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (106). Prepared as an inseparable ~2:1 mixture

of *E/Z* isomers in several steps from **105** by the same sequence as described for the synthesis of **103**. **106**: ^{1}H NMR (mixture of rotamers and *E/Z* isomers) δ 7.45-7.25 (m, 5 H), 6.28, 6.26 (2d, 0.3 H, *J* = 7.6 Hz), 5.95, 5.93 (2d, 0.7 H, *J* = 13.6 Hz), 5.70-5.50 (m, 0.7 H), 5.30-4.95 (m, 2.3 H), 4.45-4.25 (m, 1 H), 4.10-3.95 (m, 1 H), 3.80, 3.53 (2s, 3 H), 3.60-3.40 (m, 1 H), 3.35, 3.17 (2s, 3 H), 2.90-2.70, 2.45-2.10 (2m, 3 H), 2.00-1.40 (m, 4 H).

(2*S*,3a*R*,4*RS*,7a*R*)-3a-Hydroxy-4-isopropenyl-6-oxooctahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (107). To a solution of **1** (4.58 g, 13.3 mmol) in THF (50 mL) was added CuI (758 mg, 3.98 mmol) and isopropenyl magnesium bromide (0.5M in THF, 53 mL) at –20 °C. The reaction mixture was warmed to room temperature for 2 h, quenched with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (250 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **107** as an inseparable ~1:1 mixture of diastereomers (2.44 g, 47%): ^{1}H NMR (mixture of rotamers and diastereomers) δ 7.40-7.15 (m, 5 H), 5.20-4.60 (m, 4 H), 4.50-4.30 (m, 1 H), 4.17, 3.86 (2bs, 1 H, -O*H*), 4.20-3.90 (m, 1 H), 3.63, 3.61, 3.43, 3.24 (4s, 3 H), 3.20-2.70 (m, 2 H), 2.60-1.85 (m, 5 H), 1.74 (s, 3 H); ^{13}C NMR (mixture of rotamers and diastereomers) δ 209.3, 207.9, 207.3, 174.5, 174.2, 173.6, 173.5, 154.9, 154.6, 154.5, 154.2, 144.1, 143.9, 142.9, 136.2, 136.0, 128.6, 128.5, 128.2, 128.0, 115.0, 114.3, 113.9, 80.5, 80.4, 79.6, 79.4, 67.6, 67.4, 67.2, 66.5, 66.2, 64.9, 64.2, 59.5, 59.3, 57.8, 57.7, 53.0, 52.7, 52.6, 52.5, 47.6, 47.0, 44.9, 44.0, 43.1, 42.3, 42.0, 41.9, 41.3, 40.6, 36.1, 34.8, 23.8, 23.6, 23.0; MS (EI) *m/z* (relative intensity) 387 (M^+, 3), 369 (2), 328 (12), 284 (30), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{25}NO_6$ 387.1682, found 387.1673.

(2*S*,3a*R*,4*R*,6*R*,7a*R*)-4-(2-Azido-1-methyl-vinyl)-3a-hydroxy-6-methoxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (108). Prepared in several steps

from **107** by a similar sequence as described in the synthesis of **103**. **108**: IR (neat) 3444, 2952, 2104, 1705, 1650, 1413, 1351 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.40-7.20 (m, 5 H), 6.10 (bs, 1 H), 5.25-4.95 (m, 2 H), 4.50-4.30 (m, 1 H), 4.20-3.75 (m, 2 H), 3.82, 3.53 (2s, 3 H), 3.50-3.20 (m, 1 H), 3.37, 3.32 (2s, 3 H), 2.90-2.70, 2.60-2.40 (2m, 3 H), 2.05-1.70 (m, 2 H), 1.65 (s, 3 H), 1.50-1.30 (m, 1 H), 1.05-0.80 (m, 1 H); ^{13}C NMR (mixture of rotamers) δ 175.4, 175.2, 154.8, 153.8, 136.3, 136.0, 128.7, 128.6, 128.3, 128.1, 126.0, 124.2, 80.3, 79.4, 75.9, 67.6, 66.1, 65.9, 57.4, 57.1, 56.4, 56.3, 53.3, 52.9, 45.7, 45.6, 36.5, 36.0, 35.5, 34.9, 33.6, 33.1, 14.8, 14.6; MS (EI) *m/z* (relative intensity) 444 (M^+, <1), 426 (<1), 385 (10), 91 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{28}N_4O_6$ 444.2009, found 444.2019.

(**2*S*,3a*R*,4*S*,6*S*,7a*R*)-4-(2-Azido-1-methylvinyl)-3a-hydroxy-6-methoxy-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (109).** Prepared in several steps from **107** by a similar sequence described for the synthesis of **106**. **109**: IR (neat) 3451, 3033, 2951, 2826, 2100, 1701 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.45-7.25 (m, 5 H), 6.11 (s, 1 H), 5.30-4.90 (m, 2 H), 4.50-4.35 (m, 1 H), 4.00-3.85 (m, 1 H), 3.76, 3.47 (2s, 3 H), 3.60-3.45 (m, 1 H), 3.36, 3.15 (s, 3 H), 3.35-3.25, 3.10-3.05 (2m, 1 H), 2.70-2.55 (m, 1 H), 2.38 (dd, 1 H, J = 8.9, 6.0 Hz), 2.25-1.65 (m, 4 H), 1.76 (s, 3 H); ^{13}C NMR (mixture of rotamers) δ 174.9, 174.2, 155.3, 154.1, 136.3, 128.6, 128.3, 128.2, 128.1, 127.4, 127.3, 122.7, 122.4, 82.0, 79.9, 74.9, 67.5, 67.1, 64.6, 64.1, 58.9, 58.6, 56.1, 55.9, 52.8, 52.3, 40.2, 38.6, 38.2, 30.6, 30.2, 29.7, 29.3, 18.3; MS (EI) *m/z* (relative intensity) 444 (M^+, <1), 426 (<1), 385 (3), 91 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{28}N_4O_6$ 444.2009, found 444.2020.

(2*S*,3a*R*,4*R*,7a*S*)-4-Dimethylcarbamoylmethyl-3a-(trimethylsilanyloxy)-2,3,3a,4,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (110). Prepared according to literature procedures:[94] ^1H NMR (mixture of rotamers) δ 7.40-7.20 (m, 5 H), 5.80-

5.60 (m, 2 H), 5.20-4.85 (m, 2 H), 4.45-4.30 (m, 1 H), 3.95-3.80 (m, 1 H), 3.65, 3.44 (2s, 3 H), 2.94, 2.93 (2s, 3 H), 2.88 (s, 3 H), 2.80-2.00 (m, 7 H), 0.04 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 172.4, 171.6, 171.5, 171.3, 155.0, 154.3, 136.4, 136.2, 132.1, 131.0, 128.3, 128.2, 127.9, 127.8, 124.7, 124.6, 84.0, 82.0, 67.0, 66.6, 63.5, 58.2, 51.8, 51.7, 41.2, 40.7, 40.1, 39.5, 37.0, 35.3, 33.5, 29.6, 2.2.

(1a*R*,3a*S*,4*S*,5a*R*,7*S*,8a*R*)-4-Iodo-2-oxo-8a-(trimethylsilanyloxy)-decahydro-3-oxa-6-aza-*as*-indacene-6,7-dicarboxylic acid 6-benzyl ester 7-methyl ester (111). To a solution of **110** (520 mg, 1.07 mmol) in pH-6 phosphate buffer (5 mL) and THF (5 mL) was added I_2 (1.36 g, 5.34 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature and quenched with saturated aqueous $Na_2S_2O_3$ solution until the purple color disappeared. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **111** (470 mg, 74%) as a white foam: $[\alpha]_D$ –8.1 (*c* 1.0, CH_2Cl_2); IR (neat) 3027, 2950, 2894, 1782, 1752, 1708, 1414, 1260 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 373 °K) δ 7.55-7.30 (m, 5 H), 5.20, 5.14 (AB, 2 H, *J* = 12.3 Hz), 5.06 (dd, 1 H, *J* = 8.4, 8.3 Hz), 4.55-4.45 (m, 1 H), 4.39 (dd, 1 H, *J* = 8.4, 8.3 Hz), 4.08 (dd, 1 H, *J* = 8.2, 8.0 Hz), 3.68 (bs. 3 H), 3.20-3.00 (m, 1 H), 2.95-2.75 (m, 2 H), 2.70-2.45 (m, 2 H), 2.25-2.00 (m, 2 H), 0.23 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 174.3, 172.1, 171.8, 154.4, 153.6, 135.6, 135.5, 128.6, 128.5, 128.4, 128.3, 128.0, 86.6, 86.4, 80.6, 80.0, 68.0, 67.4, 62.1, 61.7, 58.5, 58.1, 52.6, 52.3, 40.9, 40.8, 39.2, 38.9, 38.3, 37.8, 31.1, 31.0, 19.5, 1.7; MS (EI) *m/z* (relative intensity) 587 (M^+, <1), 572 (1), 528 (3), 484 (4), 416 (4); HRMS (EI) *m/z* calcd for $C_{23}H_{30}NO_7SiI$ 587.0836, found 587.0846.

(1a*R*,3a*S*,4*S*,5a*R*,7*S*,8a*R*)-2-Oxo-8a-(trimethylsilanyloxy)-decahydro-3-oxa-6-aza-*as*-indacene-6,7-dicarboxylic acid 6-benzyl ester 7-methyl ester (112). To a solution of **111** (460 mg, 0.78 mmol) in dry benzene (15 mL) was added AIBN (26 mg, 0.016 mmol) and *n*-Bu_3SnH (0.25 mL, 0.94 mmol) at room temperature. The reaction mixture was heated at reflux for 1 h, cooled to room temperature and concentrated under reduced pressure. The crude residue was washed with hexanes and purified by column chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **112** (340 mg, 95%) as a white foam: $[\alpha]_D$ −32.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3032, 2950, 2899, 1772, 1752, 1711, 1414, 1127 cm^{-1}; ^1H NMR (DMSO-d_6, 373 °K) δ 7.45-7.30 (m, 5 H), 5.14, 5.08 (AB, 2 H, *J* = 12.5 Hz), 4.67 (dd, 1 H, *J* = 12.5, 6.2 Hz), 4.36 (appt, 1 H, *J* = 8.2 Hz), 3.86 (dd, 1 H, *J* = 6.2, 5.8 Hz), 3.63 (s, 3 H), 2.75-2.35 (m, 4 H), 2.30-2.10 (m, 1 H), 2.00-1.70 (m, 4 H), 0.16 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 176.6, 176.4, 172.6, 172.4, 155.2, 153.9, 135.9, 128.6, 128.5, 128.4, 79.9, 78.9, 78.2, 78.0, 67.8, 67.2, 61.2, 61.0, 58.4, 58.1, 52.5, 52.2, 40.2, 40.1, 39.9, 39.2, 32.4, 32.2, 21.7, 20.2, 1.8; MS (EI) *m/z* (relative intensity) 461 (M^+, 1), 446 (3), 358 (3), 220 (85), 91 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{31}NO_7Si$ 461.1870, found 461.1882.

(1a*R*,3a*S*,5a*R*,7*S*,8a*R*)-1-Methanesulfonyloxymethylene-2-oxo-8a-(trimethyl-silanyloxy)-decahydro-3-oxa-6-aza-*as*-indacene-6,7-dicarboxylic acid 6-benzyl ester 7-methyl ester (113). To a solution of **112** (1.40 g, 3.03 mmol) in THF (20 mL) was added LHMDS (1.0M in hexanes, 4.3 mL) at −78 °C. The reaction mixture was stirred for 30 min, treated with ethyl formate (2.3 mL, 28 mmol) at −78 °C, stirred for 1 h at −78 °C, quenched with saturated aqueous NH_4Cl solution and warmed to room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2

(20 mL) and treated with TEA (2.0 mL, excess) and MsCl (1.0 mL, excess). The reaction mixture was stirred for 1 h at room temperature, diluted with EtOAc (100 mL) and washed with brine (50 mL) and 1N NaOH. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **113** (1.38 g, 80%) as a white foam: $[\alpha]_D$ +9.9 (*c* 1.0, CH_2Cl_2); IR (neat) 3027, 2960, 2893, 1754, 1696 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.80, 7.79 (2s, 1 H), 7.40-7.20 (m, 5 H), 5.20-4.80 (m, 2 H), 4.70-4.45 (m, 1 H), 4.40-4.10 (m, 1 H), 3.95-3.75 (m, 1 H), 3.77, 3.43 (2s. 3 H), 3.24, 3.22 (2s, 3 H), 3.05-2.95 (m, 1 H), 2.70-2.20 (m, 2 H), 2.20-1.50 (m, 4 H), 0.14, 0.09 (2s, 9 H); ^{13}C NMR (mixture of rotamers) δ 172.6, 172.4, 169.8, 155.2, 153.9, 141.4, 135.8, 128.6, 128.5, 117.9, 117.5, 81.4, 80.5, 77.2, 77.0, 67.9, 67.4, 61.5, 61.1, 58.6, 58.3, 52.7, 52.4, 42.6, 42.3, 39.8, 38.9, 23.0, 21.8, 21.4, 21.2, 2.2; MS (EI) *m/z* (relative intensity); 567 (M^+, 1), 488 (4), 444 (18), 91 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{33}NO_{10}SiS$ 567.1594, found 567.1612.

(1a*R*,3a*S*,5a*R*,7*S*,8a*R*)-1-azidomethylene-2-oxo-8a-(trimethyl-silanyloxy)-decahydro-3-oxa-6-aza-*as*-indacene-6,7-dicarboxylic acid 6-benzyl ester 7-methyl ester (114). A solution of **113** (0.18 g, 0.32 mmol) in EtOH (3 mL) was treated with NaN_3 (0.21 g, 3.2 mmol) at room temperature. The reaction mixture was stirred for 14 h at room temperature, diluted with EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **114** (114 mg, 70%) as a white foam: $[\alpha]_D$ +12.0 (*c* 0.5, CH_2Cl_2); IR (neat) 3032, 2945, 2899, 2100 (N_3), 1752, 1706, 1640, 1413 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.50 (s, 1 H), 7.45-7.25 (m, 5 H), 5.25-4.85 (m, 2 H), 4.55-4.35 (m, 1 H), 4.33-4.25 (m, 1 H), 3.90-3.70 (m, 1 H), 3.77, 3.42 (2s. 3 H), 2.90-2.70

(m, 2 H), 2.55-2.25 (m, 1 H), 2.20-1.80 (m, 3 H), 1.80-1.70, 1.60-1.40 (2m, 1 H), 0.07 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 172.9, 172.7, 170.7, 155.2, 153.9, 136.0, 135.9, 135.4, 135.0, 128.7, 128.6, 128.5, 128.4, 128.2, 118.7, 118.4, 81.7, 80.9, 76.9, 76.7, 67.8, 67.3, 61.7, 61.4, 58.8, 58.4, 52.6, 52.3, 42.7, 42.6, 39.8, 39.2, 23.1, 21.8, 21.6, 1.8; MS (EI) *m/z* (relative intensity); 486 ([M–N_2]$^+$, 3), 471 (13), 427 (10); HRMS (EI) *m/z* calcd for $C_{24}H_{30}N_2O_7Si$ (M–N_2) 486.1822, found 486.1823.

(1a*R*,3a*S*,5a*R*,7*S*,8a*R*)-1-azidomethylene-2-oxo-8a-(hydroxy)-decahydro-3-oxa-6-aza-*as*-indacene-6,7-dicarboxylic acid 6-benzyl ester 7-methyl ester (115). To a solution of **114** (0.25 g, 0.49 mmol) in THF (20 mL) was added HF-pyridine complex (4 mL, excess) at room temperature. The reaction mixture was stirred for 20 h at room temperature, diluted with EtOAc (200 mL) and washed with saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:2) to give **115** (200 mg, 93%) as a white foam: $[\alpha]_D$ −7.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3421, 3063, 2955, 2890, 2110 (N_3), 1747, 1700, 1650, 1414 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 7.60 (s, 1 H), 7.45-7.25 (m, 5 H), 5.20-4.90 (m, 2 H), 4.70-4.50 (m, 1 H), 4.40-4.25 (m, 1 H), 4.00-3.80 (m, 1 H), 3.72, 3.47 (2bs. 3 H), 3.20-3.00 (m, 1 H), 2.75-2.55 (m, 1 H), 2.40-2.10 (m, 1 H), 2.10-1.80 (m, 3 H), 1.70-1.45 (m, 1 H); ^{13}C NMR (mixture of rotamers) δ 173.0, 172.9, 171.4, 171.2, 155.1, 154.2, 137.5, 137.4, 135.9, 128.4, 128.2, 115.8, 115.7, 79.4, 78.5, 76.9, 76.7, 67.5, 67.1, 63.0, 62.4, 58.3, 58.1, 52.5, 52.3, 42.6, 42.2, 41.5, 23.2, 22.4, 22.0; MS (EI) *m/z* (relative intensity); 414 ([M–N_2]$^+$, 35), 355 (4), 311 (7), 279 (35), 221 (33), 91 9(100); HRMS (EI) *m/z* calcd for $C_{21}H_{22}NO_7$ (M–N_2) 414.1427, found 414.1431.

(3a*R*,4*R*,6a*R*,8*S*,9a*R*)-7-((benzoyloxy)carbonyl)-8-(methoxycarbonyl)-3a,4,5,6,6a,7,8,9-octahydro-dihydrofuro[3,4,c]furan-1(3H)-one-indole (116). To a solution of **115** (22 mg, 0.050 mmol) in CH_2Cl_2 (1 mL) was added $PhI(OAc)_2$ (40 mg, 0.13 mmol) and I_2 (25 mg, 0.10 mmol) at room temperature. The reaction mixture was heated at reflux for 14 h, cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:1) to give **116** (10 mg, 50%) as a white foam: IR (neat) (no $-N_3$ and no -OH) 2919, 2848, 1793, 1706, 1409, 1342, 1112 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.90 (s, 1 H), 7.50-7.20 (m, 5 H), 5.30-5.00 (m, 2 H), 4.73, 4.65 (2d, 1 H, J = 8.7 Hz), 4.40-4.25 (m, 1 H), 3.80-3.50 (m, 1 H), 3.79, 3.63 (2s. 3 H), 3.30-3.05 (m, 1 H), 2.70-2.25 (m, 4 H), 2.15-1.85 (m, 2 H); ^{13}C NMR (mixture of rotamers) δ 172.2, 172.0, 164.7, 163.0, 162.5, 154.8, 136.2, 135.9, 128.8, 128.7, 128.4, 128.3, 128.0, 112.4, 109.9, 96.3, 96.2, 91.2, 90.3, 77.4, 69.7, 69.0, 67.9, 67.8, 60.2, 60.0, 53.1, 52.9, 40.0, 38.9, 32.8, 32.5, 29.6, 28.8.

5-[2-(3-Acetoxy-4-azidomethylene-5-oxo-tetrahydro-furan-2-yl)-ethyl]-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (117). A solution of $PhI(OAc)_2$ (612 mg, 1.90 mmol) and I_2 (247 mg, 0.970 mmol) in CH_2Cl_2 (3 mL) was irradiated at reflux for 20 min with a halogen lamp. To this solution was added **115** (86 mg, 0.19 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was irradiated at reflux for 30 min, cooled to room temperature, diluted with EtOAc (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **117** (40 mg, 41%) as a white foam: $[\alpha]_D$ −16.4 (*c* 0.5, CH_2Cl_2); IR (neat) 3037, 2955, 2924, 2848, 2120 (N_3), 1757, 1706, 1413 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.51 (s, 1 H), 7.40-7.20 (m, 5 H), 6.62 (s, 1 H), 5.35-5.00 (m, 2.5 H), 4.90-4.70 (m, 1.5 H), 4.15-4.05 (m, 1 H), 3.76, 3.51 (2s. 3

H), 3.00-2.80 (m, 1 H), 2.65-2.45 (m, 1 H), 2.20 (s, 3 H), 2.20-1.80 (m, 3 H), 1.75-1.40 (m, 1 H); ^{13}C NMR (mixture of rotamers) δ 209.5, 209.1, 172.3, 169.9, 169.4, 155.0, 152.1, 152.4, 135.7, 130.0, 128.7, 128.6, 128.4, 81.2, 81.0, 77.6, 68.3, 67.8, 62.0, 61.6, 56.0, 52.9, 52.7, 40.3, 39.8, 29.0, 27.8, 27.2, 27.0, 20.8; MS (EI) *m/z* (relative intensity) 472 ($[M–N_2]^+$, 4.5), 444 (1.5), 430 (4.5); HRMS (EI) *m/z* calcd for $C_{23}H_{24}N_2O_9$ (M–N_2) 472.1482, found 472.1489.

(2*S*,3a*R*,4*S*,7a*R*)-3a-Hydroxy-6-oxo-4-(trimethylsilanylmethyl)-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (128). To a solution of Mg (0.43 g, 18 mmol) in Et_2O (35 mL) was added $TMSCH_2Br$ (2.50 mL, 17.5 mmol) at room temperature. The solution was stirred for 1 h until it became homogeneous and added to the slurry of **1** (1.2 g, 3.5 mmol) and CuI (0.67 g, 3.3 mmol) in THF (40 mL) at –20 °C. The reaction mixture was slowly warmed to room temperature, stirred for 2 h, quenched with saturated aqueous NH_4Cl solution (100 mL), diluted with EtOAc (500 mL) and washed with brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **128** (950 mg, 63%) as a white foam: $[\alpha]_D$ –22.4 (*c* 1.0, CH_2Cl_2); IR (neat) 3400, 3068, 2950, 2899, 1680, 1414, 1352 cm^{-1}; ^{1}H NMR (DMSO-d_6, 373 °K) δ 7.50-7.30 (m, 5 H), 5.15, 5.10 (AB, 2 H, J = 14.0 Hz), 4.70-4.30 (m, 2 H), 4.15 (dd, 1 H, *J* = 6.4, 6.3 Hz), 3.66 (s, 3 H), 2.88 (dd, 1 H, *J* = 14.6, 6.6 Hz), 2.70-2.40 (m, 2 H), 2.35-2.10 (m, 3 H), 2.03-1.98 (m, 1 H), 1,17 (d, 1 H, *J* = 14.6 Hz), 0.37 (dd, 1 H, *J* = 14.0, 9.7 Hz), 0.08 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 207.7, 206.9, 175.6, 175.4, 154.6, 153.9, 135.9, 128.7, 128.6, 128.4, 128.1, 81.2, 80.5, 67.9, 67.7, 66.6, 66.1, 57.4, 53.3, 52.9, 45.3, 44.3, 37.7, 37.5, 34.7, 33.5, 18.8, 18.5, –0.7; MS (EI) *m/z* (relative intensity) 433 (M^+, <1), 418 (3), 330 (30), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{28}NO_6Si$ (M–CH_3) 418.1686, found 418.1669.

(2*S*,3a*R*,4*S*,7a*R*)-3a-Hydroxy-6-(ethylene)-dioxo-4-(trimethylsilanylmethyl)-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (129). A solution of **128** (43 mg, 0.10 mmol), ethylene glycol (56 μL, 1.0 mmol) and p-toluenesulfonic acid monohydrate (1.9 mg, 0.010 mmol) in benzene (2 mL) was heated at reflux for 14 h. The reaction mixture was cooled room temperature, diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **129** (35 mg, 73%) as a white foam: $[\alpha]_D$ −5.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3457, 3032, 2945, 2894, 1696, 1414, 1362 cm^{-1}; ^1H NMR (DMSO-d_6, 373 °K) δ 7.50-7.30 (m, 5 H), 5.15, 5.08 (AB, 2 H, *J* = 12.3 Hz), 4.42 (d, 1 H, *J* = 10.1 Hz), 4.30-4.10 (m, 1 H), 4.05-3.80 (m, 5 H), 3.65 (bs, 3 H), 2.60-2.40 (m, 1 H), 2.40-2.20 (m, 1 H), 2.20-2.05 (m, 1 H), 1.88 (d, 1 H, *J* = 13.5 Hz), 1.75-1.60 (m, 1 H), 1.50-1.30 (m, 2 H), 1.08 (dd, 1 H, *J* = 14.5, 3.3 Hz), 0.29 (dd, 1 H, *J* = 14.4, 10.8 Hz), 0.07 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 175.5, 175.3, 154.9, 153.9, 136.6, 136.2, 128.6, 128.3, 128.1, 127.7, 107.1, 81.2, 80.3, 67.5, 67.4, 65.3, 65.1, 64.8, 64.7, 64.5, 64.4, 57.1, 56.9, 53.2, 52.8, 39.9, 39.6, 38.4, 37.7, 36.4, 36.3, 34.7, 33.6, 17.7, -0.5; MS (EI) *m/z* (relative intensity) 477 (M^+, 3), 462 (42), 418 (90), 374 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{35}NO_7Si$ 477.2183, found 477.2172.

(2*S*,5*R*)-5-[4-Acetoxy-2-oxo-5-(trimethylsilanyl)-pentyl]-4-oxopyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (130). To a solution of **128** (0.91 g, 2.1 mmol) in CH_2Cl_2 was added $PhI(OAc)_2$ (2.0 g, 6.2 mmol) and I_2 (1.6 g, 6.3 mmol) at room temperature. The reaction mixture was heated at reflux for 12 h, cooled to room temperature, diluted with EtOAc (200 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was

purified by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) to give **130** (540 mg, 54%) as a white foam: $[\alpha]_D$ -52.3 (*c* 2.0, CH_2Cl_2); IR (neat) 3032, 2955, 2893, 1767, 1737, 1716, 1408, 1352, 1245 cm^{-1}; ^1H NMR (DMSO-d_6, 373 °K) δ 7.50-7.30 (m, 5 H), 5.30-5.10 (m, 3 H), 4.72 (dd. 1 H, *J* = 10.1, 3.9 Hz), 4.18 (dd, 1 H, *J* = 4.3, 3.8 Hz), 3.62 (s, 3 H), 3.53-3.20 (m, 1 H), 3.26 (dd, 1 H, *J* =18, 10 Hz), 3.06 (dd, 1 H, *J* = 18, 3.4 Hz), 2.80-2.50 (m, 3 H), 1.96 (s, 3H), 0.99 (d, 2 H, *J* = 6.8 Hz), 0.07 (s, 9 H); ^{13}C NMR (DMSO-d_6, 373 ^oK) δ 208.0, 204.2, 171.5, 168.6, 153.5, 135.6, 127.7 (2C), 127.3, 127.1 (2C), 68.0, 66.3, 58.0, 55.7, 51.4, 48.6, 43.9, 38.8, 22.4, 20.1 –1.7 (3C); MS (EI) *m/z* (relative intensity) 431 ($[M–AcOH]^+$, 80), 372 (70), 296 (90), 91(100); HRMS (EI) *m/z* calcd for $C_{22}H_{29}NO_6Si$ (M–$C_4H_4O_2$) 431.1764, found 431.1764.

(2*S*,5*R*)-5-[4-Acetoxy-2-((ethylene)-dioxo)-5-(trimethylsilanyl)-pentyl]-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (131). To a solution of **129** (0.21 g, 0.44 mmol) in CH_2Cl_2 (10 mL) was added $PhI(OAc)_2$ (0.42 g, 1.3 mmol) and I_2 (0.33 g, 1.3 mmol) at room temperature. The reaction mixture was stirred for 14 h at room temperature, diluted with EtOAc (100 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 3:1) to give **131** (115 mg, 50%) as a colorless oil. $[\alpha]_D$ -53.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3032, 2960, 2889, 1757, 1731, 1711, 1413, 1352, 1250 cm^{-1}; ^1H NMR (DMSO-d_6, 373 °K) δ 7.50-7.30 (m, 5 H), 5.30-5.10 (m, 3 H), 4.75-4.60 (m. 1 H), 4.10-3.60 (m, 5 H), 3.65 (s, 3 H), 3.13 (dd, 1 H, *J* =18.4, 10.1 Hz), 2.65-2.50 (m, 2 H), 2.30-2.15 (m, 1 H), 2.10-1.90 (m, 1 H), 1.95 (s, 3 H), 1.90-1.75 (m, 1 H), 1.00-0.90 (m, 2 H), 0.05 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 209.2, 208.9, 172.8, 170.6, 170.4, 154.6, 136.0, 128.8, 128.5, 128.1, 109.1, 68.6, 68.3, 68.1, 67.6, 64.5, 64.3, 60.6, 59.9, 56.4, 52.8, 52.6, 45.4, 45.2, 40.1, 39.7, 38.6, 37.8, 24.7, 21.8, -0.7; MS (EI) *m/z* (relative intensity) 476

([M-OAc]$^+$, 37), 432 (10), 362 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{34}NO_7Si$ (M–$C_2H_3O_2$), 476.2105, found 476. 2083.

(2*S*,3a*R*,4*S*,7*R*)-7-Allyl-3a-hydroxy-6-oxo-4-(trimethylsilanylmethyl)-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (132). To a solution of **128** (4.82 g, 11.1 mmol) in THF (100 mL) was added LHMDS (1.0 M in THF, 27.8 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C, treated with allyl iodide (5.08 mL, 55.6 mmol), slowly warmed to –20 °C for 3 h, quenched with saturated aqueous NH_4Cl solution (100 mL) and diluted with brine (200 mL). The reaction mixture was extracted with EtOAc (300 mL×2), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 3:1) to give recovered **128** (750 mg, 16%) and **132** (3.98 g, 76%) as a white foam: $[\alpha]_D$ –17.4 (*c* 1.0, CH_2Cl_2); IR (neat) 3437, 2952, 2898, 1716, 1409, 1345, 1248, 1226 cm^{-1}; ^{1}H NMR (DMSO-d_6, 373 °K) δ 7.50-7.30 (m, 5 H), 5.90-5.60 (m, 1 H), 5.12 (bs, 2 H), 5.20-4.85 (m, 2 H), 4.65 (d, 1 H, *J* = 9.6 Hz), 4.01 (d, 2 H, *J* = 4.0 Hz), 3.65 (bs, 3 H), 2.80-2.05 (m, 7 H), 1.94 (d, 1 H, *J* = 9.4 Hz), 1.20 (dd, 1 H, *J* = 14.6, 2.9 Hz), 0.34 (dd, 1 H, *J* = 14.4, 10.1 Hz), 0.08 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 208.8, 208.0, 175.9, 175.7, 154.9, 154.3, 135.8, 135.6, 135.5, 128.7, 128.6, 128.4, 116.9, 116.7, 81.6, 80.8, 71.3, 71.2, 68.2, 67.8, 57.3, 55.8, 55.5, 53.4, 52.9, 45.3, 44.9, 37.4, 37.0, 35.0, 34.0, 33.0, 32.1, 18.8, 18.7, –0.6 (3C); MS (EI) *m/z* (relative intensity) 473 (M$^+$, 9), 414 (25), 370 (44), 338 (28), 320 (30); HRMS (EI) *m/z* calcd for $C_{25}H_{35}NO_6Si$ 473.2234, found 473.2229.

(2*S*,3a*R*,4*S*,7*R*)-7-Allyl-3a-Hydroxy-6-(ethylene)-dioxo-4-(trimethylsilanylmethyl)-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (133). A solution of **132** (2.90 g, 6.12 mmol), *p*-TsOH·H_2O (116 mg, 6.10 mmol) and ethylene glycol (3.41 mL, 61.2 mmol) in benzene (120 mL) was heated at reflux for 20 h, cooled to room temperature, diluted

with EtOAc (500 mL) and washed with saturated aqueous $NaHCO_3$ solution (250 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give **133** (2.66 g, 84%) as a white foam: $[\alpha]_D$ −12.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3453, 2952, 2892, 1710, 1411, 1351, 1247, 1220 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.40-7.20 (m, 5 H), 5.90-5.60 (m, 1 H), 5.15-4.65 (m, 4 H), 4.40-3.80 (m, 7 H), 3.78, 3.37 (2s, 3 H), 2.45-2.25 (m, 2 H), 2.25-2.05 (m, 2 H), 1.80-1.70 (m, 2 H), 1.60-1.45 (m, 1 H), 1.25-1.00 (m, 2 H), 0.16 (dd, 1 H, *J* = 13.4, 12.2 Hz), 0.00 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 175.6, 175.5, 155.1, 154.4, 138.9, 138.4, 135.8, 128.3, 128.1, 128.0, 113.2, 113.0, 108.9, 108.8, 81.2, 80.4, 70.0, 67.5, 64.9, 64.8, 64.3, 56.7, 56.5, 53.0, 52.5, 49.4, 48.5, 39.5, 39.4, 35.3, 35.0, 33.8, 30.3, 17.3, –0.7; MS (EI) *m/z* (relative intensity) 517 (M^+, 12), 414 (11), 364 (28), 338 (28), 243 (85), 91 (100), HRMS (EI) *m/z* calcd for $C_{27}H_{39}NO_7Si$ 517.2496, found 517.2471.

(2*S*,3a*R*,4*S*,7*R*)-3a-Hydroxy-7-(2-oxoethyl)-6-(ethylene)-dioxo-4-(trimethylsilanylmethyl)-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (134). To a solution of **133** (0.20 g, 0.39 mmol) in H_2O-dioxane (1:3, 4 mL) was added OsO_4 (2.5% in BuOH, 0.2 mL), $NaIO_4$ (410 mg, 1.93 mmol) and 2,6-lutidine (90 μl, 0.78 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature, diluted with EtOAc (50 mL) and washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **134** (0.17 g, 85%) as a white solid: Mp 152-155 °C (CH_2Cl_2); $[\alpha]_D$ −10.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3453, 2966, 2884, 1716, 1696, 1409, 1352, 1214 cm^{-1}; ^1H NMR (mixture of rotamers) δ 9.71, 9.36 (2s, 1 H), 7.50-7.30 (m, 5 H), 5.24, 5.08 and 5.15, 4.98 (2AB, 2 H, *J* = 12.0 Hz), 4.88, 4.56 (2s, 1 H, -O*H*), 4.44, 4.18 (2d, 1 H, *J* = 9.9 Hz), 4.15-3.70 (m, 5 H),

3.90, 3.76 (2s, 3 H), 2.85-2.45 (m, 2 H), 2.40-2.05 (m, 3 H), 1.95-1.80 (m, 2 H), 1.35-1.10 (m, 2 H), 0.27 (dd, 1 H, *J* = 14.0, 10.8 Hz), 0.08 (s, 9 H); ^{1}H NMR (DMSO-d_6 at 373 °K) δ 9.68 (bs, 1 H), 7.50-7.30 (m, 5 H), 5.25-5.00 (m, 2 H), 4.49 (d, 1 H, *J* = 9.8 Hz), 4.10-3.90 (m, 2 H), 3.96 (s, 3 H), 3.85-3.55 (m, 4 H), 2.71 (dd, 1 H, *J* = 14.1, 10.3 Hz), 2.60 (dd, 1 H, *J* = 3.8, 1.9 Hz), 2.50-2.30 (m, 2 H), 2.25-2.05 (m, 1 H), 1.95-1.80 (m, 1 H), 1.84 (dd, 1 H, *J* = 13.8, 4.5 Hz), 1.37 (t, 1 H, *J* = 13.6 Hz), 1.12 (dd, 1 H, *J* = 14.5, 3.7 Hz), 0.36 (dd, 1 H, *J* = 14.5, 10.6 Hz), 0.12 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 201.1, 200.2, 175.7, 154.9, 154.7, 135.7, 135.6, 128.7, 128.6, 128.5, 128.4, 128.3, 108.2, 108.0, 81.3, 80.5, 69.5, 69.0, 67.9, 69.8, 65.1, 65.0, 64.3, 64.0, 57.1, 56.7, 53.3, 52.8, 44.6, 44.2, 41.4, 40.9, 38.6, 35.5, 35.3, 34.8, 33.8, 17.4, 0.6; MS (EI) *m/z* (relative intensity) 519 (M^+, 0.5), 504 (2), 416 (13), 185 (25), 91 (100), 73 (32); HRMS (EI) *m/z* calcd for $C_{26}H_{37}NO_8Si$ 519.2288, found 519.2300.

(2*S*,3a*R*,4*S*,7*R*,7a*R*)-3a-Hydroxy-7-(2-hydroxyethyl)-6-(ethylene)-dioxo-4-(trimethylsilanylmethyl)-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (135). To a solution of **134** (840 mg, 1.62 mmol) in THF-MeOH (1:1, 30 mL) was added $NaBH_4$ (306 mg, 8.08 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, quenched with brine (100 mL) and extracted with EtOAc (250 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:4) to give **135** (780 mg, 93%) as a white foam: $[\alpha]_D$ −8.3 (*c* 1.0, CH_2Cl_2); IR (neat) 3411, 2945, 2879, 1726, 1690, 1408, 1357, 1219 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 7.50-7.30 (m, 5 H), 5.26, 4.97 and 5.08, 4.98 (2AB, 2 H, *J* = 12.1 Hz), 4.70, 4.30 (2bs, 1 H, -O*H*), 4.29, 4.13 (2d, 1 H, *J* = 9.4 Hz), 4.10-3.85 (m, 5 H), 3.80, 3.38 (2s, 3 H), 3.60-3.50 (m, 1 H), 3.35-3.20 (m, 1 H), 2.50-1.90 (m, 3 H), 1.85-1.50 (m, 4 H), 1.20-1.05 (m, 2 H), 0.16 (dd, 1 H, *J* = 14.2, 11.5 Hz), 0.00 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 175.8, 175.7 (1C), 155.4,

155.0 (1C), 136.0, 135.8 (1C), 128.8, 128.6, 128.5, 128.4 (5C), 109.0, 108.9 (1C), 81.3, 80.5 (1C), 70.4, 70.1 (1C), 67.8, 67.7 (1C), 64.8, 64.4, 64.3 (2C), 62.2, 62.1 (1C), 56.9, 56.8 (1C), 53.2, 52.7 (1C), 46.7, 45.8 (1C), 38.7 (1C), 35.4, 35.2 (1C), 35.0, 33.9 (1C), 29.2, 29.0 (1C), 17.3 (1C), –0.6 (3C); MS (EI) *m/z* (relative intensity) 503 ([M–H_2O], <1), 368 (9), 324 (10), 185 (20), 91 (100); HRMS (EI) *m/z* calcd for $C_{26}H_{37}NO_7Si$ (M–H_2O) 503.2339, found 503.2318.

(2*S*,3a*R*,4*S*,7*R*,7a*R*)-3a-Hydroxy-7-(2-tert-butyldimethylsilyloxyethyl)-6-(ethylene)-dioxo-4-(trimethylsilanylmethyl)-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (136). To a solution of **135** (150 mg, 0.288 mmol) in CH_2Cl_2 was added TBSCl (65 mg, 0.43 mmol), imidazole (29 mg, 0.43 mmol) and DMAP (3.7 mg, 0.030 mmol) at 0 °C. The reaction mixture was stirred for 30 min, diluted with EtOAc (50 mL) and washed with H_2O (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 4:1) to give **136** (180 mg, 98%) as a white foam: $[\alpha]_D$ –2.3 (*c* 1.0, CH_2Cl_2); IR (neat) 3446, 2955, 2878, 2845, 1721, 1705, 1408, 1250, 1221, 1081 cm^{-1}; ^1H NMR (mixture of rotamers) δ 7.50-7.30 (m, 5 H), 5.14, 4.98 (AB, 1.2 H, *J* = 11.9 Hz) 5.14 (s, 0.8 H), 4.74, 4.41 (2bs, 1 H, -O*H*), 4.30, 4.29 (2d, 1 H, *J* = 9.3 Hz), 4.15-3.85 (m, 5 H), 3.84, 3.37 (2s, 3 H), 3.70-3.40 (m, 2 H), 2.55-2.35 (m, 1 H), 2.25-1.50 (m, 6 H), 1.20-1.05 (m, 2 H), 0.93-0.89 (3s, 9 H), 0.19 (m, 1 H), 0.10-0.01 (3s, 15 H); ^1H NMR (DMSO-d_6 at 373 °K) δ 7.50-7.30 (m, 5 H), 5.30-5.00 (m, 2 H), 4.40-4.25 (m, 2 H), 4.15-3.85 (m, 5 H), 3.80-3.50 (m, 4 H), 2.95 (bs, 1 H), 2.70-2.55 (m, 1 H), 2.20-2.00 (m, 1 H), 1.95-1.70 (m, 5 H), 1.28 (t, 1 H, *J* =13.6 Hz), 1.11 (dd, 1 H, *J* = 14.4, 3.4 Hz), 0.98 (s, 9 H), 0.32 (dd, 1 H, *J* = 14.5, 10.6 Hz), 0.11 (s, 15 H); ^{13}C NMR (mixture of rotamers) δ 175.8, 155.4, 154.9, 136.0, 135.9, 128.5, 128.4, 128.3, 128.1, 109.6, 109.3, 81.3, 80.5, 70.4, 70.3, 67.7, 65.1, 64.9, 64.4, 63.0, 62.7, 56.9, 56.7, 53.2, 45.3, 44.7, 39.2, 39.1, 35.4, 35.2, 29.5, 29.3, 26.1, 25.8, 18.4, 17.4,

–0.6, –3.4, –5.1; MS (ESI) *m/z* (relative intensity) 658 ([M+Na]$^+$, 100), (2), 486 (50); HRMS (ESI) *m/z* calcd for $C_{32}H_{53}NO_8SiNa$ (M+Na) 658.3207, found 658.3237.

5-[1-{2-[2-Acetoxy-3-(trimethylsilanyl)-propyl]-[1,3]dioxolan-2-yl}-3-(*tert*-butyldimethyl-silanyloxy)-propyl]-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (137) and **7-Acetoxy-6-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-11-oxo-12-(trimethylsilanylmethyl)-1,4-dioxa-8-aza-spiro[4.8]tridecane-8,9-dicarboxylic acid 8-benzyl ester 9-methyl ester (138).** To a solution of **136** (150 mg, 0.236 mmol) in CH_2Cl_2 (5 mL) was added iodobenzene diacetate (0.23 g, 0.71 mmol) and iodine (0.18 g, 0.71 mmol) at room temperature. The reaction mixture was stirred for 18 h at room temperature, diluted with EtOAc (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 5:1) to give **138** (38 mg, 23%) and **137** (17 mg, 10%) along with recovered **136** (13 mg, 9%). **137**: $[\alpha]_D$ –21.0 (*c* 0.5, CH_2Cl_2); IR (neat) 2958, 2927, 2887, 2850, 1754, 1640, 1410, 1349, 1250, 1097 cm^{-1}; ^{1}H NMR (mixture of rotamers) δ 7.50-7.25 (m, 5 H), 5.40-5.00 (m, 3 H), 4.70-4.50 (m, 1 H), 4.23 (bs, 1 H), 4.00-3.40 (m, 9 H), 3.20-2.95, 2.75-2.65 (2m, 2 H), 2.50-2.30 (m, 1 H), 2.20-1.60 (m, 4H), 1.96 (s, 3 H), 0.90 (s, 9 H), 1.00-0.80 (m, 2 H), 0.08 (s, 6 H), -0.03 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 209.7, 209.3, 172.8, 170.3, 154.1, 136.0, 128.6, 111.2, 68.0, 67.9, 67.4, 65.5, 64.2, 62.4, 62.1, 58.0, 56.2, 52.4, 42.5, 40.7, 30.4, 30.2, 26.1, 24.8, 21.7, 21.4, 18.4, 1.1, -0.8, -5.2; MS (ESI) *m/z* (relative intensity) 716 ([M+Na], 100), 634 (72), 520 (40); HRMS (ESI) *m/z* calcd for $C_{34}H_{55}NO_{10}NaSi_2$ (M+Na) 716.3262 , found 716.3294. **138**: $[\alpha]_D$ –33.0 (*c* 1.0, CH_2Cl_2); IR (neat) 2958, 2926, 2893, 2857, 1751, 1703, 1424, 1315, 1247, 1098 cm^{-1}; ^{1}H NMR (rotamers) δ 7.50-7.30 (m, 5 H), 6.78, 6.69 (2d, 1 H, *J* = 10.1 Hz) 5.34, 5.12 and 5.24, 5.14 (2AB, 2 H, *J* = 12.4 Hz), 4.25-4.05,

4.00-3.80 (2m, 3 H), 3.75-3.45 (m, 3 H), 3.65, 3.36 (2s, 3 H), 3.45-3.20 (m, 1 H), 3.00 (d, 1 H, *J* = 12.3 Hz), 2.85-2.65 (m, 1 H), 1.99, 1.90 (2s, 3 H), 1.85-1.60 (m, 4 H), 1.50-1.30 (m. 1 H), 1.15-1.05 (m, 1 H), 0.89 (s, 9 H). 0.65-0.50 (m, 1 H), 0.05 (s, 6 H), -0.04 (s, 9 H); ^{13}C NMR (mixture of rotamers) δ 216.4, 170.5, 170.4, 169.0, 168.5, 154.6, 136.3, 135.7, 128.9, 128.6, 128.5, 128.4, 128.2, 128.1, 110.4, 110.2, 78.9, 68.1, 64.8, 64.7, 62.6, 55.0, 52.8, 52.6, 46.3, 44.0, 43.7, 42.7, 40.6, 39.7, 30.8, 30.6, 26.1, 20.9, 20.8, 18.4, 17.5, 1.12, -0.9, -5.1; MS (ESI) *m/z* (relative intensity) 716 ([M+Na], 48), 634 (100), 590 (20); HRMS (ESI) *m/z* calcd for $C_{34}H_{55}NO_{10}NaSi_2$ (M+Na) 716.3262 , found 716.3263.

(2*S*,3a*R*,4*S*,7*R*,7a*R*)-7-Allyl-3a-hydroxy-6-(ethylene)-dioxo-4-(trimethyl-silanylmethyl)-octahydro-indole-2-carboxylic acid 2-methyl ester (139). A solution of Et_3SiH (1.77 mL, 11.1 mmol), $Pd(OAc)_2$ (99 mg, 0.44 mmol) and TEA (0.12 mL, 0.88 mmol) in CH_2Cl_2 (20 mL) was stirred for 30 min at room temperature. To this solution was added **133** (2.30 g, 4.44 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 20 h at room temperature, quenched with saturated aqueous $NaHCO_3$ solution (100 mL), stirred for 3 h and extracted with CH_2Cl_2 (250 mL×2). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1 → 1:2) to give **139** (1.44 g, 85%) as a white solid: Mp. 113-116 °C (CH_2Cl_2); $[\alpha]_D$ +13.1 (*c* 1.0, CH_2Cl_2); IR (neat) 3480, 2955, 2888, 1736, 1634, 1434, 1250, 1209 cm^{-1}; ^{1}H NMR δ 6.00-5.80 (m, 1 H), 5.00 (dd, 1 H, *J* = 17.0, 1.5 Hz), 4.90 (d, I H, *J* = 10.0 Hz), 4.05-3.80 (m, 5 H), 3.72 (s, 3 H), 2.91 (d, 1 H, *J* = 11.0 Hz), 2.85-2.70 (m, 1 H), 2.60-2.40 (m, 1 H), 2.35-2.15 (m, 3 H), 2.10-1.95 (m, 1 H), 1.82 (dd, 1 H, *J* = 14.1, 1.6 Hz), 1.74 (dd, 1 H, *J* = 13.8, 4.3 Hz), 1.60-1.40 (m, 1 H), 1.16 (t, 1 H, *J* = 13.5 Hz), 1.06 (dd, 1 H, *J* = 14.5, 2.7 Hz), 0.23 (dd, 1 H, *J* = 14.4, 11.5 Hz), 0.00 (s, 9 H); ^{13}C NMR δ 176.7, 139.1, 114.6, 109.6, 82.8, 70.5, 65.1, 64.3, 56.2, 52.5, 47.5,

39.7, 36.3, 35.7, 31.8, 17.8, -0.6 (3C); MS (EI) *m/z* (relative intensity) 383 (M^+, 3), 324 (60), 73 (100), HRMS (EI) *m/z* calcd for $C_{19}H_{33}NO_5Si$ 383.2128, found 383.2120.

(2*S*,3a*R*,4*S*,7*R*),7a*R*)-1-Acryloyl-7-allyl-3a-hydroxy-6-(ethylene)-dioxo-4-(trimethylsilanylmethyl)-octahydroindole-2-carboxylic acid methyl ester (140). To a solution of **139** (1.44 g, 3.75 mmol) in CH_2Cl_2 (40 mL) was added TEA (2.61 mL, 18.8 mmol) and acroyl chloride (0.61 mL, 7.5 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, quenched with brine (100 mL) and extracted with EtOAc (250 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 2:1) to give **140** (1.46 g, 89%) as a white foam: $[\alpha]_D$ +11.6 (*c* 1.0, CH_2Cl_2); IR (neat) 3436, 2950, 2893, 1710, 1650, 1613, 1429, 1362, 1214 cm^{-1}; ^1H NMR δ 6.50 (dd, 1 H, *J* = 16.7, 9.9 Hz), 6.37 (dd, 1 H, *J* = 16.7, 2.1 Hz), 5.80-5.60 (m, 2 H), 4.85 (dd, 1 H, *J* = 8.4, 1.5 Hz), 4.81 (s, 1 H), 4.74 (s, 1 H), 4.33 (dd, 1 H, *J* = 10.2, 1.3 Hz), 4.20-3.85 (m, 5 H), 3.81 (s, 3 H), 2.41 (dd, 1 H, *J* = 14.6, 10.3 Hz), 2.30-2.10 (m, 2 H), 2.05-1.95 (m, 1 H), 1.85-1.70 (m, 2 H), 1.65-1.50 (m, 1 H), 1.18 (t, 1 H, *J* = 13.8 Hz), 1.09 (dd, 1 H, *J* = 14.3, 3.0 Hz), 0.18 (dd, 1 H, *J* = 14.3, 11.1 Hz), 0.00 (s, 9 H); ^{13}C NMR δ 175.6, 165.6, 137.8, 129.1, 127.9, 114.2, 108.9, 81.6, 70.5, 65.1, 64.4, 56.8, 53.1, 48.9, 39.6, 35.1, 33.1, 30.2, 17.3, -0.6 (3C); MS (EI) *m/z* (relative intensity) 437 (M^+, 24), 422 (15), 382 (23), 332 (13), 246 (15), 185 (80), 73 (100), HRMS (EI) *m/z* calcd for $C_{22}H_{35}NO_6Si$ 437.2234, found 437.2233.

(2*S*,7a*R*,7aa*R*,10*S*,10a*R*)-10a-Hydroxy-8-(ethylene)-dioxo-4-oxo-10-(trimethylsilanylmethyl)-1,2,4,7,7a,8,9,10,10a,10b-decahydroazepino[3,2,1-*hi*]indole-2-carboxylic acid methyl ester (141). To a solution of **140** (1.35 g, 3.09 mmol) in CH_2Cl_2 (1 L) was added second-generation Grubb's catalyst[128] (131 mg, 0.150 mmol) at room temperature. The reaction mixture was heated at reflux for 20 h, cooled to room temperature and concentrated

under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:3) to give **141** (1.22 g, 94%) as a white foam: $[\alpha]_D$ +5.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3421, 2945, 2883, 1752, 1721, 1593, 1450, 1316, 1250 cm^{-1}; ^1H NMR δ 6.21 (dt, 1 H, *J* = 12.6, 4.2 Hz), 5.88 (dt, 1 H, *J* = 12.6, 2.1 Hz), 4.58 (d, 1 H, *J* = 9.9 Hz), 4.29 (s, 1 H, -O*H*), 4.20-3.85 (m, 4 H), 3.78 (s, 3 H), 3.72 (d, 1 H, *J* = 9.7 Hz), 2.65-2.40 (m, 2 H), 2.35-2.10 (m, 2 H), 2.10-2.00 (m, 1 H). 1.92 (d, 1 H, J = 14.1 Hz) 1.75 (dd, 1 H, *J* = 13.8, 3.6 Hz), 1.20 (t, 1 H, *J* = 13.6 Hz), 1.07 (dd, 1 H, *J* = 14.3, 2.7 Hz), 0.24 (dd, 1 H, *J* = 14.4, 11.5 Hz), 0.00 (s, 9 H); ^{13}C NMR δ 175.5, 166.6, 140.0, 123.8, 108.4, 82.6, 69.2, 65.8, 64.5, 57.7, 53.0, 47.6, 38.2, 36.0, 33.0, 29.3, 16.9, -0.6 (3C); MS (EI) *m/z* (relative intensity) 409 (M^+, 1), 394 (13), 350 (100), 73 (48), HRMS (EI) *m/z* calcd for $C_{20}H_{31}NO_6Si$ 409.1921, found 409.1917.

(2*S*,7a*R*,7aa*R*,10*S*,10a*R*)-10a-Hydroxy-8-(ethylene)-dioxo-4-oxo-10-(trimethylsilanylmethyl)-dodecahydroazepino[3,2,1-*hi*]indole-2-carboxylic acid methyl ester (142). To a solution of **141** (1.15g, 2.81 mmol) in MeOH (20 mL) was added 10 % Pd-C (100 mg). The solution was hydrogenated in a Parr-hydrogenator at 40 psi H_2 for 3 h, filtered through silica pad and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (EtOAc) to give **142** (1.02 g, 89%) as a white foam: $[\alpha]_D$ −6.4 (*c* 1.0, CH_2Cl_2); IR (neat) 3431, 2955, 2884, 1726, 1650, 1455, 1419, 1183 cm^{-1}; ^1H NMR δ 4.47 (bs, 1 H, -O*H*), 4.42 (d, 1 H, *J* = 10.4 Hz), 4.05-3.85 (m, 4 H), 3.79 (d, 1 H, *J* = 6.7 Hz), 3.77 (s, 3 H), 2.60-2.40 (m, 2 H), 2.35-2.00 (m, 3 H), 2.00-1.80 (m, 2 H), 1.72 (dd, 1 H, J = 13.9, 3.8 Hz), 1.65-1.35 (m, 3 H), 1.17 (t, 1 H, *J* = 13.7 Hz), 1.04 (dd, 1 H, *J* = 14.3, 2.6 Hz), 0.20 (dd, 1 H, *J* = 14.3, 11.4 Hz), 0.00 (s, 9 H); ^{13}C NMR δ 175.8, 174.9, 108.6, 82.2, 71.6, 65.7, 64.5, 57.3, 53.0, 48.0, 38.7, 36.9, 35.8, 33.1, 28.6, 23.0, 17.1, -0.6 (3C); MS (ESI) *m/z* (relative intensity) 434

([M+Na]$^+$, 1), 394 (35), 355 (30); HRMS (ESI) *m/z* 434.1975 calcd for $C_{20}H_{33}NO_6SiNa$ (M+Na), found 434.1989.

(2*S*,7a*R*,7aa*R*,10*S*,10a*R*)-Hydroxy-4,8-dioxo-10-(trimethylsilanylmethyl)-dodecahydroazepino[3,2,1-*hi*]indole-2-carboxylic acid methyl ester (143). To a solution of **142** (0.28 g, 0.68 mmol) in MeOH (13 mL) was slowly added concentrated HCl (1.3 mL) at room temperature. The reaction mixture was stirred for 2 d at room temperature, quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EtOAc (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1: 4) to give **143** (226 mg, 96%) as a white foam: $[\alpha]_D$ –23.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3431, 2946, 2889, 1754, 1716, 1639, 1455, 1440, 1245,1224, 1188 cm^{-1}; ^{1}H NMR δ 4.54 (d, 1 H, *J* = 10.3 Hz), 3.80 (d, 1 H, *J* = 12.9 Hz), 3.78 (s, 3 H), 2.65-2.45 (m, 3 H), 2.40-2.25 (m, 1 H), 2.25-1.90 (m, 5 H), 1.60-1.30 (m, 2 H), 1.15 (d, 1 H, *J* = 14.3 Hz), 0.33 (dd, 1 H, *J* = 14.3, 9.3 Hz), 0.00 (s, 9 H); ^{13}C NMR δ 206.4, 175.3, 174.5, 81.8, 73.3, 57.2, 53.2, 52.7, 44.8, 38.9, 36.7, 33.0, 29.5, 22.4, 18.5, -0.7 (3C); MS (EI) *m/z* (relative intensity) 367 (M$^+$, 3), 352 (55), 308 (100), 292 (18), 73 (19); HRMS (EI) *m/z* calcd for $C_{18}H_{29}NO_5Si$ 367.1815, found 367.1830.

(3*S*,9*R*,9a*R*)-9-[3-Acetoxy-4-(trimethylsilanyl)-butyryl]-1,5-dioxooctahydro-pyrrolo[1,2-*a*]azepine-3-carboxylic acid methyl ester (145). A solution of **143** (88 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was treated with $PhI(OAc)_2$ (230 mg, 0.714 mmol) and I_2 (180 mg, 0.709 mmol) at room temperature. The reaction mixture was stirred for 2 d, diluted with EtOAc (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:3) to give **145** (20 mg, 25 %) as a colorless oil:

$[\alpha]_D$ –24.3 (*c* 1.0, CH_2Cl_2); IR (neat) 2943, 1736, 1705, 1654, 1434, 1403, 1368,1238, 1163 cm^{-1}; ^1H NMR (mixture of diastereomers) δ 5.40-5.25 (m, 1 H), 4.90-4.75 (m, 1 H), 4.71 (dd, 1 H, *J* = 10.9, 10.1 Hz), 3.76 (s, 3 H), 3.00-2.80 (m, 2 H), 2.75-2.45 (m, 5 H), 2.02, 2.00 (2s, 3 H), 1.95-1.75 (m, 2 H), 1.75-1.55 (m, 2 H), 1.06 (dd, 2 H, *J* = 9.7, 7.2 Hz), 0.06 (s, 9 H); ^{13}C NMR (mixture of diastereomers) δ 208.8, 208.5, 206.2, 174.6, 174.5, 172.1, 170.0, 69.1, 63.3, 63.0, 55.3, 53.9, 53.0, 50.0, 49.3, 38.8, 38.7, 36.2, 30.1, 23.2, 21.5, 20.4, 20.2, –0.8; MS (EI) *m/z* (relative intensity) 425 (M^+, <1), 365 (40), 296 (42), 236 (70), 73 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{31}NO_7Si$ 425.1870, found 425.1889.

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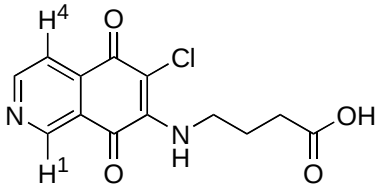
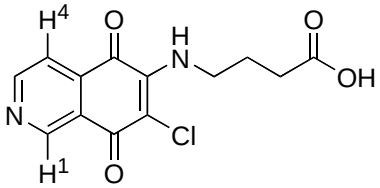


vs.



H^1 δ 9.13 ppm(s) in MeOH-d_4

H^4 δ 7.92 ppm(d, *J* = 5.0 Hz) in MeOH-d_4

H^1 δ 9.17 ppm(s) in MeOH-d_4

H^4 δ 7.88 ppm(d, *J* = 4.9 Hz) in MeOH-d_4

δ H^1-H^4 = 1.21 < δ H^1-H^4 = 1.29

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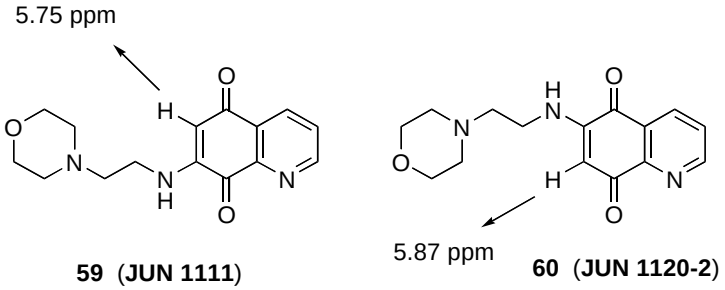

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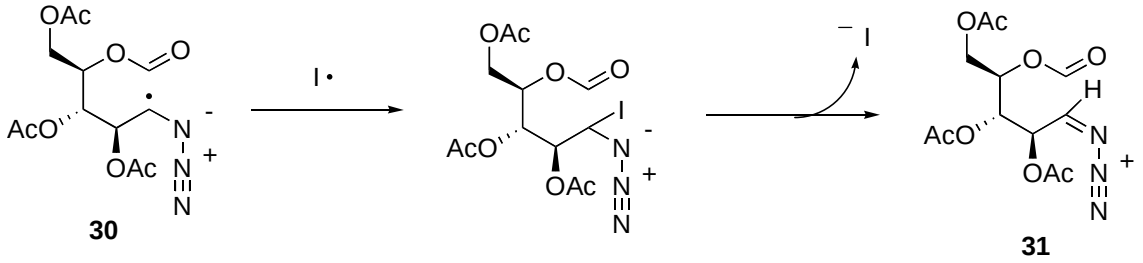
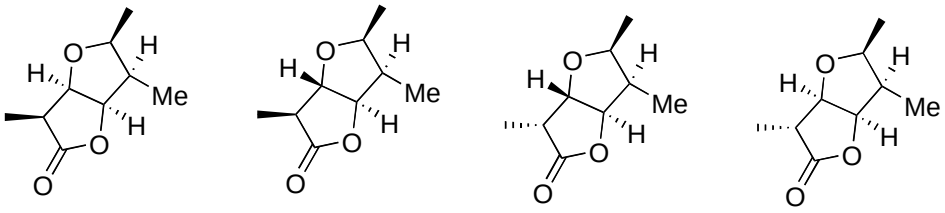
97. Oxidation of radical intermediate **30** to carbocation **31** presumably proceeds via an iodocompound:



For another transformation of azides into nitriles, see: The Chemistry of the Azido group, Patai, S. Ed.: Interscience New York, **1971**: pp 348, 441.

98. MM2 minimized energy calculations (Chem 3-D) with the simplified A/B ring system of parvistemonine were done for four possible diastereomers:

4-possible diastereomers



21.13 35.15 36.83 22.01

steric energy (kcal/mol) by MM2 (Chem 3D pro) for minimized conformations

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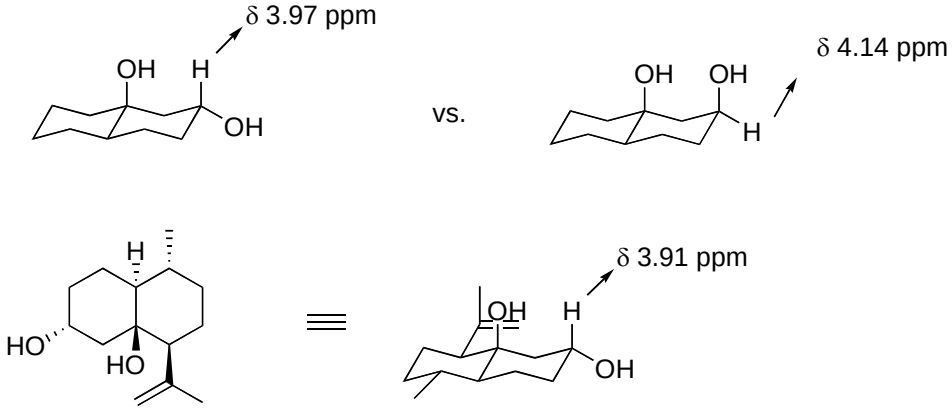
110. Initially, we assigned this compound as the β-alcohol assuming a sodium borohydride attack from the less hindered face, but chemical shift analysis of **74** supported torsional control as the controlling factor. The assignment of the stereochemistry of the secondary alcohol of **74** was established on the basis of the NMR signals (*vide infra*).



74

For NMR analysis, see (a) Gula, M. J.; Vitale, D. E.; Dostal, J. M.; Trometer, J. D.; Spencer, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 4400. (b) Senda, Y.; Kikuchi, N.; Inui. A.; Itoh, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 237.

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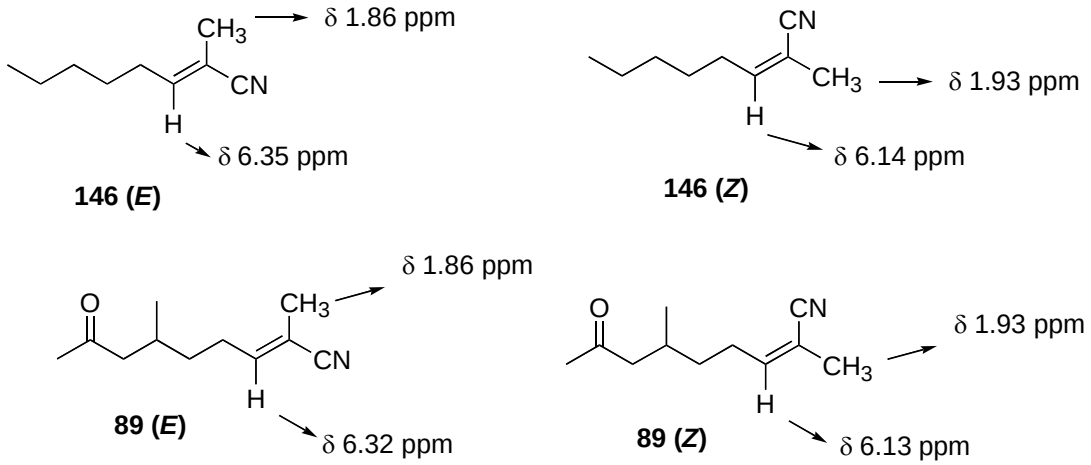
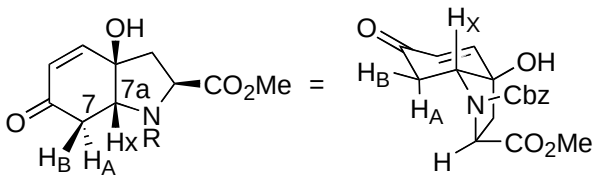
115. Tertiary alcohol **88** was obtained as a single diastereomer presumably via equatorial attack of MeMgBr to the carbonyl group of **87**. For examples of equatorial attack, see (a) Panev, S.; Dimitrov, V. *Tetyrahedron Asym.* **2000**, *11*, 1517. (b) Jauch, J.; Schurig, V. *Tetrahedron Asym.* **1997**, *8*, 169.

116. The (*E/Z*) configuration of **89** was determined by the comparison of NMR spectra of **89 (*E*)** and **(*Z*)** with those of **146 (*E*)** and **(*Z*)**, see: Yoneda, R.; Harusawa, S.; Kurihara, T. *J. Chem. Perkin. Trans. I* **1998**, 3163.

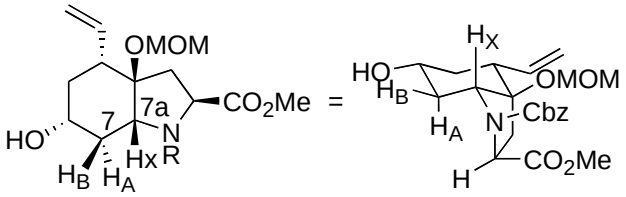


117. The stereochemistry of **96** was determined by the coupling constant of protons at C(7) and C(7a) of compounds **96-104** in ^{1}H NMR based on the previous ^{1}H NMR assignment of compound **1** (see references 86(a) and 76(c)). The stereochemistry of **105** (**96-1**) was also assigned by similar methods.



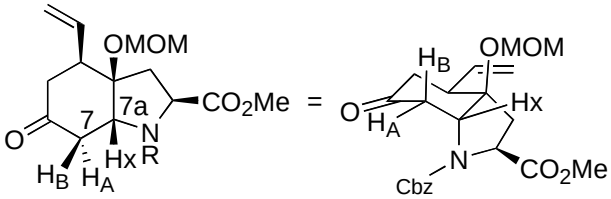
J_{AX} = 9.5 Hz
J_{BX} = 5.9 Hz
δ H_X = 4.21 (dd, 1 H, *J* = 9.5, 5.9 Hz)

1



J_{AX} = 10.5 Hz
J_{BX} = 4.3 Hz
δ H_X = 4.27 (dd, 1 H, *J* = 10.5, 4.3 Hz)

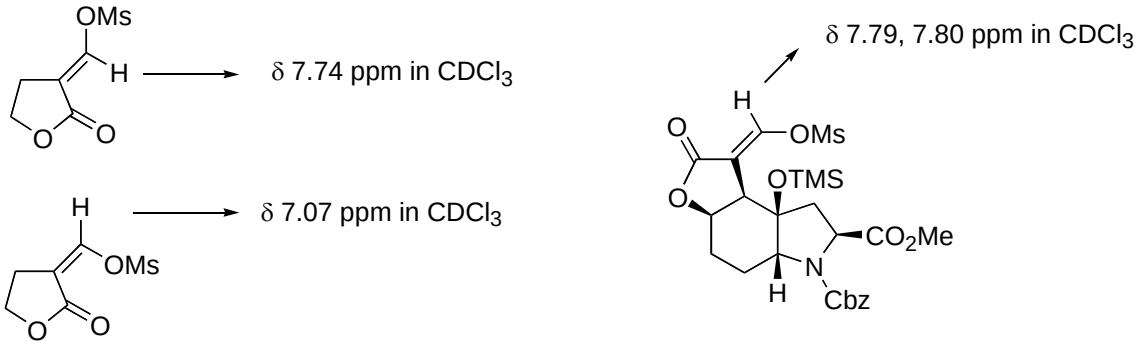
97



δ H_X = 4.35 (dd, 1 H, *J* = 7.0, 6.8 Hz)

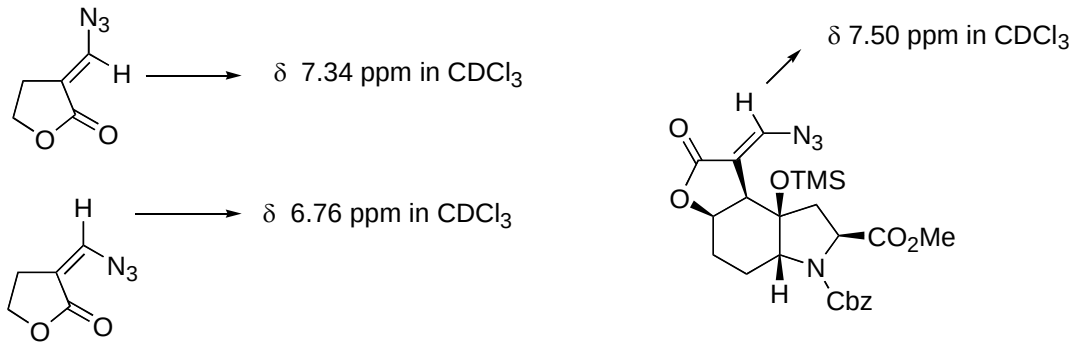
96-1

118. Only (*E*)-vinyl mesylate **113** was obtained. The (*E/Z*)-configuration of the vinyl mesylate **113** was determined by the ^{1}H NMR chemical shift of the vinyl proton, see: Jonas, J. *Coll. Czech. Chem. Commun.* **1984**, *49*, 1907.



113

119. Only (*E*)-vinyl azide **114** was obtained. The (*E/Z*)-configuration of the vinyl azide **114** was determined by the ^{1}H NMR chemical shift of the vinyl proton, see: Movzal, C.; Jurko, Z.; Jonas, J. *Coll. Czech. Chem. Commun.* **1984**, *49*, 2509.



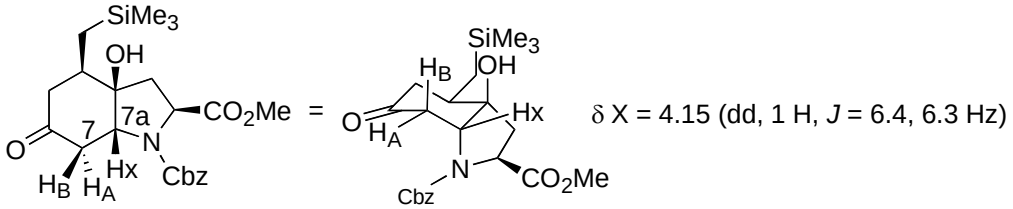
114

120. In *Silicon Reagents in Organic Synthesis*, E. W. Colvin Academic Press, 1988, 3-4 pp and references cited therein.

121. In "Classics in Total Synthesis", Nicolau, K. C.; Sorensen, E. J. VCH, 1996 pp 610.

122. Hatcher, M. A.; Borstnik, K.; Posner, G. H. *Tetrahedron Lett.* **2003**, *44*, 5407.

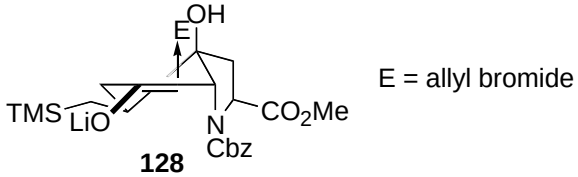
123. Only a single diastereomer was obtained presumably via nucleophilic attack from the less-hindered β-face of **1**. The stereochemistry of **128** was determined by the coupling constants of protons at C(7) and C(7a) in the ^{1}H NMR:



128

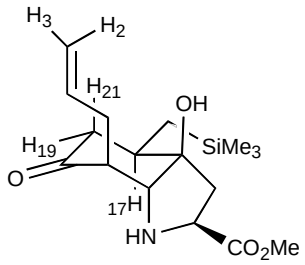
124. Though we believe that we got single diastereomers based on ^{1}H NMR and ^{13}C NMR analyses, we have been not able to assign the exact stereochemistry of **130** and **131**. Efforts to obtain a single crystal, including chemical derivatizations, failed to provide crystals suitable for X-ray analysis.

125. Only a single diastereomer was isolated after work-up and purification by chromatography on SiO_2. The stereochemistry of this reaction could be interpreted by the preference of axial alkylation of **128**:



128

The stereochemistry of **132** was determined by 2D NMR analyses of **139**. Major interactions in the NOESY of **139**:



139

NOE effect in NOESY spectra

H_3 and H_{21}

H_2 and H_{21}

H_{19} and H_{17}

126. (a) Ozonolysis of **133** led to an unidentified product. (b) For an improved procedure, 2,6-lutidine was used, see: Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.

127. The stereochemistry of **138** was tentatively determined by previous results in our group. See reference (94).

128. We could not determine the exact stereochemistry at C4 of **137** and it was hard to tell whether we obtained **137** as a single diastereomer or a mixture of diastereomers due to the low resolution of NMR spectra of **137** in $CDCl_3$. **137** readily decomposed at 373°K in DMSO-d_6.

129. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

130. In contrast to **130** and **131**, compound **145** was obtained as a ~1:1 mixture of diastereomers. This result prevented us from making a tentative assignment of the stereochemistry of these fragmentation products.