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Studies towards total synthesis of MPC1001F - a triketopiperazine-dihydrooxepin natural product

by

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DEDICATED TO

MY PARENTS AND MY WIFE DEBJANI

ABSTRACT

The thesis describes synthetic studies towards MPC1001F, a triketopiperazine-dihydrooxepin natural product. Another related member of this class of natural products is MPC1001 with an epidithiodioxopiperazine core and potent antitumor activity. Our goal was to construct the molecular skeleton of the comparatively simpler MPC1001F first so that the knowledge gained during this project can be applied to the synthesis of the more complex MPC1001. None of these MPC natural products have yet been synthesized. An enantioselective synthesis of the tricyclic core of MPC1001F is discussed first, by a route which followed the strategy on a related core, already established in our group. The main synthetic challenges encountered in this route are discussed. These involved oxidation of an alcohol without epimerization next to the resulting aldehyde, oxidation of an alcohol in the presence of selenium, and construction of a tetrahydrooxepin ring via a conjugate addition-elimination process. An insurmountable obstacle in this route led us to explore a different strategy.

In the next section, several unsuccessful approaches towards the core, starting from already-synthesized intermediates from the first route, are described. Finally, I designed a new short enantioselective sequence towards the core structure which is shown in the third section of this thesis. The synthesis of the tricyclic core has been achieved following this new strategy. The last few steps to the fully functionalized core are still being studied.

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I would like to thank my supervisor Dr. D. L. J. Clive for his support and guidance throughout my Ph.D. program.

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LIST OF ABBREVIATIONS

Ac	Acetyl
AD	Asymmetric dihydroxylation
AIBN	2,2'-azobisisobutyronitrile
APT	Attached proton test
Ar	Aromatic ring
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bop	Bis(2-oxo-3-oxazolidinyl)phosphonic
brsm	Based on recovered starting material
Bu	*n*-Butyl
t-Bu (or Bu-*t*)	*tert*-Butyl
Bz	Benzoyl
CD	Circular Dichroism
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DHP	3,4-dihydropyran
DIBAL	Diisobutylaluminum hydride
DKP	Diketopiperazine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane

DMF	*N*,*N*-Dimethylformamide
DMF-DMA	Dimethylformamide dimethyl acetal
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DP	Desired product
EDCI	*N*-Ethyl-*N*-(3-dimethylaminopropyl)carbodiimide
dr	Diastereomeric ratio
Et	Ethyl
ETP	Epidithiodioxopiperazine
Fmoc	[(9-fluorenylmethyl)oxy]carbonyl
FTIR	Fourier transform infrared spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid
ImH	Imidazole
LDA	Lithium diisopropylamide
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
MEM	(Methoxyethoxy)methyl
mp	Melting point
MS	Molecular sieves
MW	Microwave
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-Methyl morpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl
py	Pyridine
quant.	Quantitative yield
rt	Room temperature
SM	Starting material
TBAF	Tetrabutylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Teoc	Trimethylsilylethyl carbamate
THP	Tetrahydropyranyl
TPAP	Tetrapropylammonium perruthenate
Ts	*p*-Toluenesulfonyl
TBS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl

TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

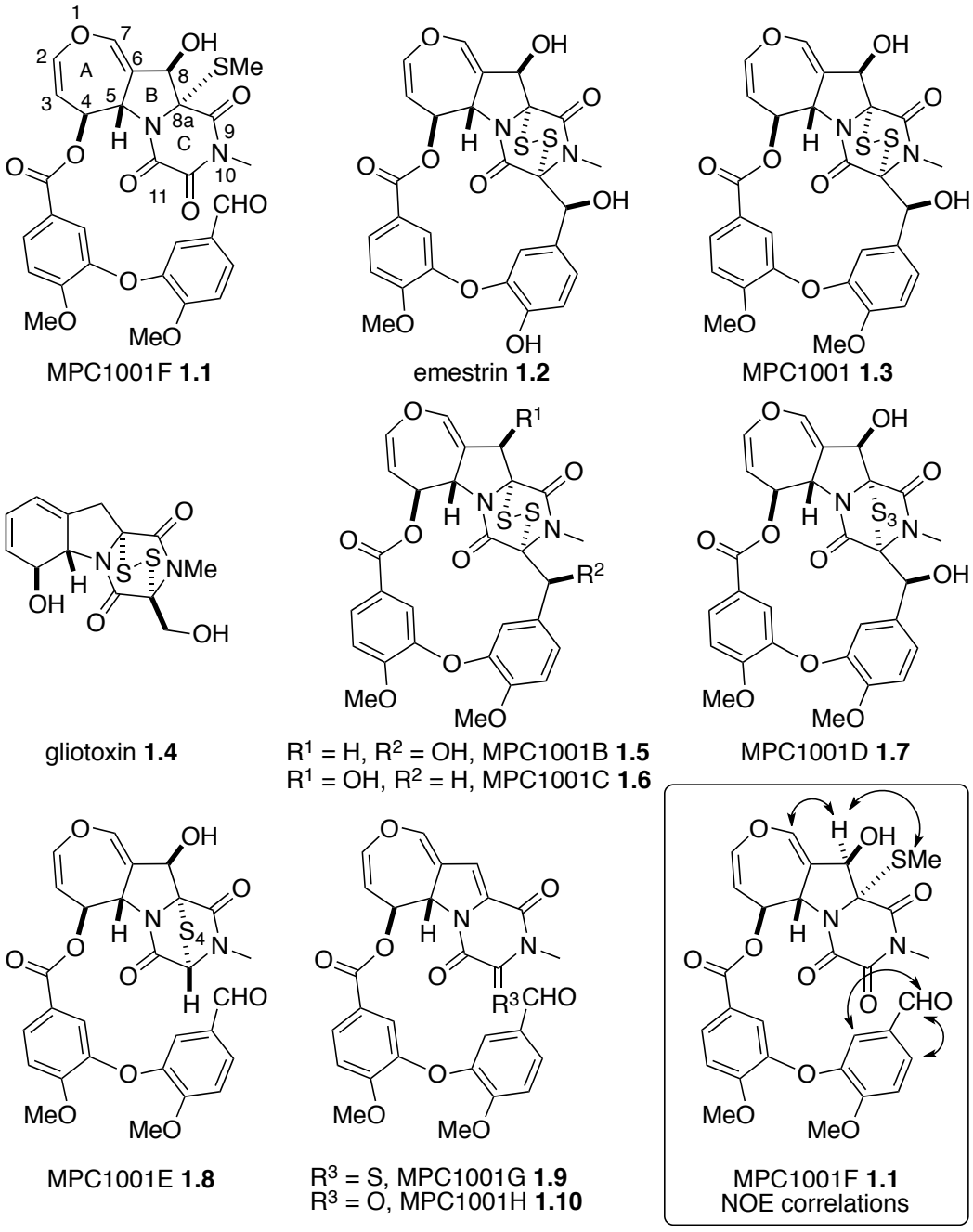
1. Introduction

1.1. Isolation and structure determination of MPC1001F and biological properties of related compounds

MPC1001F (**1.1**, Scheme 1), a natural product which falls into the class of epipolythiodioxopiperazine (ETP)-dihydrooxepin compounds, possesses some specific characteristic features which have made it a unique member in its class; it should more appropriately be recognized as a member of the triketopiperazine-dihydrooxepin class of natural products. Three other biologically significant ETP-dihydrooxepins (**1.2**, **1.3**, **1.4**) are also shown in Scheme 1, and it can be seen that MPC1001F is structurally closely related to emestrin (**1.2**) and MPC1001 (**1.3**), although **1.1** has a somewhat simpler molecular architecture.

There are at least 14 ETPs known[1] (without including their derivatives, epipolythio and epimonothiodioxopiperazines), among which gliotoxin (**1.4**) was the first to be reported and is the most extensively studied. All ETPs are toxic fungal secondary metabolites. MPC1001F was first isolated from the fungus *Cladorrhinum* sp. KY4922, which was found in a soil sample from Indonesia in the year 2004.[2] Along with MPC1001F, seven other structurally related new compounds were also isolated, including MPC1001 and MPC1001B, C, D, E, G and H (Scheme 1). These compounds were classified into four different types, I-IV. Most of the members including MPC1001 (**1.3**), fall into Type I having dithio and trithio (only for MPC1001D, **1.7**) bridges. Type II members do not possess

any sulfur bridge. Types III and IV have unique features: Type III (MPC1001E, **1.8**) has a tetrathio bridge, whereas the Type IV member, MPC1001F (**1.1**), is a



Scheme 1. MPC1001F and other ETP natural products

monothiotriketopiperazine, containing an SMe unit. In this connection it is worth mentioning that MPC1001 (**1.3**) was also isolated in 2005, from a fungus found in Musk Ox dung collected in Alaska.[3] The structure and relative stereochemistry of MPC1001 were determined by extensive NMR experiments[2b] and, finally, the absolute configuration was assigned by comparing the CD spectra of MPC1001 and emestrin (the structure of emestrin was established by X-ray crytallography[4]). The structure of MPC1001F was then established by comparing its NMR data with that of MPC1001. This comparison confirmed the existence of the oxepin and benzoate subunits in **1.1**. The presence of an SMe group was confirmed by FABMS analysis. ^{13}C NMR, NOE, LSPD and HMBC correlations confirmed the rest of the structure.[2b] The significant NOE correlations are highlighted in Scheme 1.

It has long been known that the presence of the sulfur atoms in the form of the disulfide bridge is an essential feature for the biological activity of ETPs. The desulfurized version of gliotoxin showed no activity against lymphosarcoma tumor cells, even at a concentration of 800 μg/mL, whereas a 1μg/mL concentration of gliotoxin itself was good enough for complete growth inhibition of tumor cells.[5] In a report published in 1974,[6] Middleton showed that derivatives of sporidesmin (an ETP) lacking the disulfide bridge, or having two thiomethyl groups in its place, were absolutely inactive towards swelling of mitochondria. Hence, it is not surprising that MPC1001F was not found to show any biological activity.

It was initially thought that the oxepin ring might not contribute to the biological properties, but some synthetic derivatives of aranotin (an ETP-dihydrooxepin class of natural product) where the dihydrooxepin units were replaced by other aromatic groups, did not show the activity possessed by aranotin itself.[7] Hence, one may suspect that the reactive enol ether segment in the dihydrooxepin unit might also be crucial (as is the ETP core) for the biological properties of these compounds. However, the dihydrooxepin unit is not by itself sufficient for activity, as revealed by MPC1001F.

Despite its lack of activity, we were interested in the total synthesis of MPC1001F. Our group has been working on the total synthesis of MPC1001 for the last few years. MPC1001 is biologically very important, and it is worth mentioning some of its biological properties. Our eventual goal was to use the synthetic knowledge gained during the synthesis of MPC1001F towards the subsequent synthesis of MPC1001. None of these MPC compounds (shown in Scheme 1) have been synthetically achieved.

MPC1001 exhibits antimicrobial activity against Gram positive bacteria (e.g. *Staphylococcus aureus*), but demonstrates comparatively weak effects towards Gram negative bacteria.[2c] It has also been found to be about 40 times more effective in terms of its antiproliferative activity against the human prostate cancer cell line DU145 than known antitumor agents like etoposide.[2c] The IC_{50} value of etoposide, for example is 400 nM while that for MPC1001 is only 9.3 nM. In 2005 it was discovered that MPC1001 (along with several other ETPs, including emestrin) is an effective chemokine receptor 2 (CCR2) antagonist; it

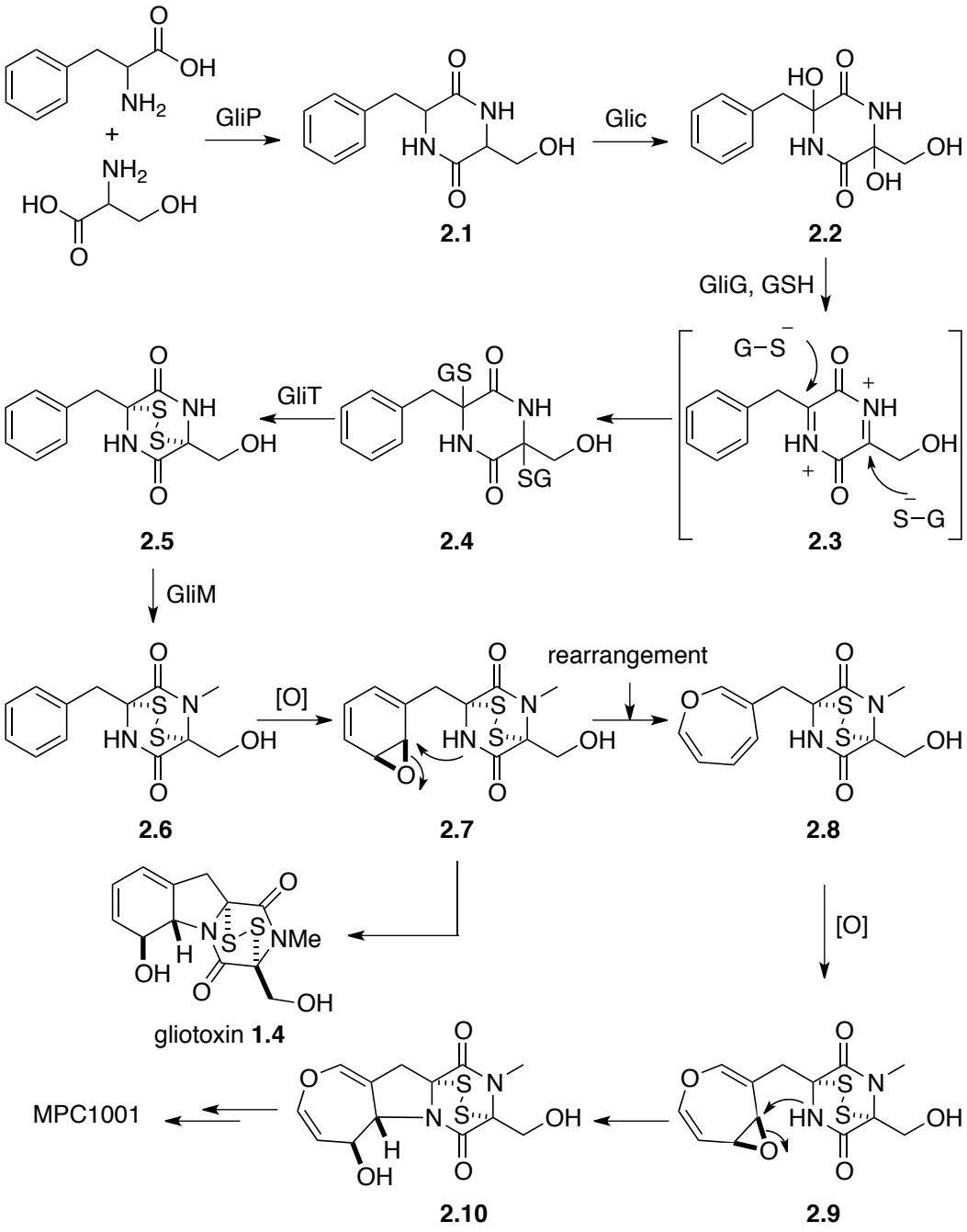
inhibits the binding of monocyte chemoattractant protein-1 (MCP-1) to CCR2 with an excellent IC_{50} value (0.8 μM).[3] The MCP-1-CCR2 complex is associated with diseases like rheumatoid arthritis and atherosclerosis. Hence MPC1001 could possibly have a beneficial therapeutic effect against these diseases.

There are several other ETPs which are known to have activity against viruses,[8] fungi[4] and bacteria.[9] Two possible mechanisms are proposed to account for the cytotoxicity of ETPs. As mentioned earlier, the disulfide bridge is an essential moiety contributing to the biological activity. It is believed that a thiol group on a protein can form a mixed disulfide bond with an ETP in an oxidative manner, thus deactivating the functions of that protein.[5,6,10] For example, cysteine residues can participate in mixed disulfide bond formation.[11] The second mechanism involves generation of deleterious reactive oxygen species (superoxide or peroxide), formed in a redox cycle.[12] The dithio bridge can be reduced to the dithiol in the presence of cellular glutathione[12e] and then the dithiol can be oxidized under aerobic conditions, generating the reactive oxygen species.

1.2. General biosynthetic origins of ETP-dihydrooxepin class of natural products

Although extensive research on biological pathways towards emestrin and MPC1001 and related structures have not been reported, it is hypothesized that emestrin could be generated by the combination of an ETP unit (which is formed

from two molecules of phenylalanine) and one molecule of benzoic acid.[4] Earlier research on the biosynthesis of gliotoxin using isotopic labeling and feeding



Scheme 2. General biosynthetic proposals of ETP-dihydrooxepin compounds

GliP = gliotoxin peptide synthetase; GliC = gliotoxin cytochrome P450 enzyme; GliG = a gene enabled to code for a glutathione-S-transferase; GliM = gliotoxin methyl transferase; GliT = gliotoxin thioredoxin reductase; GSH = glutathione.

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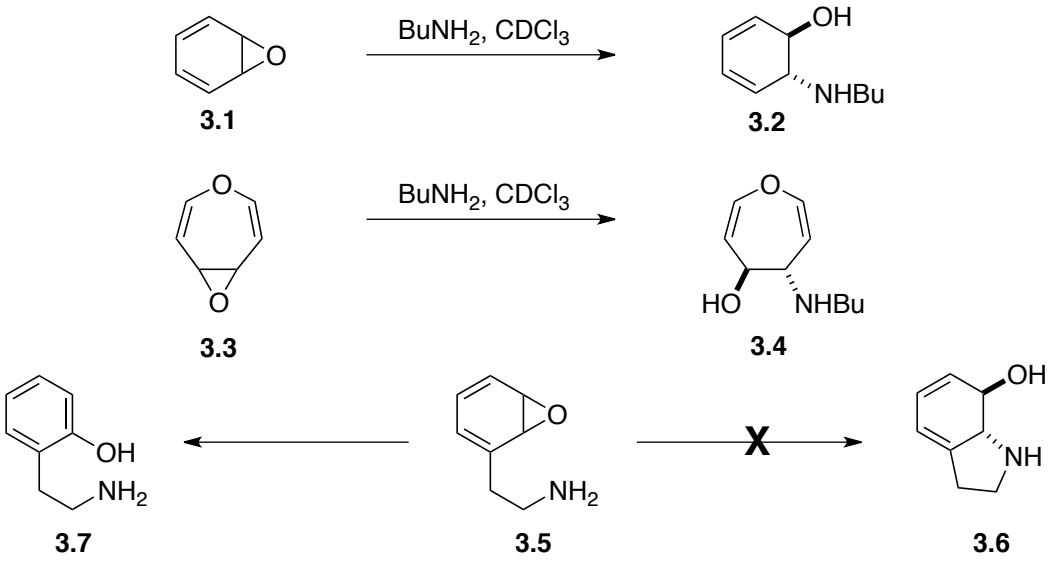
studies revealed that the DKP ring could be synthesized from phenylalanine and serine.[1a,13] A related ETP, sirodesmin (not shown in this discussion), was proved to come from serine and tyrosine.[14] Hence, one can speculate that the biosynthesis of MPC1001F should also follow the same pattern (Scheme 2). A general route to the ETP core of gliotoxin[1a,15] is shown in Scheme 2, based on recent research. Condensation of phenylalanine and serine in the presence of peptide synthetase (GliP, the term Gli stands for gliotoxin for all enzymes involved) produces the DKP unit **2.1**. Oxygenation of **2.1** by GliC (cytochrome P450 enzyme) generates **2.2**. Intermediate **2.2** is converted into **2.4** via intermediate iminium ion **2.3** by GliG (a gene enabled to code for a glutathione-S-transferase) and glutathione (GSH). Thioredoxin reductase (GliT) mediated oxidation finally provides the ETP core (**2.5**). Earlier labeling experiments[16] also proved that cysteine is the direct sulfur source, although methionine and sodium sulfate can also be the sources of sulfur. *N*-Methylation occurs in the presence of methyl transferase (GliM) to afford **2.6**. Finally, the synthesis of the dihydroxepin core involves formation of an arene oxide (**2.6** → **2.7**), rearrangement to an oxepin (**2.7** → **2.8**), a second oxidation to generate oxepin oxide **2.9**, and, finally, intramolecular epoxide opening with stereochemical inversion, providing the dihydrooxepin-pyrrolidine subunit (**2.10**).[17] This proposal also satisfies the relative stereochemistry around the core of **2.10**.

To validate the above proposal Rastetter *et al*. carried out a few experiments mimicking the proposed nucleophilic attack on the benzene oxide and oxepin oxide[18] (Scheme 3). Although the intermolecular reactions followed the expected pathway, the attempted intramolecular reaction with **3.5** did not give the desired bicyclic product **3.6**. However, the postulated common intermediate **2.10** can be elaborated, in principle, to different structurally related natural products, including MPC1001. The biosynthesis of MPC1001F can also be predicted to follow the same pathway, but with the difference that the disulfurization and dithiol oxidation to a disulfide bridge are not required; instead, possibly a monosulfurization occurs on the DKP intermediate **2.1**.

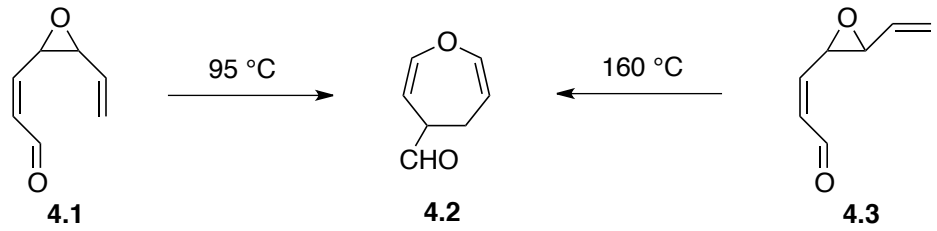


Scheme 3. Rastetter's experiments to validate biosynthetic proposal for oxepins

1.3. A review on the synthesis of dihydrooxepins

There are a few methods of constructing dihydrooxepin rings reported in the literature which will be reviewed in this section. There is a review by Snyder *et al*.[19] on the synthesis of tetrahydrooxepins, which is beyond the scope of our discussion.

Cope rearrangement is the most common method for the synthesis of dihydrooxepin rings.[20] Balci *et al*.[20a,c] reported thermal Cope rearrangement of aldehydes **4.1** and **4.3** to **4.2**.



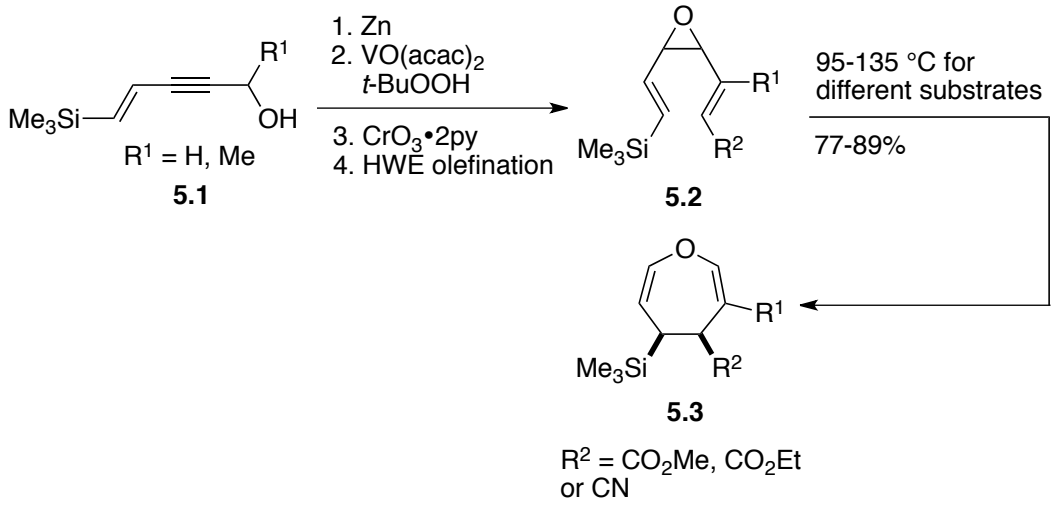
4.1 **4.2** **4.3**

Scheme 4. Dihydrooxepin synthesis by Cope rearrangement

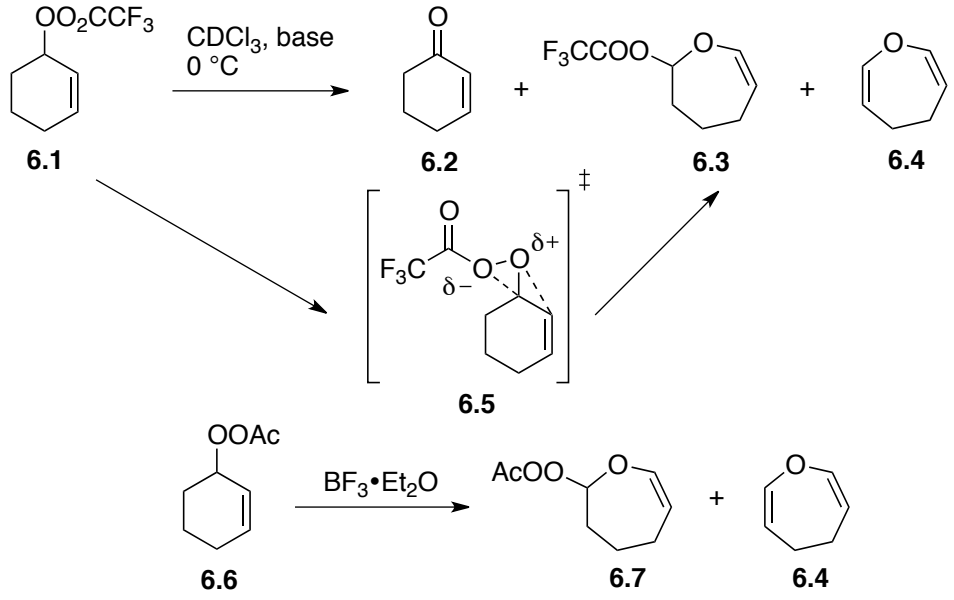
White *et al*.[20d,e] used a similar type of Cope rearrangement, as shown in Scheme 5. Starting from the propargylic alcohols **5.1**, a four-step sequence generated the epoxides **5.2** which, upon heating, afforded the dihydrooxepins **5.3** with *syn* stereochemistry.

Kishi's group[21] has explored the effect of several bases on the Criegee rearrangement of the secondary allylic hydroperoxide **6.1**. They observed three products and the ratio of **6.3** and **6.4** was shown to be dependent on the nature of the base. Using a bulky base like 2,6-di-*t*-butylpyridine they got a 98:2 ratio of

6.4:**6.3**. Use of a catalytic Lewis acid (BF_3•Et_2O) also gave the same results but none of **6.2** was observed in that case.

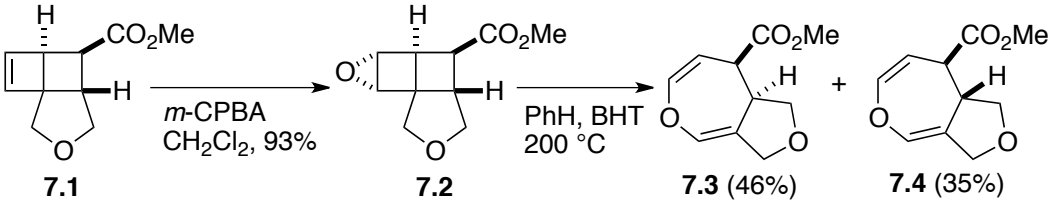


Scheme 5. White's synthesis of dihydrooxepin



Scheme 6. Dihydrooxepin synthesis using Criegee rearrangement

A tetrahydrofuran-fused dihydrooxepin synthesis was reported by Snapper's group.[22] Stereoselective epoxidation of the cyclobutene **7.1** afforded compound **7.2** which, upon heating in the presence of a radical scavenger, generated two diastereomeric dihydrooxepins, **7.3** and **7.4**. Several other examples were studied using different types of substituents on the cyclobutane and tetrahydrofuran rings of **7.1**.

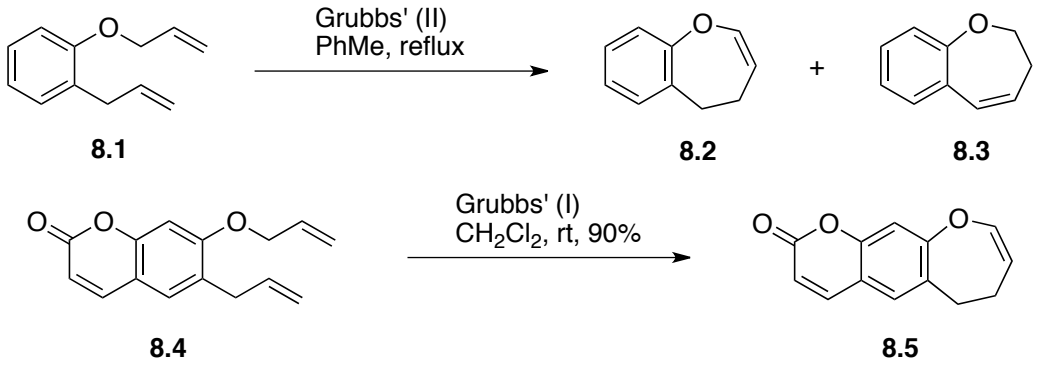


Scheme 7. Snapper's synthesis of dihydrooxepins

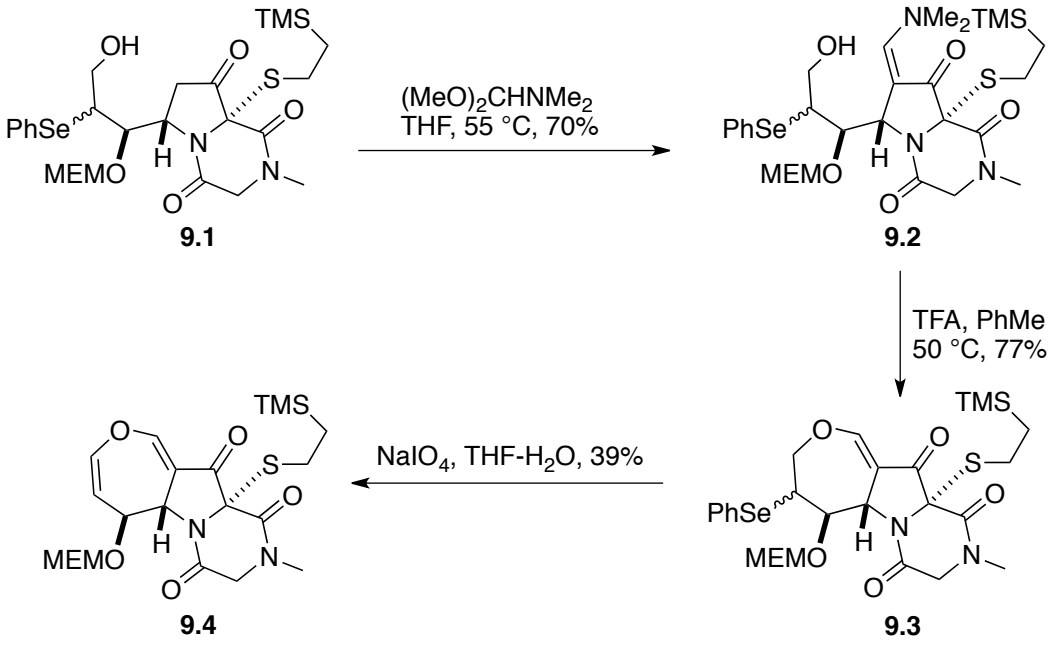
Scheme 8 shows the ring closing metathesis approach adopted by Fustero *et al*.[23a] to make benzo-fused dihydrooxepins. Starting with compound **8.1**, RCM, followed by double bond isomerization, afforded the two regioisomeric dihydrooxepins **8.2** and **8.3**. Recently, a synthesis of coumarin-fused dihydrooxepins was reported,[23b] as shown in Scheme 8. Coumarin **8.4** was treated with Grubbs' first generation catalyst to obtain **8.5** in 90% yield.

A conjugate addition-elimination and oxidative deselenylation strategy was adopted in our group, during synthetic studies towards the MPC1001 core,[24] and this approach was later used by me in my research. The ketone **9.1** was converted into the vinylogous amide **9.2**, which was then subjected to acidic

conditions to generate the tetrahydrooxepin **9.3**. Selenoxide elimination, using $NaIO_4$, afforded the desired dihydrooxepin **9.4**.[24a]

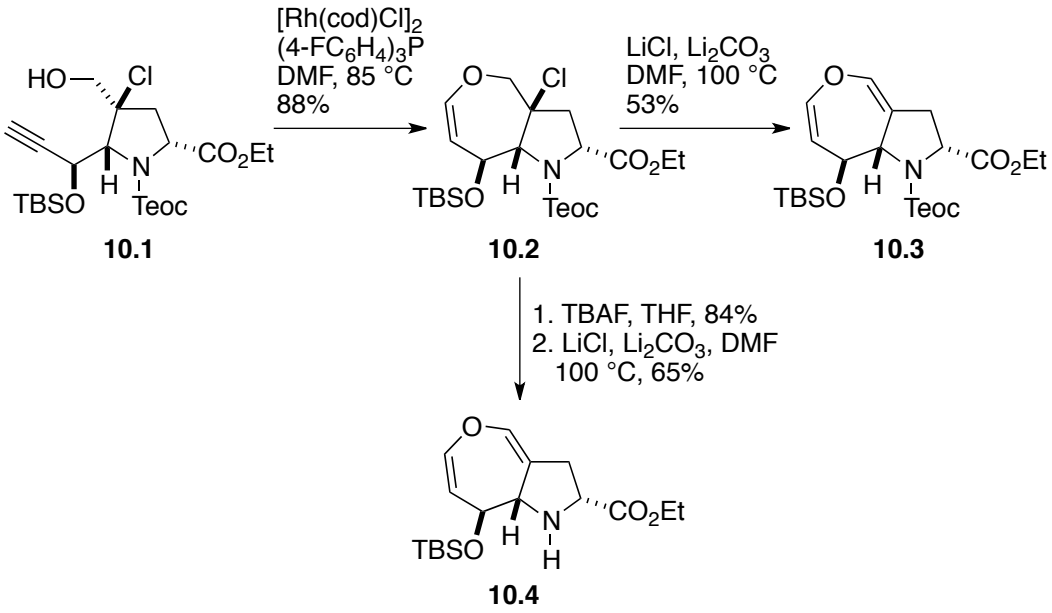


Scheme 8. RCM approaches towards dihydrooxepins



Scheme 9. Conjugate addition-elimination approach to dihydrooxepin unit

The first total synthesis of an ETP-dihydrooxepin natural product, (–)-acetylaranotin, was recently achieved by Reisman.[25] A metal-catalyzed cycloisomerization was utilized to synthesize chlorotetrahydrooxepin **10.2** from terminal alkyne **10.1** in excellent yield. Chloride elimination using LiCl and Li_2CO_3 at elevated temperature gave dihydrooxepin **10.3**. Alternatively, dihydrooxepin **10.4** was also synthesized in a two-step sequence from **10.2**, by a method which involved removal of the Teoc protecting group from nitrogen, followed by chloride elimination.



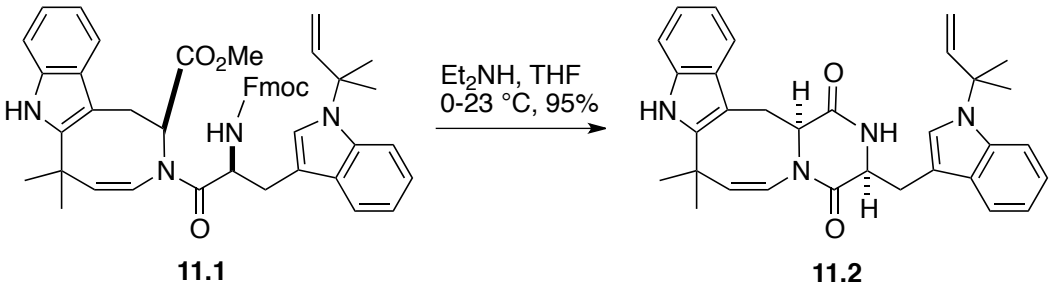
Scheme 10. Reisman's synthesis of dihydrooxepin ring

1.4. A review on the synthesis of DKP rings containing sulfur substituents

2,5-Diketopiperazines (DKP) are very common structural subunits in natural products. A recent review by Borthwick[26] covers the synthesis, reactions

and biological aspects of various DKPs, and here only a few examples of general strategies to synthesize DKPs will be discussed. Then the main discussion will focus on DKPs containing sulfur groups, as present in MPC1001F.

Since 2,5-DKPs are essentially cyclodipeptides coming from condensation of two α-amino acids, the most obvious and common synthetic approach towards this ring system is a dipeptide ester cyclization, as utilized by Corey's group during the total synthesis of okaramine N (Scheme 11).[27] Intermediate **11.1** was converted to DKP **11.2** by removal of the Fmoc protecting group on nitrogen, using Et_2NH, followed by spontaneous cyclization of the free amine onto the methyl ester.

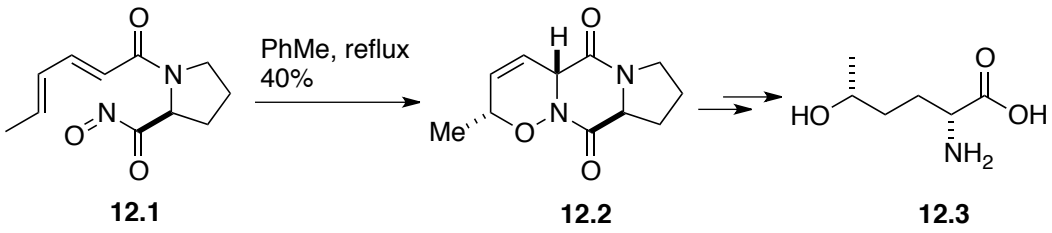


11.1 **11.2**

Scheme 11. Dipeptide ester cyclization strategy to synthesize DKP unit

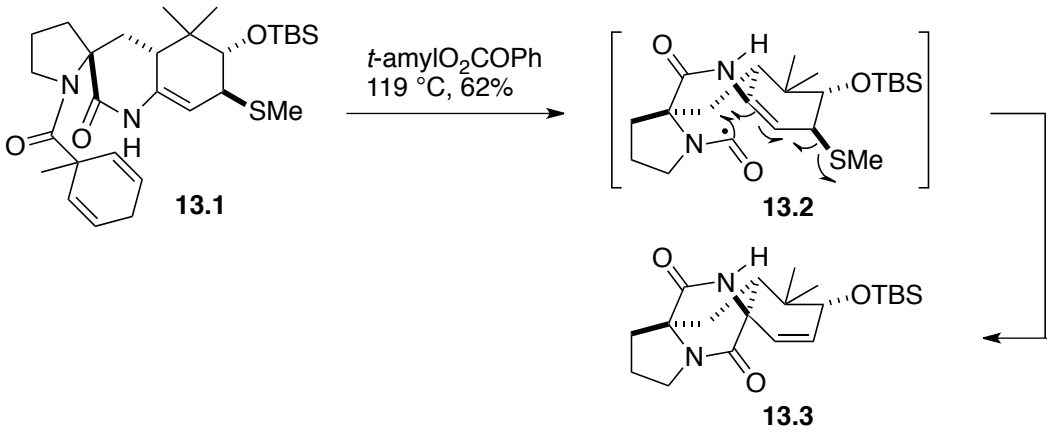
Use of the Diels-Alder reaction is also reported for the construction of the DKP ring,[28] as shown in Scheme 12. The acylnitroso compound **12.1** was converted to the DKP **12.2** in a stereospecific fashion to form an intermediate towards the synthesis of amino acid **12.3**.

The DKP core of stephacidin B was synthesized via a novel green radical cyclization approach[29] depicted in Scheme 13. The radical cyclization precursor



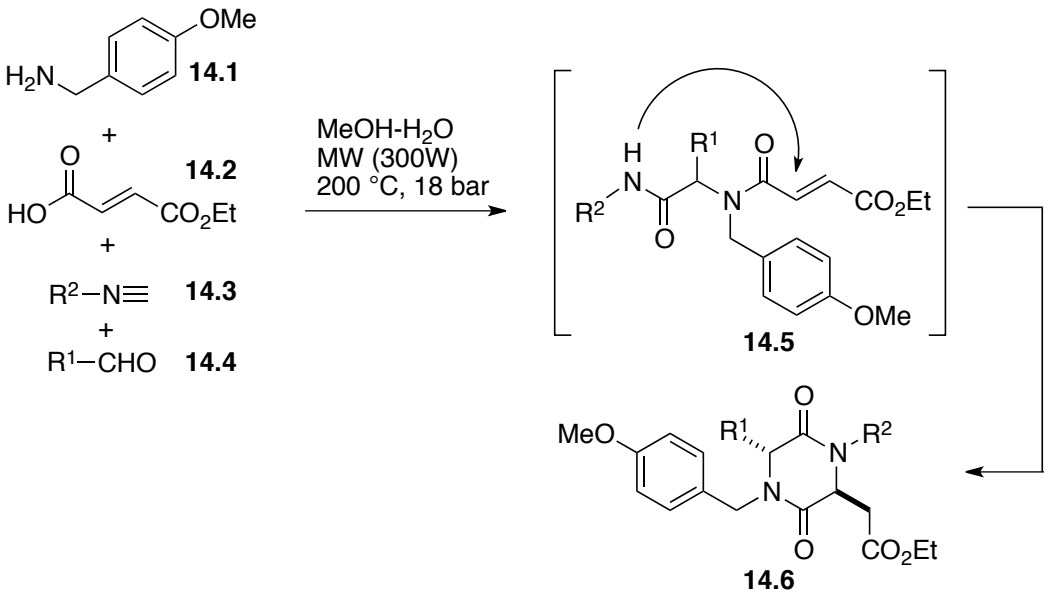
Scheme 12. Diels-Alder reaction to make DKP ring

13.1 was treated with *t*-amyl peroxybenzoate at an elevated temperature to afford the DKP core **13.3** in 62% yield.



Scheme 13. Radical cyclization method to synthesize DKP unit

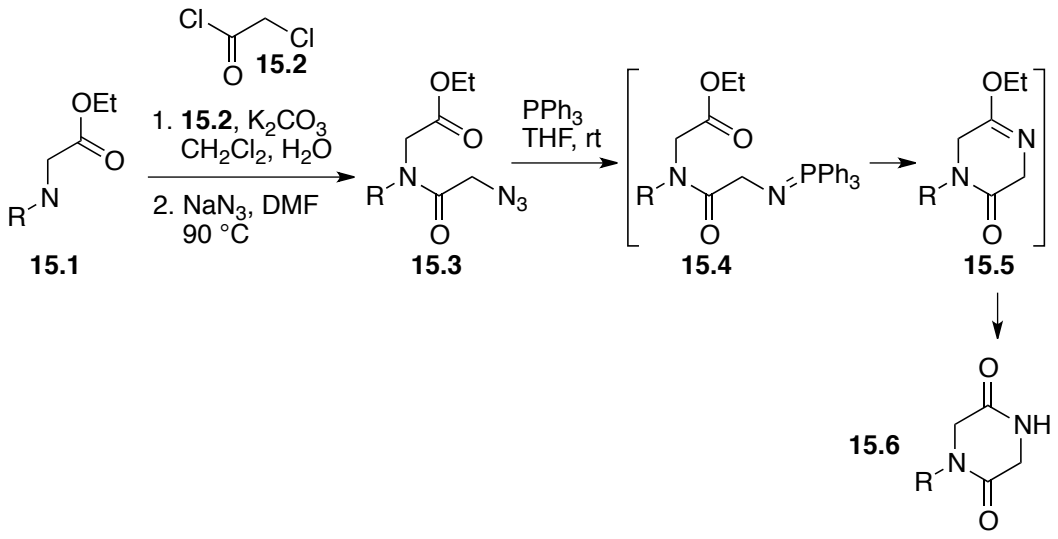
A one-pot multicomponent coupling reaction was developed by Andreana *et al*.[30] This was a four component Ugi reaction (using **14.1**, **14.2**, **14.3**, **14.4**) under microwave conditions which generated intermediates of type **14.5**. These spontaneously underwent intramolecular aza-Michael reaction affording DKPs **14.6**. Several examples were examined using different isonitriles (**14.3**) and aldehydes (**14.4**).



Scheme 14. Ugi reaction to synthesize DKP ring

Recently, an aza-Wittig sequence was used by Majumdar *et al*.[31] for the synthesis of unsymmetrical *N*-substituted DKPs. The amino esters **15.1** were converted to azides **15.3** in a simple two-step sequence. Treatment of **15.3** with Ph_3P generated iminophosphoranes **15.4**, which eventually underwent the aza-Wittig reaction, forming DKPs **15.6** via **15.5**.

During synthetic studies on MPC1001, a novel [1,3]-dipolar cycloaddition strategy (Scheme 16) was developed by Williams's group[32] to tackle the synthesis of the pyrrolidine ring which was then converted to the bicyclic pyrrolidine-DKP unit, as present in MPC1001 (and of course, also in MPC1001F). Compounds **16.1**, **16.2** and **16.3** were subjected to the three-component dipolar cycloaddition conditions, which gave a mixture of the desired pyrrolidine **16.4** and unwanted **16.6**. After extensive optimization studies, the authors were able to convert **16.6** to **16.4** by heating to a high temperature in a sealed tube. Compound **16.6**

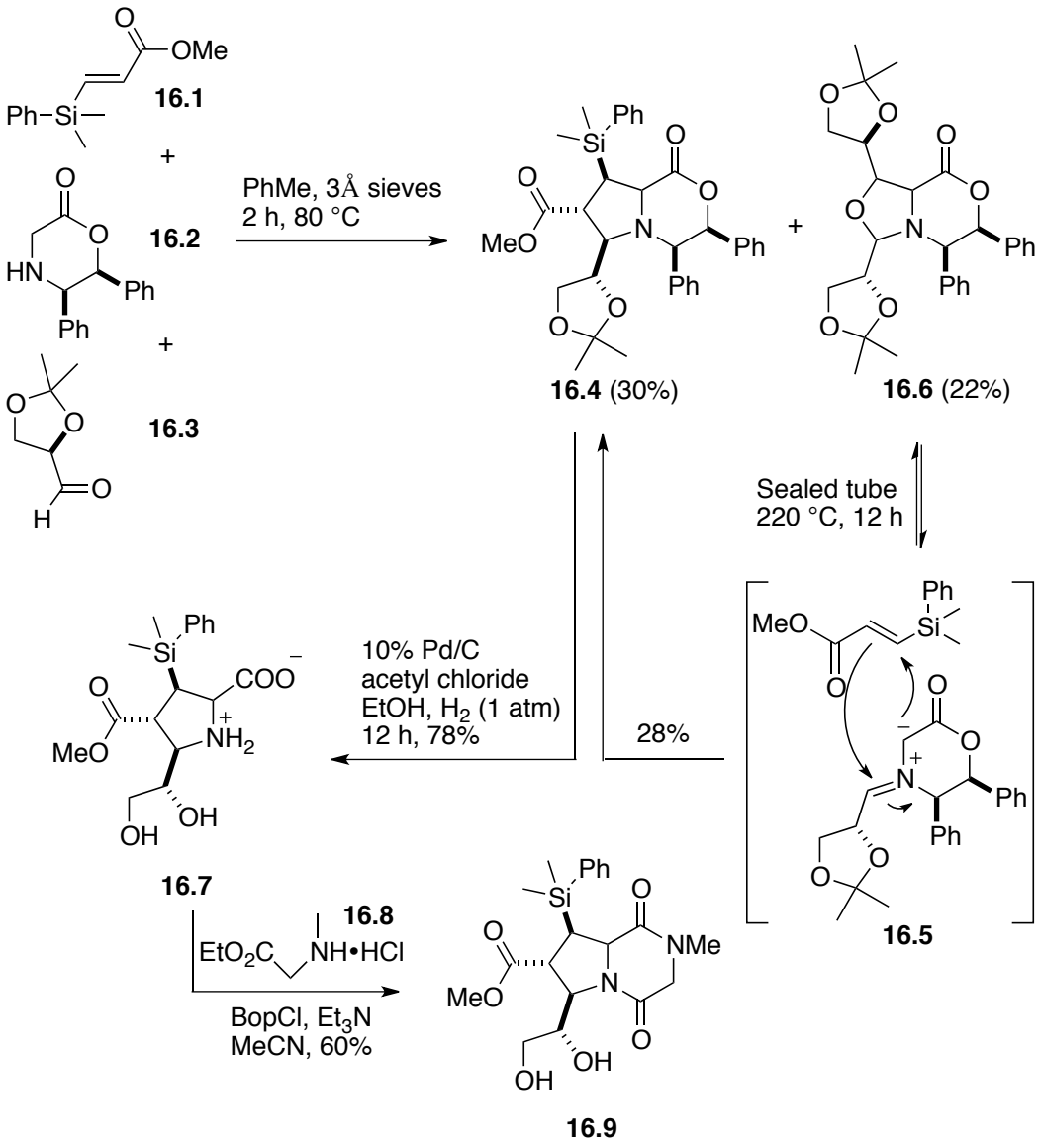


Scheme 15. Aza-Wittig approach to synthesize DKP unit

underwent a retro[1,3]/[1,3]-dipolar cycloaddition affording **16.4** in 28% yield. Removal of the chiral auxiliary from **16.4** generated the amino acid **16.7** which, upon coupling with **16.8**, gave the desired bicyclic DKP core **16.9**.

There are three general strategies to make a sulfur containing DKP. The first is to start with an appropriate sulfur containing precursor and convert that to the desired DKP, as shown in Scheme 17.[33] The second and third approaches both start with the DKP ring and an electrophilic sulfur reagent; this is the approach used in my research. Alternatively, an electrophilic DKP and a nucleophilic sulfur reagent can be used. There are two reviews[34] on ETP syntheses.

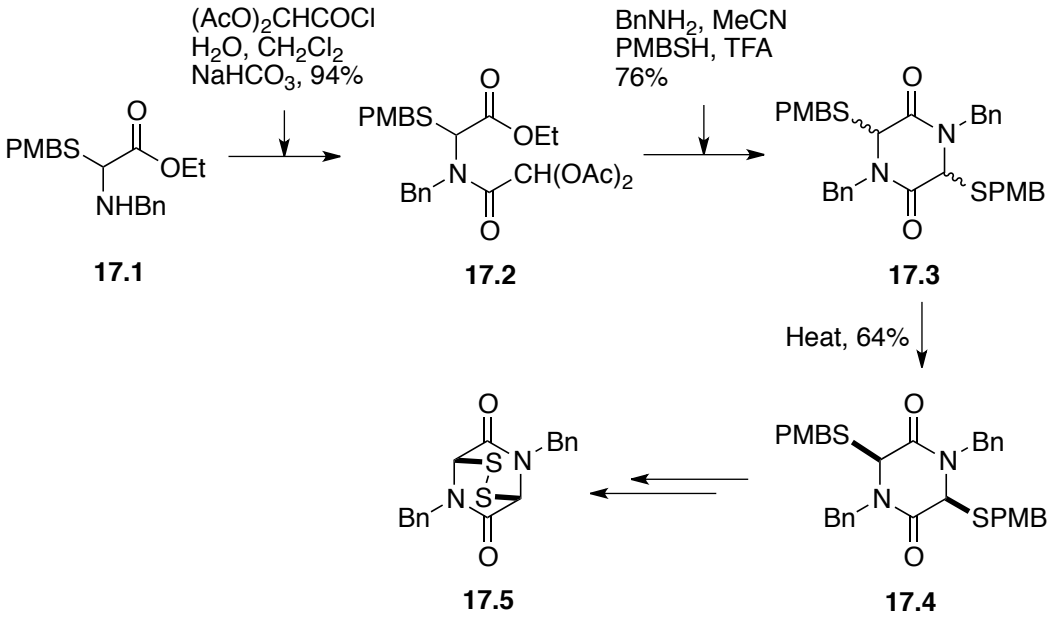
In 2006, Motherwell's group reported a short synthetic route to an ETP.[33] The sulfur-containing ester **17.1** was converted into **17.2** by using diacetoxyacetyl chloride. Treatment of **17.2** with benzylamine at room temperature in the presence of PMBSH (*p*-methoxybenzyl thiol) afforded **17.3** as a *cis*/*trans* mixture,



Scheme 16. Williams's [1,3]-dipolar cycloaddition strategy towards DKP

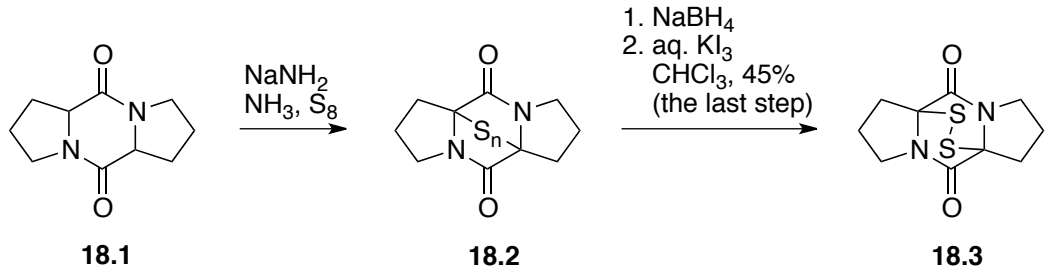
which was eventually converted into the *cis*-**17.4** by simple heating. The DKP **17.4** was then elaborated to ETP **17.5**.

Schmidt *et al*.[35] were the first to install sulfur on a DKP and to convert the product to an ETP, as shown in Scheme 18. The DKP **18.1** was treated with a strong base in the presence of the electrophile S_8 to obtain epipolythiodiketo-



Scheme 17. Motherwell's strategy to synthesize sulfur containing DKP ring

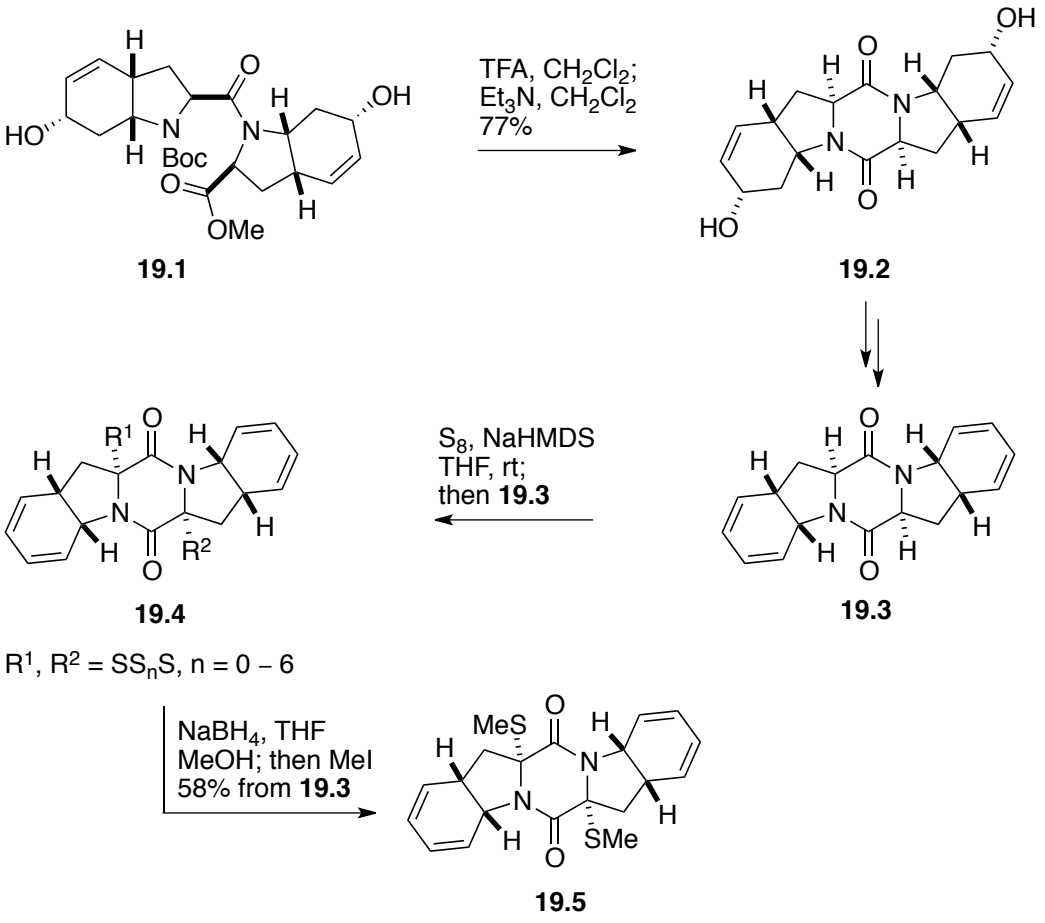
piperazine **18.2**, which then was converted to ETP **18.3** via a reduction-oxidation sequence.



Scheme 18. Schmidt's method to install sulfur on a DKP ring

Very recently, Nicolaou's group has developed a mild strategy[36a] to install sulfur on a DKP ring during the total synthesis of epicoccin G. A dipeptide ester cyclization was used (see also Scheme 11 for this strategy) to make the DKP (**19.1**

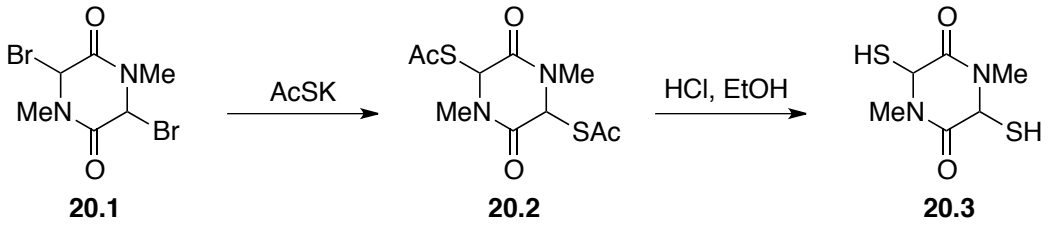
→ **19.2**). Compound **19.2** was elaborated to **19.3**, onto which the sulfur was installed, using a similar strategy to that of Schmidt[35] (**19.3** → **19.4**). The resulting polysulfides **19.4** were reduced with $NaBH_4$ and then methylation on both sulfurs gave **19.5** with two SMe groups on the DKP ring. This method was later generalized and published as a methodology.[36b]



Scheme 19. Nicolaou's synthesis of DKP unit containing SMe groups

Installation of sulfurs on a DKP ring using a nucleophilic sulfur reagent was first developed by Trown's group,[37] as shown in Scheme 20. The *bis*-bromo-

DKP **20.1** was treated with thioacetate to obtain **20.2** which was then hydrolyzed to generate *bis*-thiol-DKP **20.3**.

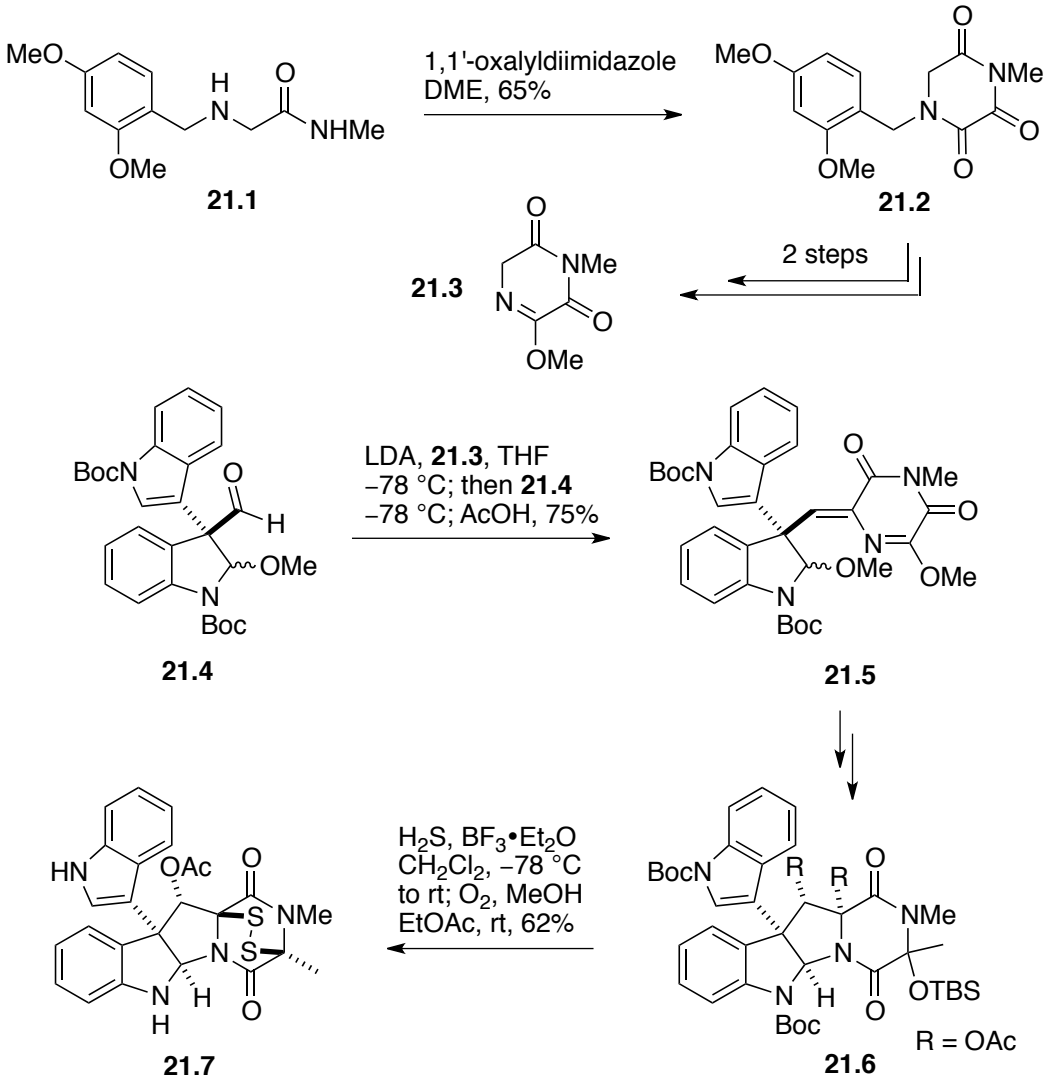


20.1 **20.2** **20.3**

Scheme 20. Trown's approach towards sulfur containing DKP ring

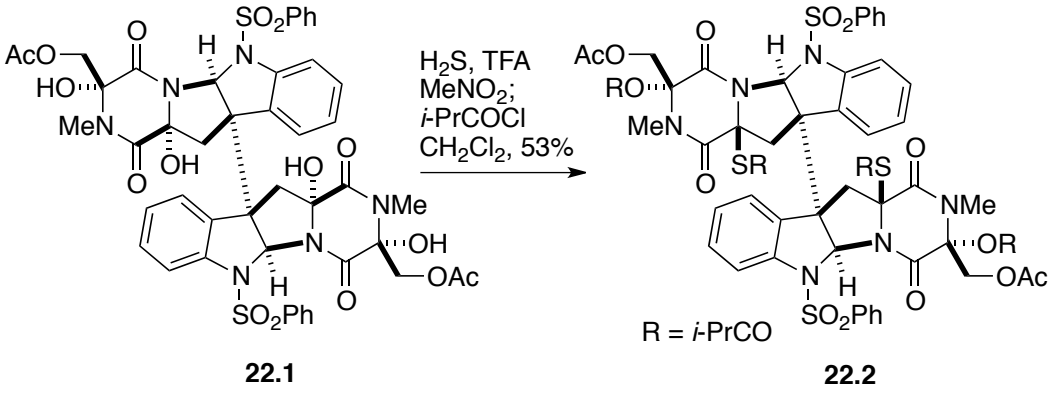
Kishi's group also used this bromination-S_N2 displacement strategy to synthesize sulfur-containing DKPs,[38] and utilized the method to carry out a total synthesis of gliotoxin[38f] (**1.4**) and several other ETP natural products.[38]

Since bromination of more complicated DKPs is not very straightforward, an alternative strategy was also developed where OH or OR groups are used instead of Br, and then later replaced by sulfur nucleophiles. Overman's group used such an approach in the total synthesis of (+)-gliocladine C.[39] The amide **21.1** was converted into the triketopiperazine **21.2** using 1,1'-oxalyldiimidazole. Compound **21.2** was then transformed into **21.3** in two steps. Coupling of **21.3** and **21.4** produced **21.5**, which was elaborated to the advanced stage intermediate diacetate **21.6**. S_N2 displacement of OAc and $OSiMe_2Bu$-*t* groups on the DKP ring by H_2S (in the presence of a Lewis acid), followed by *in situ* oxidation of the resulting thiol, gave the ETP core **21.7** of the natural product. The stereoselectivity of the sulfur introduction is controlled by the stereochemistry of both the indolyl substituent and the acetate group in **21.6**.



Scheme 21. Overman's synthesis of the ETP core of (+)-gliocladine C

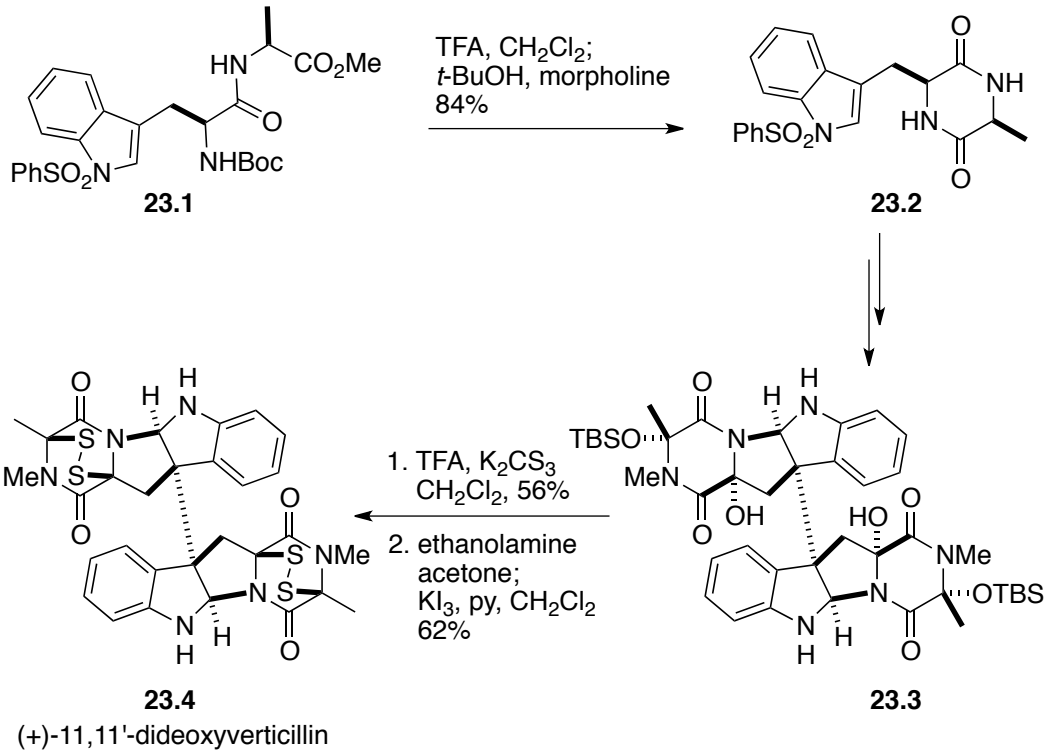
During the total synthesis of (+)-chaetocins A and C and (+)-12,12'-dideoxychetracin A (ETP natural products), Movassaghi's group[40] also used H_2S to incorporate sulfur onto DKP systems. The tetrahydroxy intermediate **22.1** was treated with H_2S under acidic conditions (CF_3CO_2H) to generate the *bis*-thiol which was protected (both thiols and both hydroxyls) affording **22.2**.



22.1 **22.2**

Scheme 22. Movassaghi's method to install sulfur on a DKP ring

Movassaghi *et al*. used a similar strategy[41] to install sulfur onto a DKP ring in the total synthesis of (+)-11,11'-dideoxyverticillin A. The DKP ring was constructed using the dipeptide ester cyclization method in the presence of



23.1 **23.2** **23.3** **23.4**

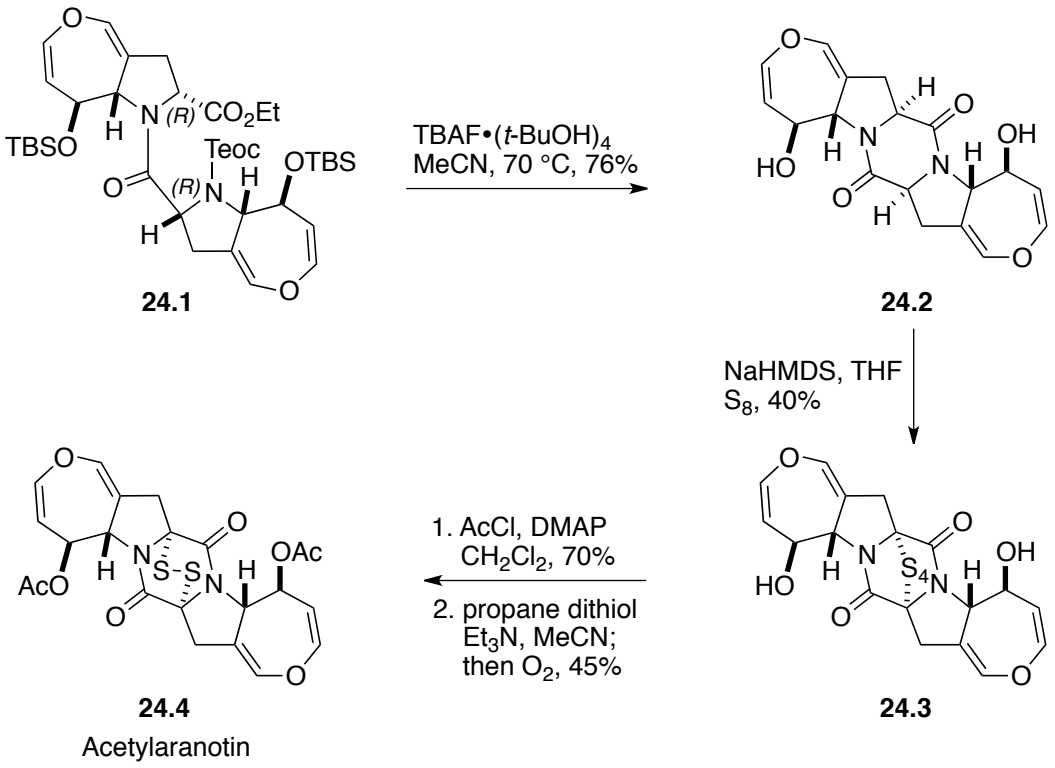
(+)-11,11'-dideoxyverticillin

Scheme 23. Synthesis of an ETP natural product by Movassaghi

CF_3CO_2H, as shown in Scheme 23 (**23.1** → **23.2**).

Intermediate **23.2** was converted into **23.3**, the precursor for sulfur incorporation. K_2CS_3 was the reagent of choice to introduce the sulfurs onto the DKP system in a *cis* fashion. Deprotection of the sulfurs and oxidation of the resulting *bis*-thiol *in situ* afforded the ETP natural product **23.4**.

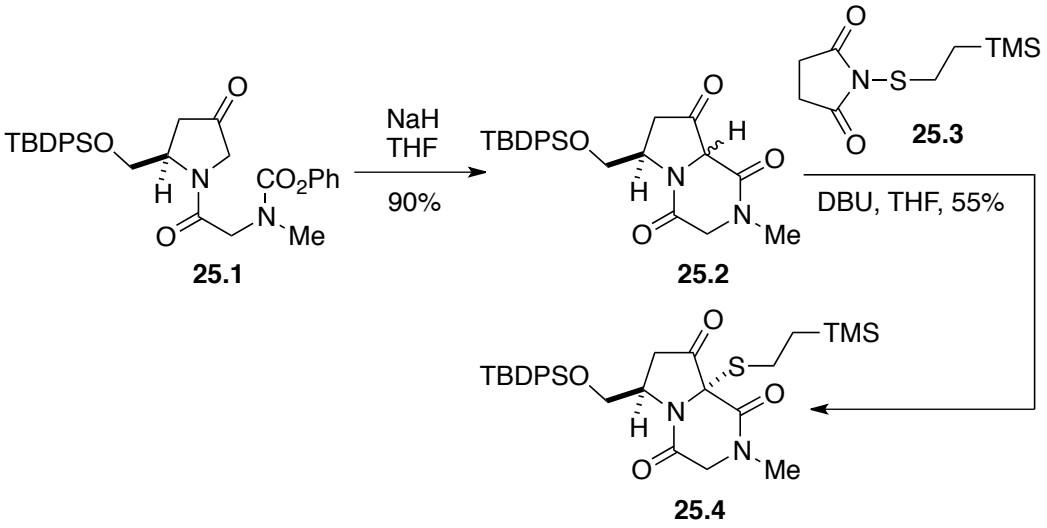
In the first total synthesis of the ETP-dihydrooxepin natural product (–)-acetylaranotin,[25] Reisman *et al*. used the most common and usual dipeptide ester cyclization method to construct the DKP system **24.2** (**24.1** → **24.2**). Interestingly, epimerization at both diketopiperazine methine positions also took place under the cyclization conditions. With **24.2** in hand, Reisman's group utilized Nicolaou's



Scheme 24. Reisman's synthesis of (–)-acetylaranotin containing an ETP core

method[36] (see Scheme 19) of installing sulfur, which afforded the tetrasulfide **24.3**. Finally, acetylation of the hydroxyls, mild reduction of the tetrasulfide to a *bis*-thiol (using propane dithiol) and aerial oxidation generated the ETP natural product **24.4**.

Recently, a Dieckmann type cyclization strategy was developed in our group during studies towards the total synthesis of MPC1001,[24a] and this strategy was later generalized as a powerful synthesis of DKPs.[42] Scheme 25 illustrates the sequence. Ketone **25.1** was subjected to NaH mediated cyclization to obtain **25.2**. Treatment of **25.2** with the electrophilic sulfur reagent **25.3** under basic conditions generated the desired sulfur-containing DKP **25.4**. Following the same strategy, synthesis of the ETP core of MPC1001 was also achieved in this laboratory.[43]

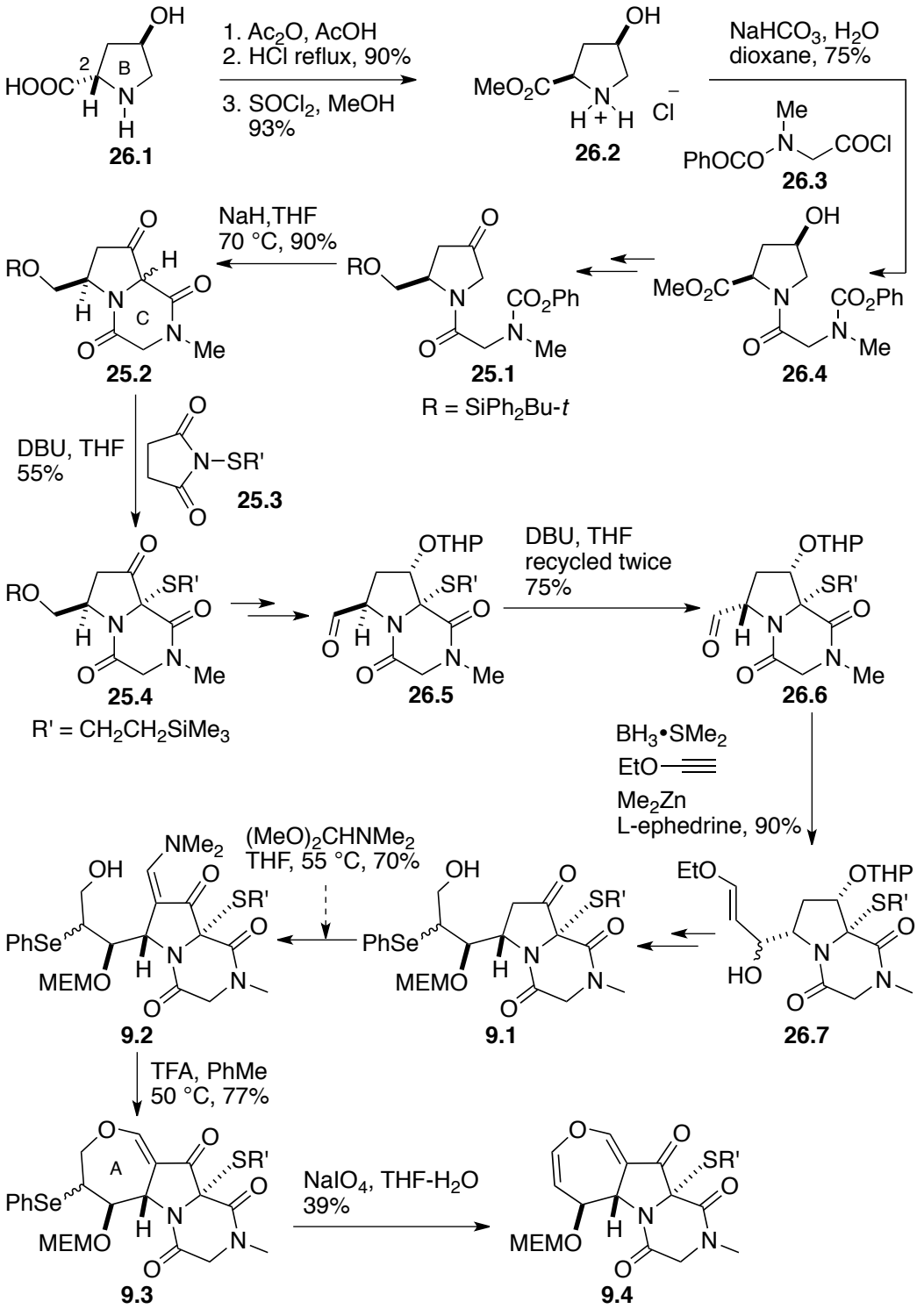


Scheme 25. Dieckmann cyclization strategy towards DKP core of MPC1001

2. Results and Discussion

2.1. Previous synthetic work in this group

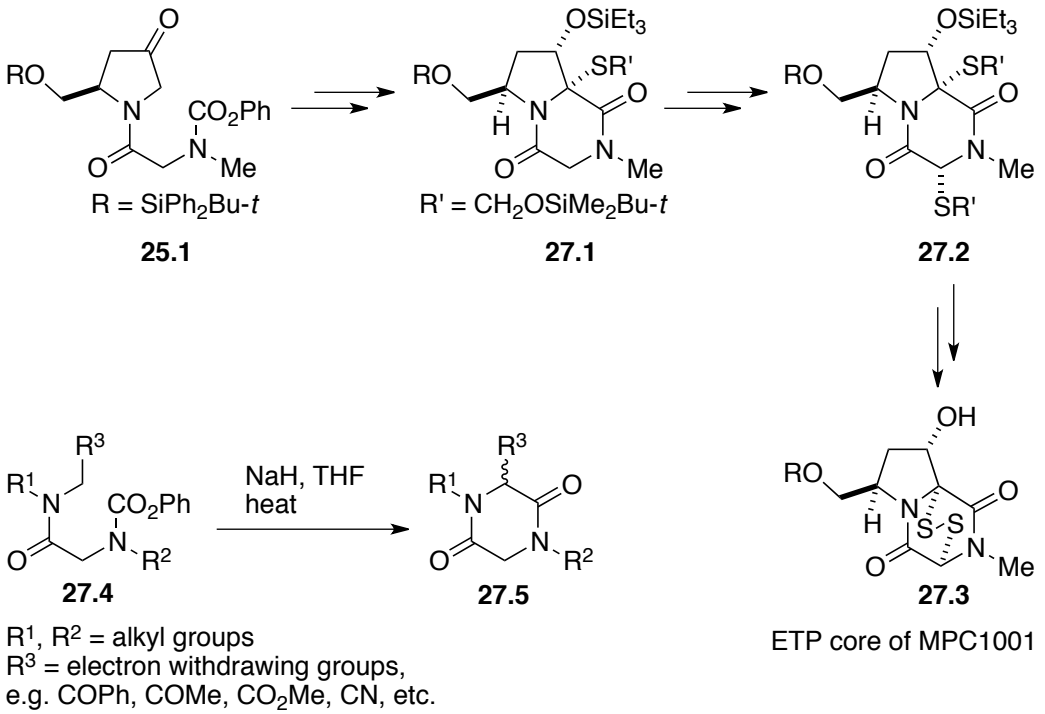
Both the bicyclic AB[24b] and tricyclic ABC[24a] core (without the disulfur bridge) of MPC1001 were synthesized in this group by Dr. Jianbiao Peng. The method developed for the construction of the AB core was successfully employed for the construction of the ABC unit. Although the initial plan was to install the C ring onto the AB system, this approach eventually did not work,[44] and the C ring was synthesized prior to making the dihydrooxepin A ring. The synthesis of the tricyclic core started with the B-ring which was made from *trans*-4-hydroxy-L-proline (**26.1**, see Scheme 26). Upon epimerization at C2 and esterification, it was converted to the salt **26.2** onto which the carbamate side chain was introduced, affording intermediate **26.4**. Some standard functional group interconversion and protection-deprotection sequences led to intermediate **25.1** where the stage was set for the key step of constructing the DKP ring. This was achieved by NaH-mediated Dieckmann type cyclization (**25.1** → **25.2**). Base-mediated installation of the sulfur unit (to reach **25.4**) was performed using a succinimide leaving group on sulfur (reagent **25.3**). From here, some standard manipulations gave aldehyde **26.5**, which was epimerized using DBU (**26.5** → **26.6**). Addition of ethoxyvinylzinc afforded **26.7**, which was converted to the advanced intermediate **9.1**, using standard selenium chemistry, followed by several other functional group manipulations. Treatment of this intermediate with



Scheme 26. Prior synthetic approach to the tricyclic core of MPC1001

dimethylformamide dimethyl acetal afforded the vinylogous amide **9.2**. Conjugate addition-elimination mediated by CF_3CO_2H then generated the desired tetrahydrooxepin ring (**9.3**). Finally, oxidative deselenylation gave the tricyclic ABC core **9.4** in low yield (39%, 27 steps from *trans*-4-hydroxy-L-proline). This intermediate was synthesized in the hope that it could be elaborated to the epithiopiperazinedione unit; unfortunately attempts to achieve this were unsuccessful,[44] and the discussion of that work is beyond the scope of this thesis.

Later on Dr. Lihong Wang used intermediate **25.1** (first made by Dr. Peng) and successfully converted it to the desired epidithiopiperazinedione unit of MPC1001,[43] as summarized in Scheme 27 (**25.1 → 27.3**). Very recently, the



Scheme 27. Other DKP-related synthetic works developed in this laboratory

NaH-mediated Dieckmann type condensation procedure, originally used by Dr. Peng and later used by both me and Dr. Wang, was generalized in this laboratory as a method for constructing piperazine-2,5-diones by Claude Larrivee Aboussafy[42] (see Scheme 27, **27.4 → 27.5**).

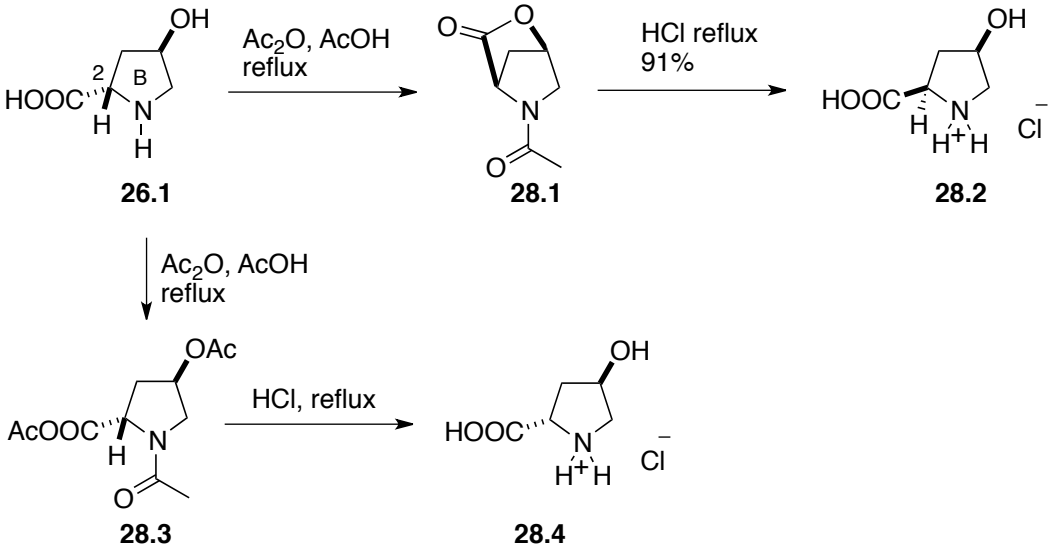
2.2 Enantioselective construction of the tricyclic ABC core of MPC1001F

As mentioned earlier, we were interested in making the comparatively simpler skeleton of MPC1001F in order to identify the difficulties and challenges associated with this structure, so that we could apply our knowledge in making the more complex member, MPC1001. Our initial strategy was very similar to what Dr. Peng had already established.

2.2.1. *Construction of the bicyclic BC system with the SMe group*

We first concentrated on making the BC ring system, as synthesis of the C ring onto the AB system proved to be troublesome according to the prior research in our group.[44] Starting with *trans*-4-hydroxy-L-proline as a source of the B ring, a literature procedure[45] was followed to epimerize the C2 center, using Ac_2O/AcOH under reflux conditions (Scheme 28). Although we started with the stereochemistry at C2 that is present in the natural product, this epimerization was necessary and the reason will be explained in due course (see **25.2 → 29.7** and **25.1 → 29.7**, Schemes 29 and 30 respectively). The strained bicyclic lactone **28.1**

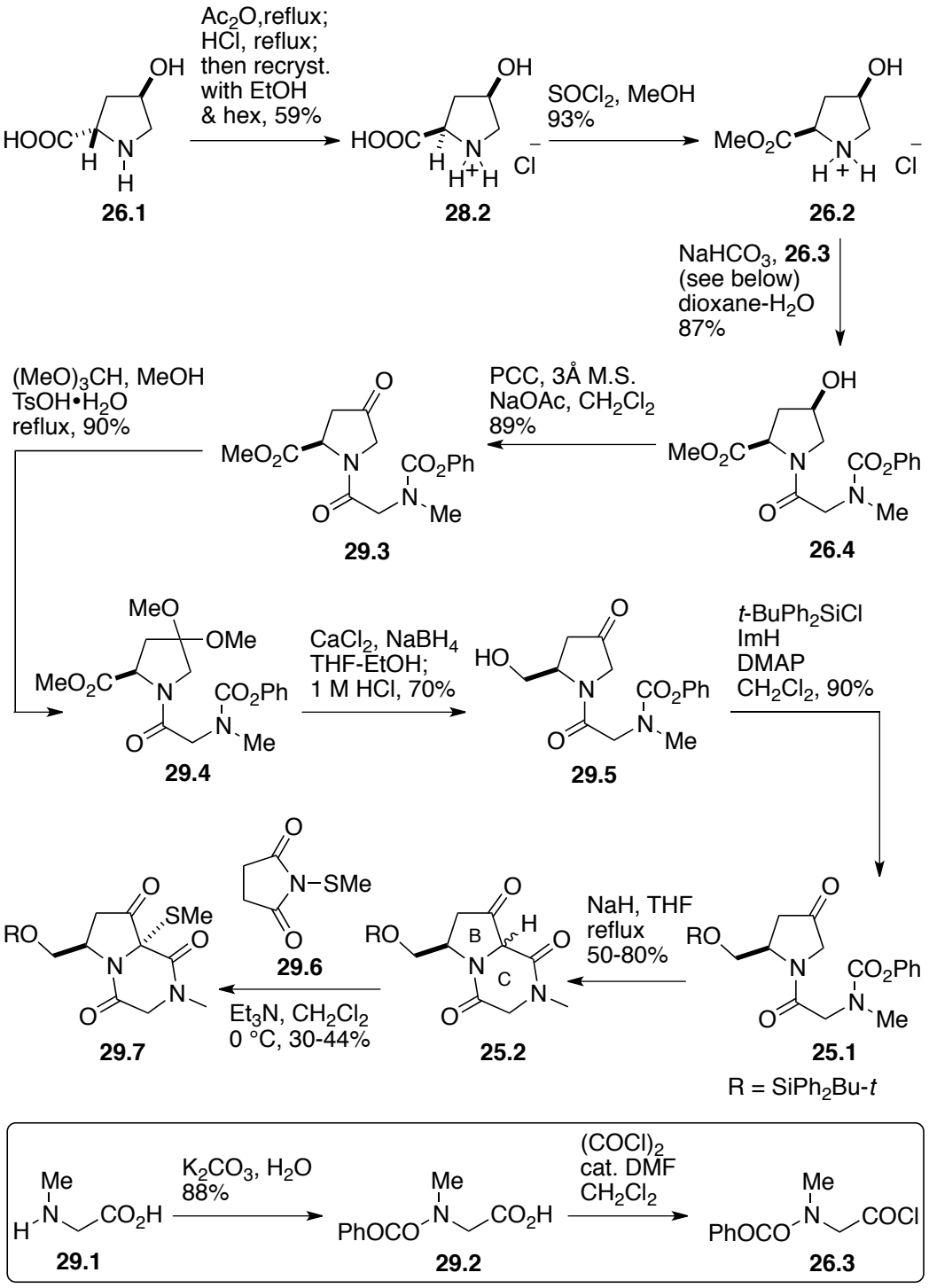
was isolated and characterized by Dr. Wang.[46] This lactone can be hydrolyzed to the desired epimerized product **28.2**. Unfortunately, the proton and carbon NMR



Scheme 28. Epimerization at C2 of *trans*-4-hydroxy-L-proline

of the product clearly showed the presence of the starting material salt (**28.4**) as well, presumably because of the formation of the acetylated product **28.3**.[45c] Hence a revised procedure was followed[46] where the hydrolyzed product was dissolved in refluxing EtOH and recrystallized using hexanes (Scheme 29). The $[\alpha]_D$ value of the recrystallized compound was much higher (13.6, MeOH, c = 0.67 vs 6.5, MeOH, c = 1.0) than that of the crude material before recrystallization.

Having the enantiomerically pure salt **28.2** in hand, the next step was to convert the acid to an ester using $SOCl_2$ (**28.2** → **26.2**). At this stage the side chain on the nitrogen was installed. Treatment of the salt **26.2** with the acid



Scheme 29. Synthesis of BC unit present in MPC1001F

chloride **26.3** under basic conditions, using THF-dioxane as solvent, afforded **26.4**

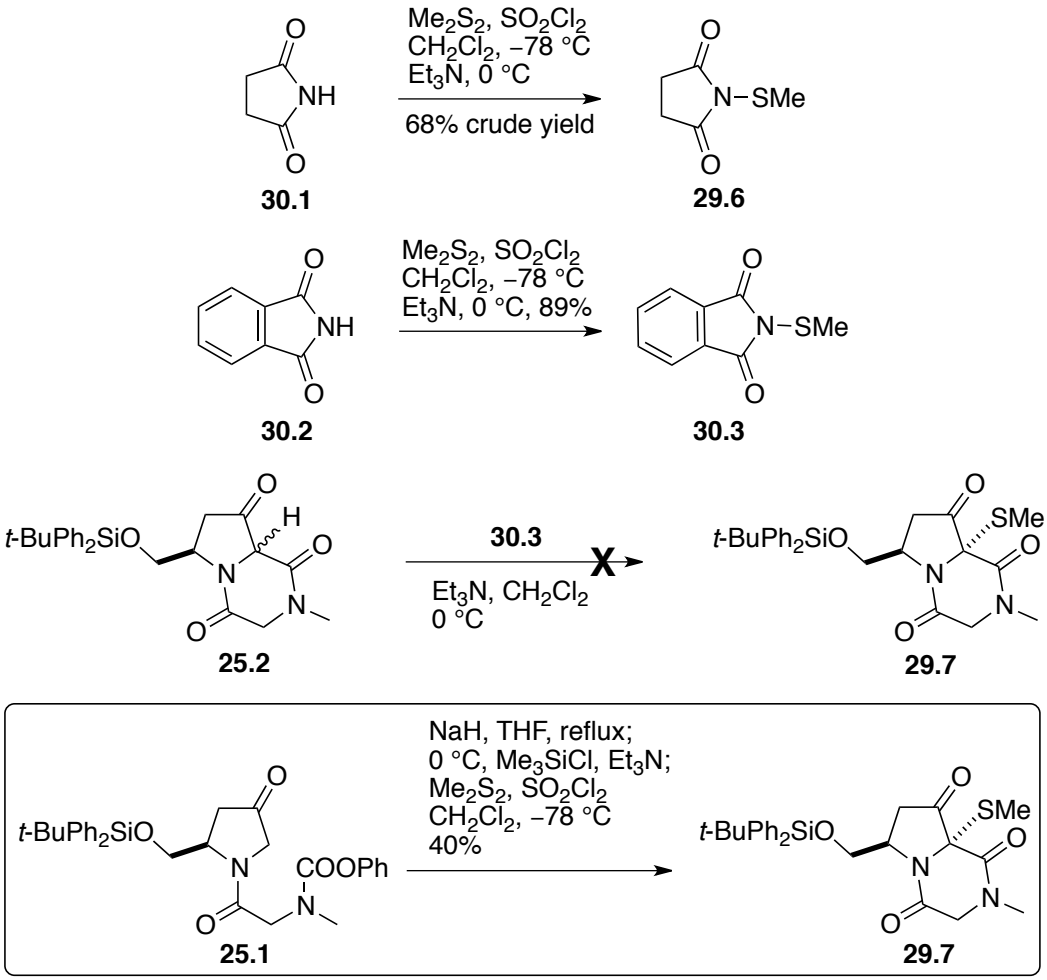
in 87% yield. Slow addition of the acid chloride was necessary to achieve a high yield. The desired acid chloride was made in two steps starting with sarcosine (**29.1**). Sarcosine was treated with PhOCOCl to afford the acid **29.2**, which was then converted to **26.3** using $(COCl)_2$ and catalytic DMF. Full characterization of the acid chloride was not performed. Swern oxidation of the secondary alcohol **26.4** was performed several times on several scales but unfortunately never yielded **29.3** in the yield (78%) reported in Dr. Peng's thesis.[44] Hence PCC oxidation was tried and it gave an excellent yield of the ketone **29.3**. An important point to mention here is no work up was done for this reaction; instead the crude product was adsorbed directly on silica gel before being loaded on the chromatography column. This procedure gave a much better yield compared to the process using aqueous work up.

The next few steps were straightforward: protection of the ketone as a ketal (**29.3 → 29.4**) so that the next step, $Ca(BH_4)_2$ reduction of the ester[47] (selective for ester over carbamate) could be performed to obtain the primary alcohol **29.5**. Quenching this reaction with aqueous HCl also removed the ketal, and protection of the primary alcohol afforded the silyl ether **25.1**. The stage was then set to do our first key reaction, the NaH-mediated Dieckmann type condensation, followed by installation of the sulfur group. Here it is important to note that the stereochemistry of the protected primary alcohol side chain should control the stereochemistry of the incoming SMe group (which was eventually the case, see **25.2 → 29.7**), hence the epimerization of the side chain carboxylic acid group in *trans*-4-hydroxy-L-proline in the very first step was required (**26.1 →**

28.2), and a bulky protecting group (*t*-$BuPh_2Si$) was also used. At first, the previously reported[24a] procedure was tried for the cyclization but, unfortunately, the desired product (**25.2**) is not very stable, and the yield varied widely (50-80%). Also, isolation of the polar ketone **25.2** caused some problems, giving rise to variable colors during workup and chromatography (blue and yellow), possibly because of decomposition. The next step was also troublesome. The succinimide-based sulfur electrophile **29.6** was used under basic conditions. The doubly activated hydrogen of **25.2** was removed to generate an enolate and the succinimide unit acted as a leaving group, to afford the product **29.7** with an SMe group. The synthesis of **29.6** is shown in Scheme 30.[48] The very low yield (30-44%) of the sulfenylation step (**25.2** → **29.7**) led us to design another similar type of electrophile, using the phthalimide unit (**30.3**, see Scheme 30), which unfortunately did not work at all, leading to recovery of **30.3** and decomposition of **25.2**. Obviously, we were in need of a new process. After several optimization studies, the best result was obtained without isolating the unstable intermediate **25.2**, rather trapping it *in situ* as a trimethylsilyl enol ether, followed by treatment with MeSCl (generated *in situ* in another reaction flask, see Scheme 30) at −78 °C. The low yield (40%) of this three-step sequence **25.1** → **29.7** (Scheme 30) was attributed to the possible formation of the unwanted diastereomer at the SMe center, although no other isolable components were observed in the crude reaction mixture.

The isolation of this product was difficult as some of the impurities had similar R_f values to that of the product. Several column chromatography runs

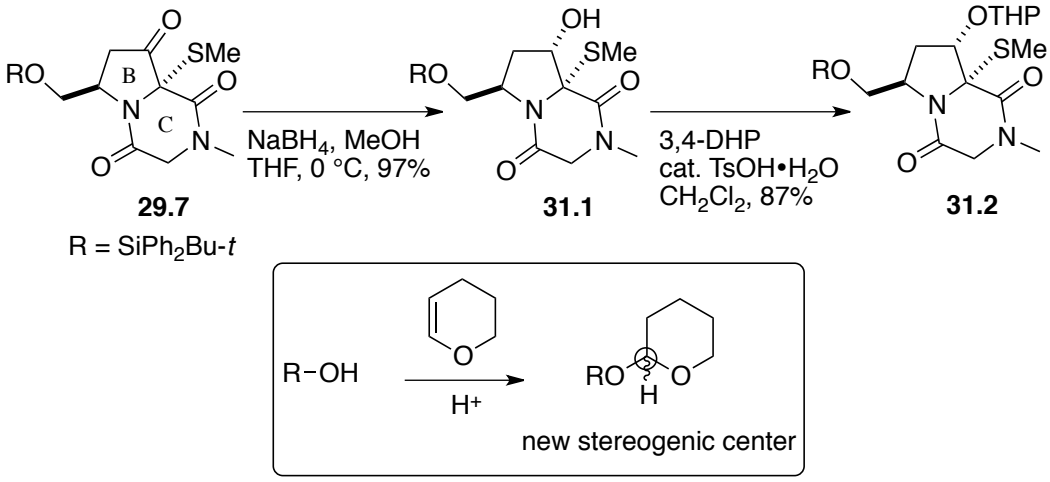
(first silica gel, then alumina) and then trituration under EtOAc at −78 °C were used to isolate the product as white crystals, the colored impurities being soluble in cold EtOAc. Concentration of the mother liquors and cooling to −78 °C gave a second crop of the product. It was also observed that the precursor **25.1** should be freshly prepared to obtain the best result in this cyclization-sulfenylation step.



Scheme 30. Strategies to install an SMe group onto the BC unit of MPC1001F

2.2.2. *The protecting group study: finding an alternative for the THP group*

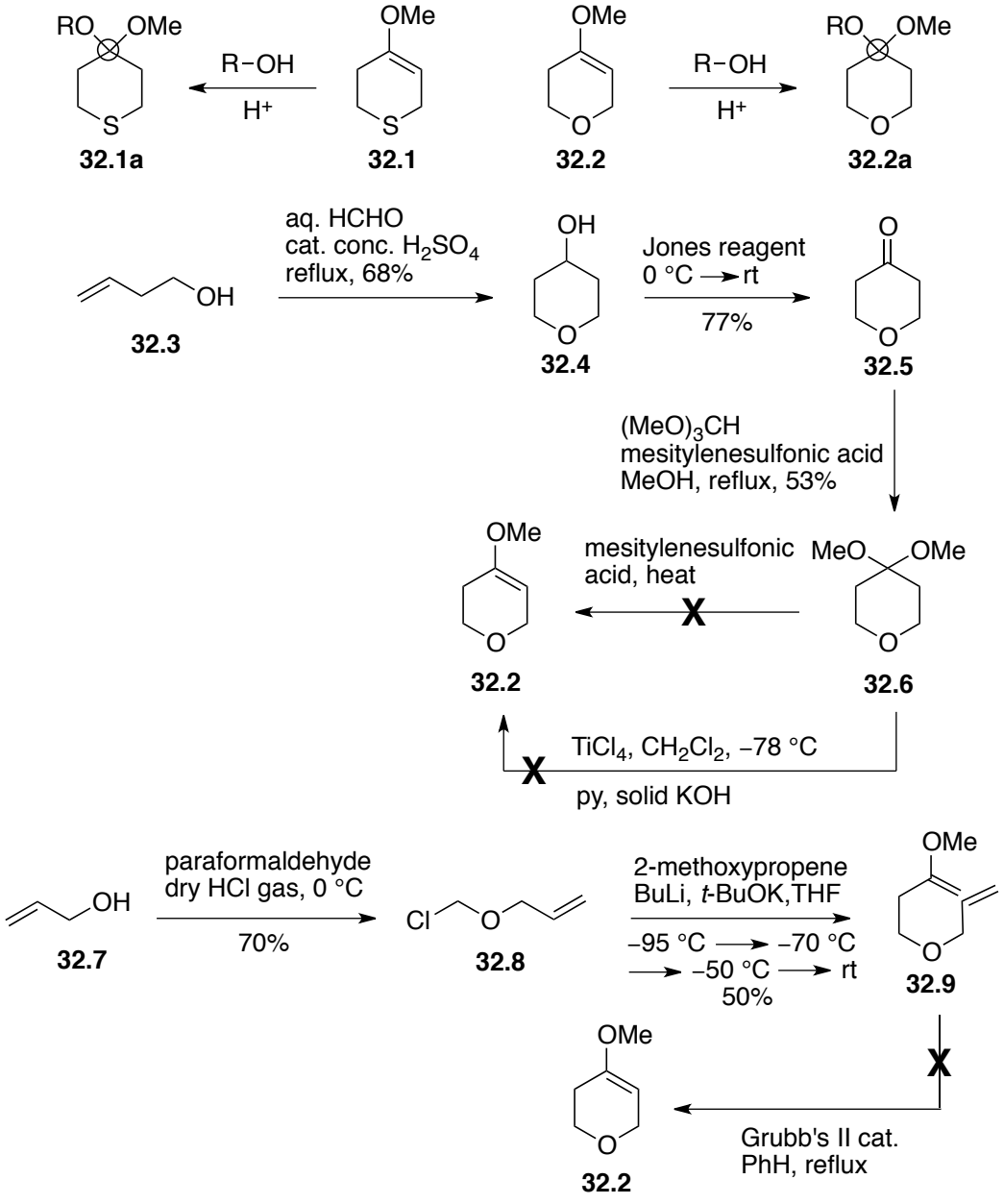
With the bicyclic BC ring in hand, our next goal was to modify the side chain so as to convert it to the dihydrooxepin unit. The first necessary step was to protect the ketone in the B-ring. As shown in prior research on MPC1001 by Dr. Peng,[44] direct protection of this type of ketone as a ketal was not possible, we followed the same sequence of reduction of the ketone (**29.7** → **31.1**) and protection of the resulting secondary alcohol as a THP-ether (**31.2**, Scheme 31), as



Scheme 31. Functional group modifications of the BC unit of MPC1001F

used in prior published work from this laboratory.[24a] But before choosing the THP protecting group, we decided to examine several other similar protecting groups, as shown in Scheme 32 (**32.1** and **32.2**). The advantage of these protecting groups is that unlike the THP group, these groups do not generate a new stereogenic center in the molecule, thus avoiding complication of the spectral

data. Especially, we were interested in the protecting group **32.2**[49] which is very popular in nucleotide chemistry[50c] and has similar stability as a THP protecting



Scheme 32. Protecting group study

group. We attempted the synthesis of **32.2** via a literature procedure,[50] starting with homoallyl alcohol **32.3**, which was converted to the ketal **32.6**.[50a] From this point, we attempted two literature procedures[50b,c] to convert ketal **32.6** to **32.2**, but both failed, leading to decomposition of 32.6. Surprised by the fact that there is no good synthesis of this apparently simple reagent **32.2** reported in the literature, we decided to spend some time on developing a new simple synthesis (Scheme 32). The starting allyl alcohol **32.7** was converted to chloromethylallyl ether **32.8** using a literature method.[51a] A simple S_N2 reaction using the anion of 2-methoxypropene (generated with Schlosser's base, at a low and controlled temperature)[51b] afforded the desired diene **32.9**. The attempted metathesis failed (**32.9** → **32.2**) and we decided to accept our previous route using THP protection.

2.2.3. *Adjusting the stereochemistry at C5: solving the problem of oxidation without epimerization*

Starting from intermediate **31.2**, the next step was removal of the silicon protecting group, which took place smoothly, yielding the primary alcohol **33.1** as a solid. An X-ray crystal structure was obtained (see Figure 1) which clearly showed the relative stereochemistry of the SMe and OTHP groups with respect to the alcohol side chain at C5. Our next task was to perform the required epimerization at C5. Parikh-Doering oxidation gave a very good yield of the aldehydes **33.2**, but unfortunately as a 1:2.1 inseparable mixture of diastereomers [the major one being the desired 5*S* (i.e. α) aldehyde]. As shown in Figure 2, the

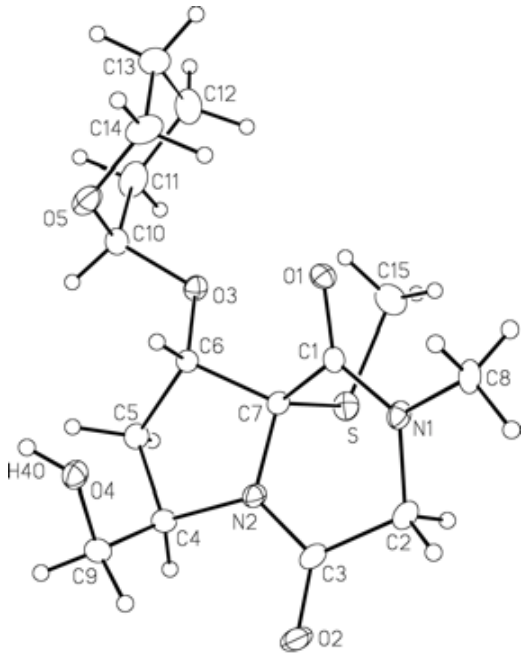
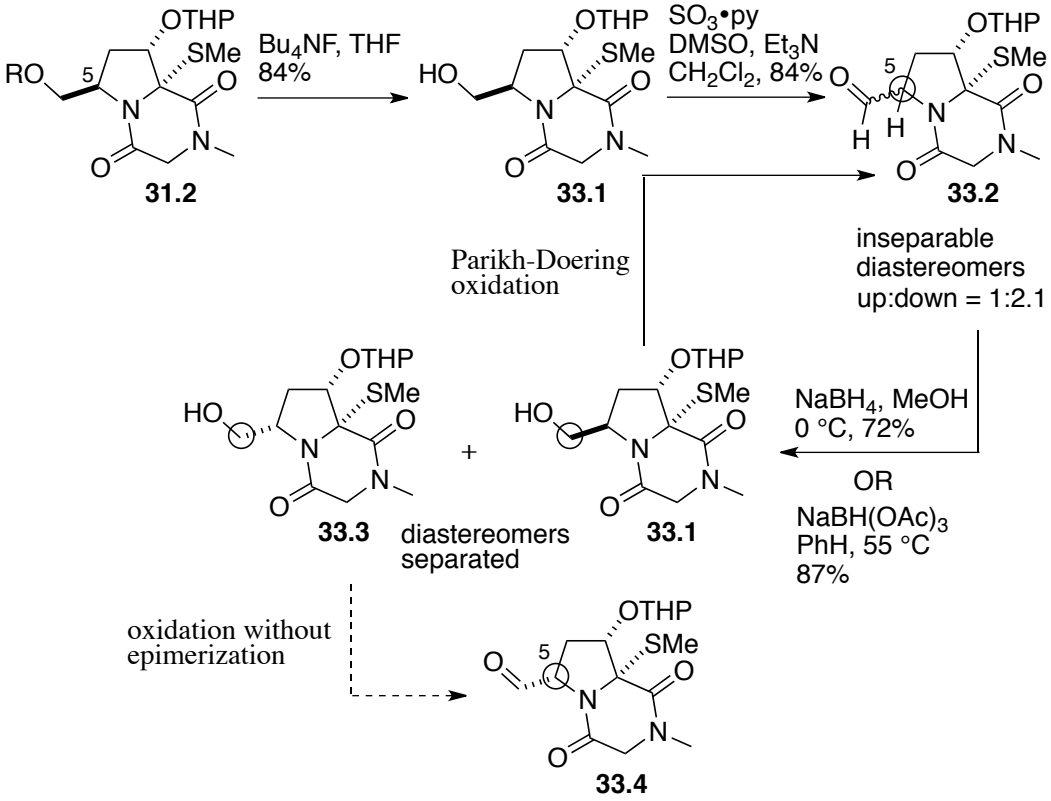


Figure 1. ORTEP diagram of alcohol **33.1**



Scheme 33. Oxidation of the primary alcohol side chain of the BC system

aldehyde H, the H α-to carbonyl and the carbonyl C, all showed two different signals (the splitting of each of these is due to presence of two diastereomers because of the THP group), confirming the presence of two aldehydes.

Several binary and ternary solvent combinations (having the same solvent strength) were tried to separate the two diastereomers, but without success. To further confirm the presence of *two* aldehydes, the mixture of aldehydes was reduced (using $NaBH_4$) and the ^{13}C NMR signal (of the mixture of alcohols **33.1** and **33.3**) of the carbon containing the primary OH group, clearly showed the presence of two alcohols by comparison with the ^{13}C NMR spectrum of intermediate **33.1** (see Figure 2). Fortunately, these two alcohols were separable

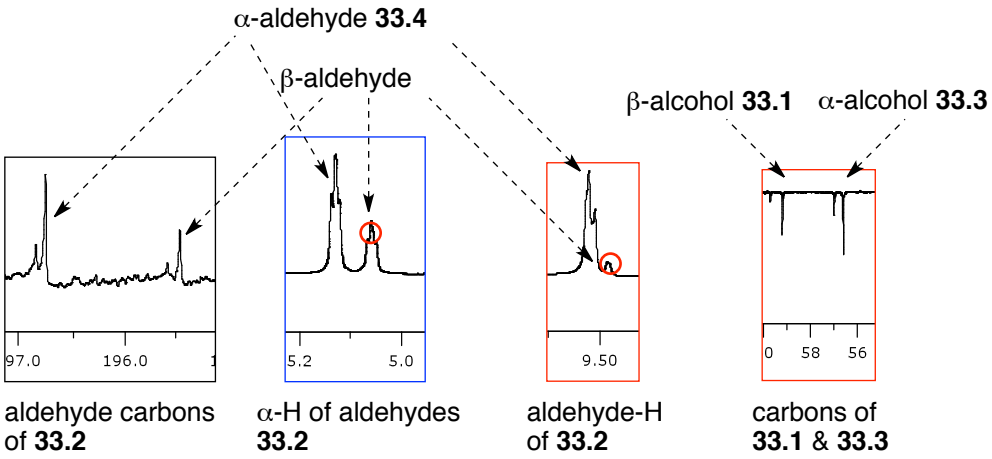
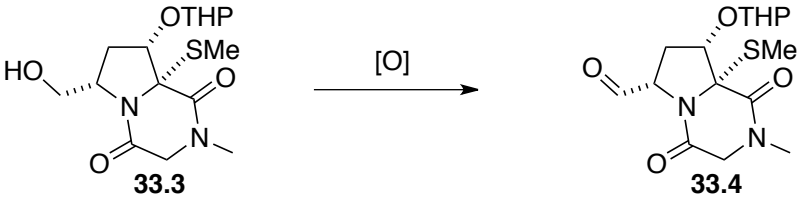


Figure 2. NMR studies

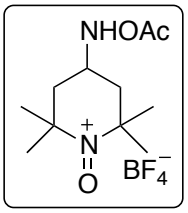
by column chromatography. Hence, we adopted the oxidation-reduction-oxidation sequence shown in Scheme 33. $NaBH(OAc)_3$ was the preferred reducing agent as $NaBH_4$ gave a poor yield of the alcohols. Upon separation, the β alcohol was subjected to the Parikh-Doering oxidation-$NaBH(OAc)_3$ reduction

sequence, and we now required an oxidation method to convert the α alcohol **33.3** to pure α aldehyde **33.4**, without epimerization.

Although formally simple, this step posed a very difficult challenge, and an extensive list of oxidation procedures was screened; the results are summarized in Table 1. DMP oxidation gave a complex mixture, whereas IBX afforded a very low yield of the aldehyde. We were particularly interested in the Ley oxidation[52] which was successfully employed in a similar type of reaction during the halichlorine synthesis in this laboratory.[53] We thought it should not cause any epimerization, but unfortunately that was not the case. Although dry NMO improved the yield slightly, significant epimerization ruled out the use of this reagent. We next focused on Swern oxidation, and both attempts with $(COCl)_2$ and $(CF_3CO)_2O$ gave a very low yield but no epimerization. The same was the case under Corey-Kim oxidation conditions.[54] It appeared that, epimerization occurs only at room temperature and not at a low temperature. TEMPO-mediated oxidation was also not very successful.[55] A similar type of reagent, the Bobbit reagent (see entry 12),[56] caused decomposition and loss of the acid sensitive THP group. Chromium(VI)-mediated oxidations under buffered conditions afforded the desired product in very low yield but did not cause any epimerization. Use of the Collins' reagent was also not very satisfactory. Finally, after trying numerous common oxidation procedures, we turned our attention to the comparatively less used Moffatt conditions. Although the soluble version of the Moffatt conditions, using EDC•HCl,[57] afforded an excellent yield of the aldehyde, we could not totally avoid epimerization. Hence, finally, the Moffatt conditions were tried



Reagents & Conditions	Yield / Comment
1. DMP, CH_2Cl_2, rt, 3.5 h	CM
2. IBX, DMSO, rt, 2 h	21% / SM recovered
3. TPAP, NMO, 4 Å M.S. MeCN, 15 min	46% / epimerization
4. TPAP, NMO (dry) 4 Å M.S., MeCN, 30 min	54% / epimerization
5. $(COCl)_2$, DMSO, −78 °C py, Et_3N,CH_2Cl_2, 4 h	38% / no epimerization
6. $(CF_3CO)_2O$, DMSO, −78 °C py, Et_3N, CH_2Cl_2, 6 h	32% / no epimerization
7. NCS, Me_2S, −25 °C, CH_2Cl_2 2 h; Et_3N, rt, overnight	very little DP
8. $PhI(OAc)_2$, TEMPO CH_2Cl_2, overnight	very little DP
9. PCC, 3Å M.S. NaOAc, CH_2Cl_2, 1.5 h	41% / SM recovered
10. CrO_3 (dry), py, CH_2Cl_2, 2 h	very little DP
11. PDC, 3Å M.S. NaOAc, CH_2Cl_2, 4 h	39% / no epimerization
12. Bobbit reagent, silica gel CH_2Cl_2, 2 d	CM / THP group lost
13. EDC•HCl, DMSO, py TFA, PhH, rt, 19 h	87% / epimerization
14. DCC, DMSO, py, TFA PhH, rt, overnight	89% / **no epimerization**



CM = complex mixture; SM = starting material; DP = desired product

Table 1. Optimization of the oxidation step

using DCC in the presence of pyridinium trifluoroacetate,[58] which gave an excellent yield (89%) of the desired aldehyde without any epimerization at all.

The ^{1}H and ^{13}C NMR comparisons clearly show (see Figure 3) the absence of the small peaks for the aldehyde H, the hydrogen α-to the carbonyl and the carbonyl carbon, confirming the absence of epimerization.

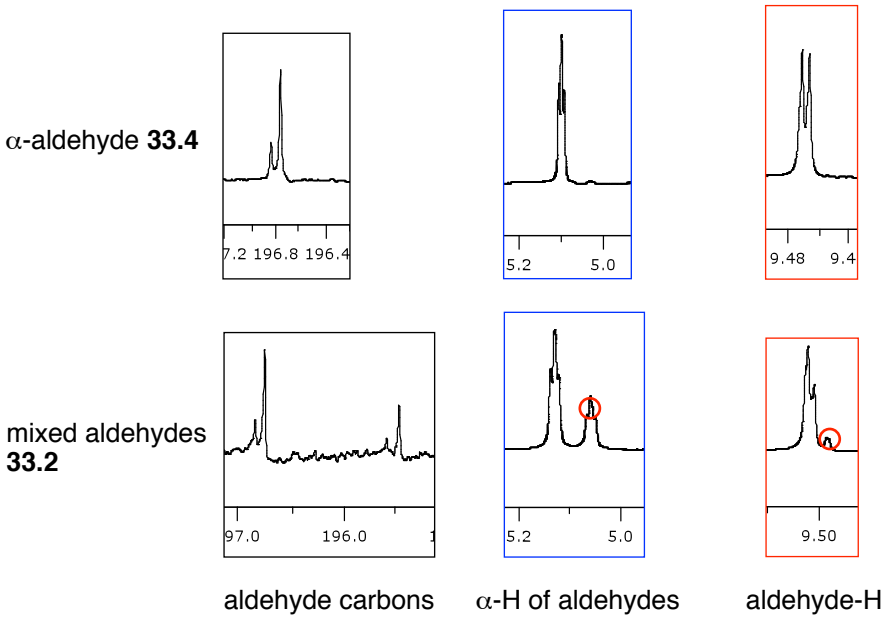


Figure 3. NMR comparisons of α and β aldehydes

2.2.4. *Construction of the side chain on the desired α-aldehyde*

Having the C5 stereochemistry fixed, our next task was to install the two carbon unit on the aldehyde carbon, as such a segment is present in the natural product. From the prior research by Dr. Peng,[24a] we knew that the vinylzinc-ate reagent (**34.1**, which was formed by hydroboration of ethoxyacetylene, followed by transmetallation with zinc, using Me_2Zn)[59] worked well on this aldehyde, and gave a good yield of ethoxyvinyl alcohols **34.2**, as an inseparable mixture of

epimers at the newly generated secondary hydroxyl center. Use of Et_2Zn instead of Me_2Zn gave a lower yield (65-70%) and the yield also dropped significantly in the absence of *l*-ephedrine. The diastereomers were separable in the next step when the secondary alcohols were protected as MEM ethers (**34.2** → **34.3** and **34.4**, 1:1.4 ratio). Before adding the MEMCl to the reaction mixture, it is necessary to stir the commercial MEMCl over dry K_2CO_3 to remove any HCl present, as the starting material is extremely acid sensitive. Unwanted hydrolysis of the ethoxyvinyl unit of **34.2** was observed when no K_2CO_3 was used. One of the MEM-protected compounds was crystalline and an X-ray structure was obtained (see Figure 4) which clearly showed it to be the desired isomer (**34.4**) having the MEM group β, as present in the natural product. Hence this isomer

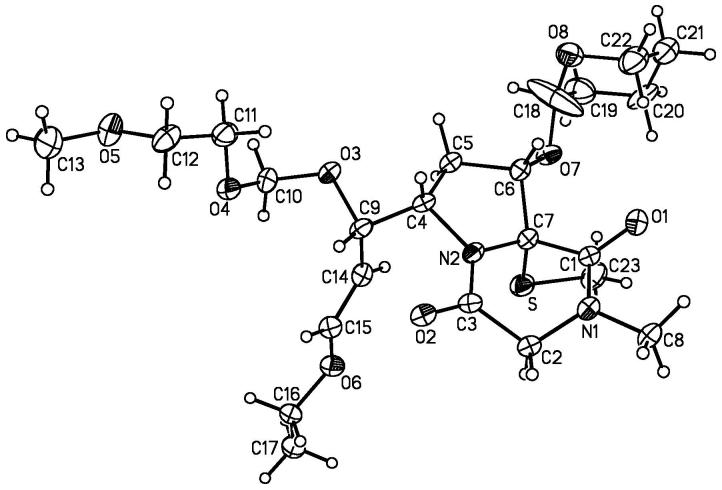
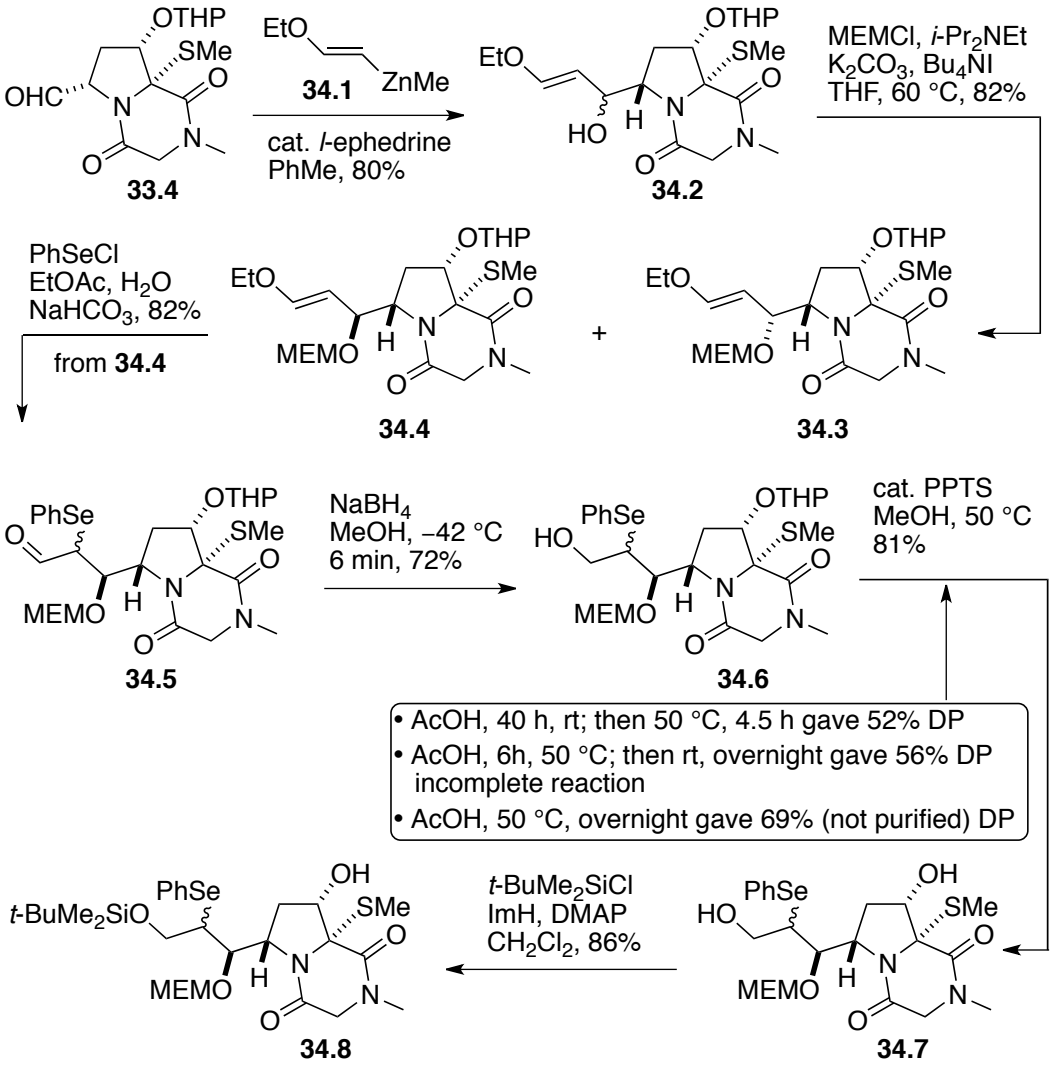


Figure 4. ORTEP diagram of **34.4**

was carried forward. The unwanted MEM-isomer **34.3** (which was an oil) was set aside for the time being, and we planned to do a Mitsunobu inversion on this

isomer in the future; however, this step was never carried out because this route was later abandoned. Our next step was to remove the ethoxyvinyl unit and install a PhSe group which could serve as a precursor to one of the double bonds in the dihydrooxepin ring. Treatment of the reactive ethoxyvinyl compound **34.4** with PhSeCl served this purpose, affording the α-phenylseleno aldehydes **34.5** in good yield. Reduction of these aldehydes in the presence of the PhSe group posed



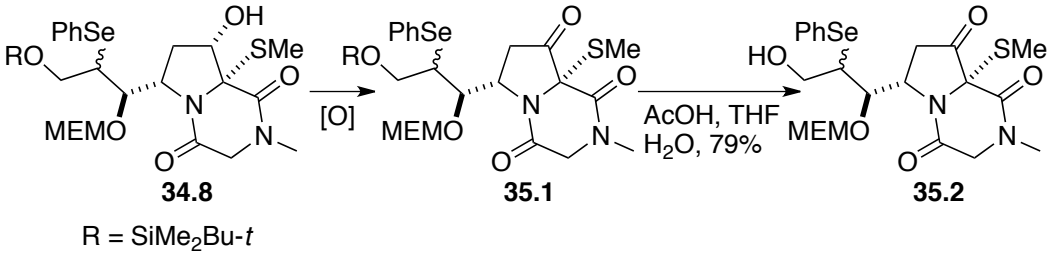
Scheme 34. Installation and modifications of the side chain on the BC unit

some problem because of unwanted cleavage of the C-Se bond. Low temperature reduction (**34.5 → 34.6**), using $NaBH_4$, was necessary to minimize this cleavage, but it could not be avoided completely. The reaction was monitored by ^1H NMR and the reaction time was found to be very important. Use of a weaker reducing agent like $NaBH(OAc)_3$ took a much longer time and an elevated temperature was required; these conditions caused a very significant amount of deselenylation. With **34.6** in hand, a sequence of deprotection, protection and oxidation reactions was adopted to go to the advanced intermediate **35.1**. Selective deprotection of the THP group in the presence of the MEM ether (**34.6 → 34.7**) was performed using catalytic pyridinium *p*-toluenesulfonate at 50 °C. The temperature was very important as too high a temperature caused removal of MEM group. Use of AcOH under different conditions (different temperatures and reaction times, see Scheme 34) gave very poor yields of **34.7**. The primary alcohol **34.7** was selectively protected using *t*-$BuMe_2SiCl$ to afford **34.8**.

2.2.5. *Oxidation of the secondary alcohol in the presence of the PhSe group*

From **34.8**, our next step was to oxidize the secondary alcohol so that we could functionalize α to the resulting ketone (Scheme 35). The presence of selenium actually made this oxidation step extremely challenging[60] because of the sensitivity of selenium to oxidation, and again this step required extensive screening of oxidation conditions (see Table 2). The Ley oxidation[52] did not work

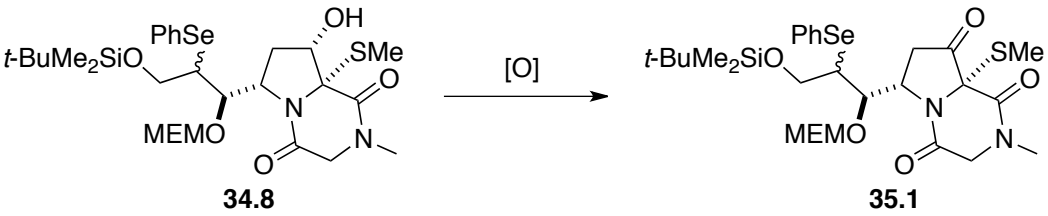
at all and the starting material was recovered. DMP oxidation (as used by Dr. Peng in his MPC1001 synthesis)[24a] led to a very poor yield and decomposition.



Scheme 35. Oxidation in the presence of a PhSe group

With IBX, the reaction was incomplete and the yield very poor. Triphenylbismuth oxycarbonate[60e,f] did not generate any ketone at all, as was the case with the Parikh-Doering reagent, and in both of these cases the starting material was recovered. Both PCC and TEMPO[55] led to decomposition, as did the Swern oxidation. Based on the literature,[60c,54] we next tried the Corey-Kim method, which was reported to be suitable for oxidation of alcohols in the presence of selenium. This reaction was tried several times under different conditions, as listed in Table 2. The best result was obtained when then NCS and Me_2S were added to the starting material with the mixture being stirred for 3 h, followed by addition of Et_3N and stirring for another 3 h. This procedure gave 68% of the desired product and some starting material. Hence a longer stirring time was used both at 0 °C and also after adding Et_3N. Prolonged stirring at –20 °C led to decomposition and a longer reaction time after adding Et_3N dropped the yield significantly. Finally, I was very pleased to find that Moffatt oxidation[58]

worked well, giving 87% yield of ketone **35.1**. Removal of the silicon protecting group then released the desired primary alcohol (**35.1** → **35.2**).

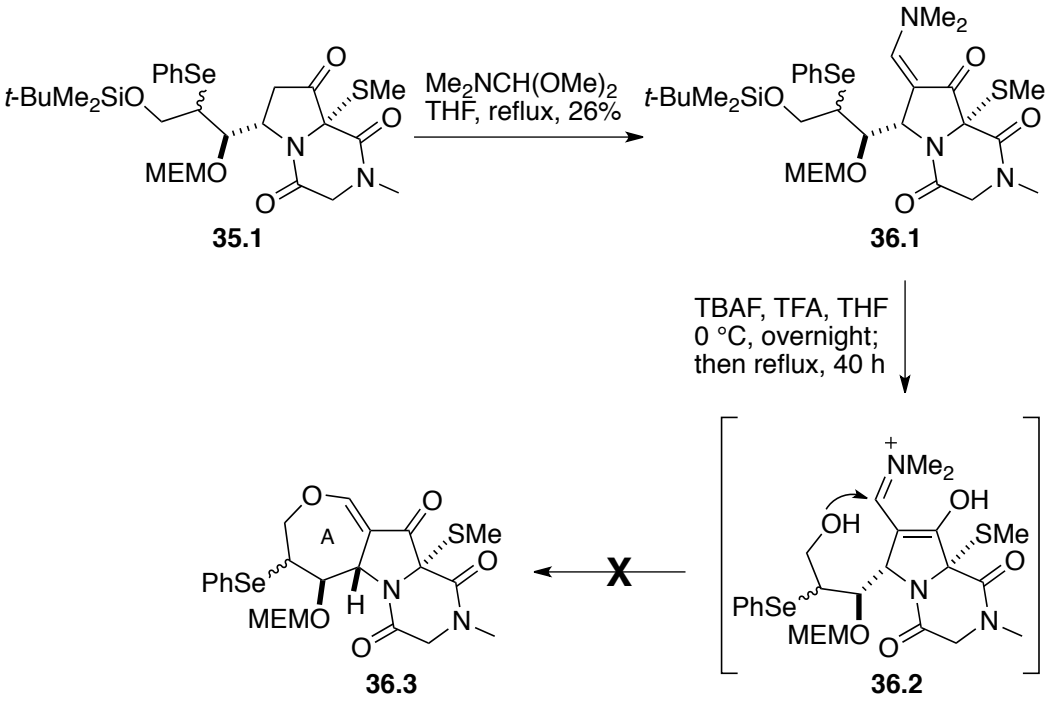


Reagents & Conditions	Yield / Comment
1. TPAP, NMO, 4Å M.S. CH_2Cl_2, 15 min	no DP / SM recovered
2. DMP, CH_2Cl_2, rt, 5 h	very little DP
3. DMP, CH_2Cl_2, rt, overnight	38% / CM
4. IBX, DMSO, rt, 5 h	55% / SM recovered
5. IBX, DMSO, rt, overnight	incomplete reaction
6. Ph_3BiCO_3, CH_2Cl_2, rt, overnight	SM recovered
7. PCC, 3Å M.S. NaOAc, CH_2Cl_2, 3 h	CM
8. $PhI(OAc)_2$, TEMPO CH_2Cl_2, overnight	CM
9. SO_3•py, DMSO, Et_3N CH_2Cl_2, overnight	no DP / SM recovered
10. $(COCl)_2$, DMSO, −78 °C Et_3N,CH_2Cl_2, 4 h	no DP / no SM
11. NCS, Me_2S, −20 °C, CH_2Cl_2 3 h; Et_3N, rt, 3 h	68% / SM recovered
12. NCS, Me_2S,−20 °C, CH_2Cl_2 3 h; Et_3N, rt, overnight	28% / SM recovered
13. NCS, Me_2S, −20 °C, CH_2Cl_2 overnight; Et_3N, rt, 2 h	no DP / little SM recovered
14. NCS, Me_2S, −20 °C, CH_2Cl_2 8 h; Et_3N, rt, 1h	no DP / little SM recovered
15. DCC, DMSO, py, TFA PhH, rt, overnight	87%

Table 2. Optimization of the second oxidation step

2.2.6. *Construction of the dihydrooxepin ring A: approach I*

Our first attempt to generate the dihydrooxepin ring, which is outlined in Scheme 36, started with ketone **35.1**. Treatment of this ketone with dimethylformamide dimethyl acetal afforded the vinylogous amide **36.1** in a very low yield. We envisaged that treatment of **36.1** with Bu_4NF buffered with



Scheme 36. First approach towards the tetrahydrooxepin A ring

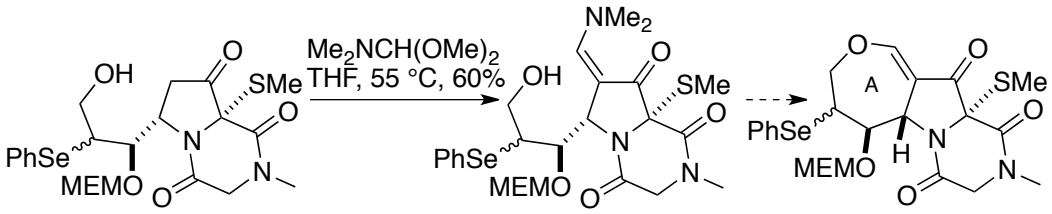
CF_3CO_2H should unmask the primary hydroxyl group (producing **36.2**), which should then perform our strategic conjugate addition elimination, affording the desired tetrahydrooxepin unit **36.3**. Unfortunately, this attempt only led to decomposition of the starting material.

2.2.7. *Construction of the dihydrooxepin ring A: approach II*

In our second approach we chose to make the vinylogous amide from the primary alcohol **35.2** (Scheme 37) and, in the event, this gave an acceptable yield (60%) of **37.1**. We tried various acids and bases to perform the conjugate addition-elimination, as summarized in Scheme 37. Heating **37.1** in neat PhMe afforded **36.3**, but this reaction was not synthetically useful because of significant recovery of starting material. Use of CF_3CO_2H (as was used by Dr. Peng in his MPC1001 synthetic work),[24a] TsOH, pyridinium *p*-toluenesulfonate in MeOH and CF_3SO_3H all led to decomposition. The weak base Et_3N resulted in recovery of starting material, whereas stronger bases such as DBU and NaH gave complex mixtures. These observations were disappointing, but we later found that CF_3CO_2H is effective provided a trace of water is present (see section 2.2.10).

2.2.8. *Construction of the dihydrooxepin ring A: approach III*

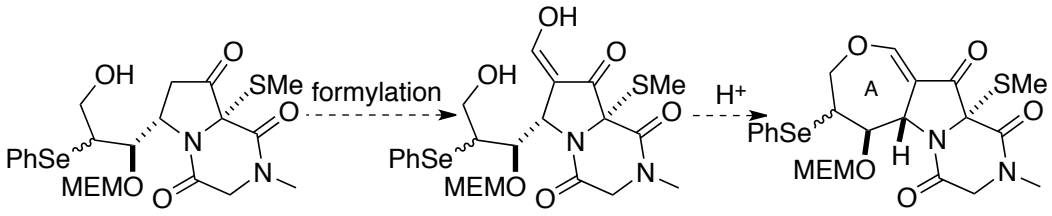
The failure of our second approach led us to think of a different route, which is outlined in Scheme 38. We proposed that the formylation of ketone **35.2** should afford the enol which, under acidic conditions, should generate ring A (**38.1** → **36.3**). Three different formylating agents were used (see Scheme 38) under different conditions. The first choice of formylating agent was EtOCHO.[61] In the presence of the bases NaOMe or Et_3N only starting material was recovered, whereas LDA, *t*-BuOK and NaH led to decomposition. Vilsmeier-Haack



Reagents & Conditions	Results
1. PhMe, 110 °C, 16 h	little DP, mainly SM
2. TFA, PhMe, 60 °C, overnight	CM
3. TsOH•H_2O, PhMe, 50 °C, 16 h	CM
4. PPTS, MeOH, 50 °C, overnight	CM
5. TfOH, PhH, 50 °C, 16 h	CM
6. Et_3N, PhMe, 50 °C, overnight	SM recovered
7. DBU, PhMe, 60 °C, overnight	CM
8. NaH, THF, 50 °C, overnight	CM

Scheme 37. Second approach towards the tetrahydrooxepin A ring

conditions[62] also failed to produce the desired enol **38.1**. Use of the very hygroscopic formylating agent ImCHO,[63] under weakly basic conditions (Et_3N) gave a very poor yield of **38.1**, whereas under acidic conditions (CF_3CO_2H) only starting material was recovered. Strong bases like NaOMe, NaH and LDA caused decomposition again. We concluded that compound **35.2** is not base-stable, presumably because of the presence of highly enolizable hydrogens α to the ketone, which could led to unwanted side reactions. These reactions were not tried with the protected alcohol as we eventually solved the problem in a different way, as will be discussed later (see section 2.2.10).



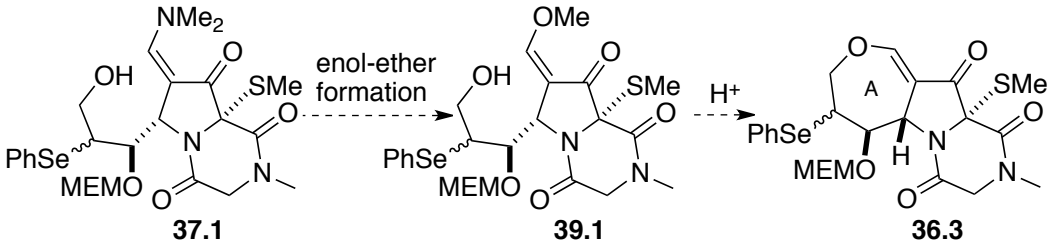
35.2 **38.1** **36.3**

Reagents & Conditions (for formylation)	Results
1. NaH, EtOCHO, THF, 0 °C	no DP
2. Et_3N, EtOCHO, THF, rt, overnight	SM recovered
3. NaOMe, EtOCHO, PhH, 0 °C	SM recovered
4. LDA, THF, −78 °C, EtOCHO	CM
5. *t*-BuOK, THF, EtOCHO, 0 °C	CM
6. $POCl_3$, DMF, CH_2Cl_2, 0 °C	CM
7. ImCHO, Et_3N, THF, rt, then 55 °C	low yield
8. ImCHO, NaOMe, THF	CM
9. ImCHO, TFA, THF, 55 °C	SM only
10. ImCHO, LDA, −78 °C, THF	CM
11. ImCHO, NaH, THF	CM

Scheme 38. Third approach towards the tetrahydrooxepin A ring

2.2.9. *Construction of the dihydrooxepin ring A: approach IV*

We wanted to convert the vinylogous amide **37.1** to the vinylogous ester **39.1** (see Scheme 39) which should theoretically afford **36.3**. As listed in Scheme 39, a few conditions were tried, but without success. When **37.1** was heated in pure MeOH only starting material was recovered, whereas heating in MeOH under acidic or basic conditions caused decomposition.

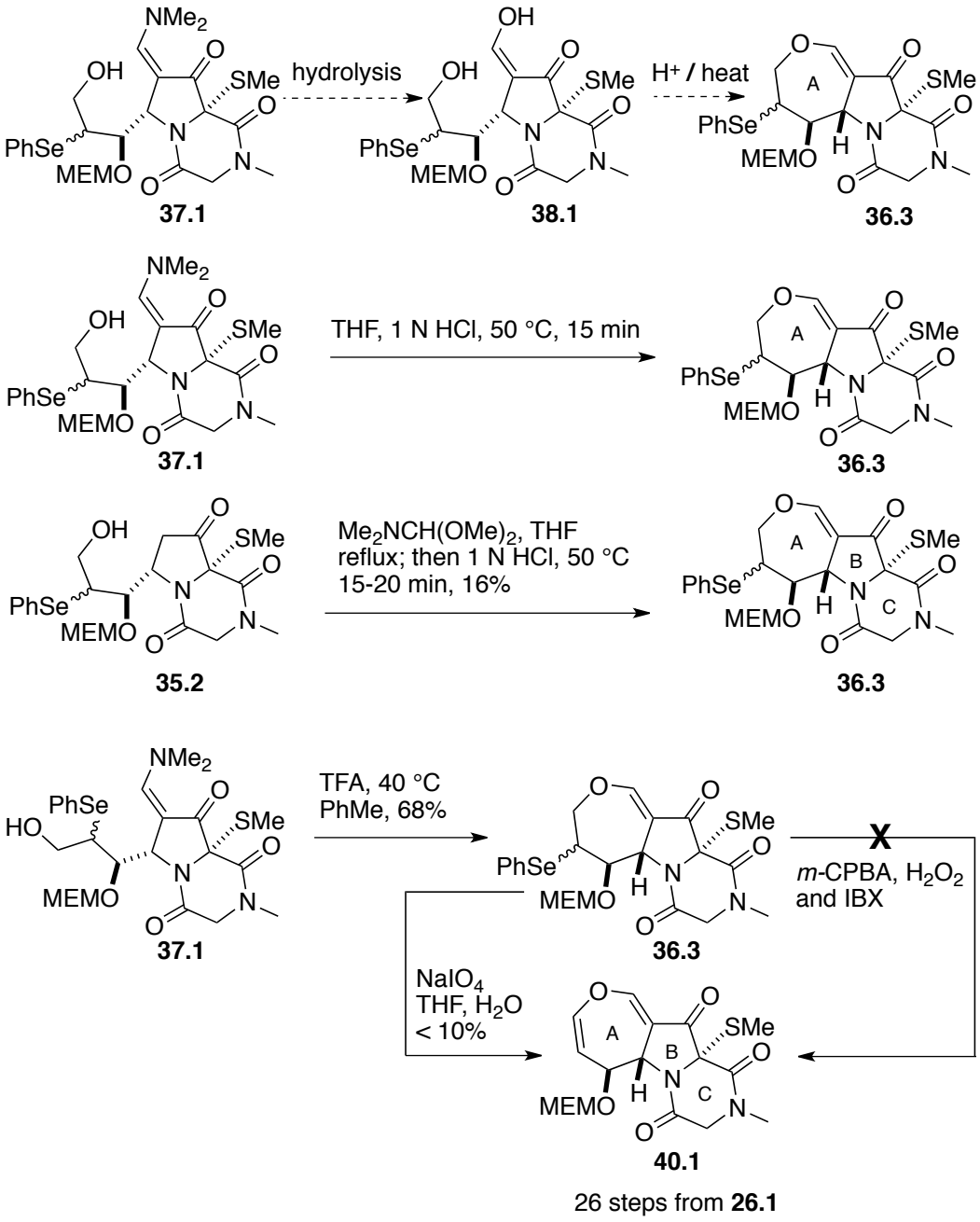


Reagents & Conditions (for enol-ether formation)	Results
1. MeOH, 60 °C, overnight	SM recovered
2. MeOH, $TsOH•H_2O$, 60 °C, 6 h	CM
3. MeOH, K_2CO_3, 60 °C, overnight	CM

Scheme 39. Fourth approach towards the tetrahydrooxepin A ring

2.2.10. *Construction of the dihydrooxepin ring A: approach V*

Finally, we envisaged that acid hydrolysis of the vinylogous amide **37.1** should generate enol **38.1** which should cyclize in situ at a suitably high temperature (see Scheme 40). To our surprise, hydrochloric acid at 50 °C worked[64] well, affording **36.3** (Scheme 40). Hence, a minor modification was made where the vinylogous amide was synthesized from ketone **35.2**, and the reaction was quenched with hydrochloric acid (1 N), affording **36.3** in 16% yield. We concluded that water was necessary for this cyclization to happen. Hence, this reaction was repeated with CF_3CO_2H in PhMe (see Scheme 37, entry 2 in section 2.2.7) using 50 mol% of water which afforded **36.3** as expected, in 42% yield. Finally, an old bottle of CF_3CO_2H (probably contaminated with some water) proved to give the best result, delivering the **36.3** in 68% yield as shown in Scheme 40.



Scheme 40. Synthesis of the tetrahydrooxepin ring

Our next goal was to perform an oxidative deselenylation of **36.3** which would finish the synthesis of the tricyclic core of MPC1001F (**40.1**) in an enantioselective fashion. Although $NaIO_4$ afforded what we suspect to be **40.1** in

<10% yield, all other reagents like *m*-CPBA, H_2O_2 and IBX led to decomposition. We reasoned that there are two possible regiochemistries for the double bond generated upon deselenylation, and also the SMe group is susceptible to oxidation under the conditions employed. Our evidence for the formation of **40.1** is based only on the ^{1}H NMR spectrum and a low resolution mass spectrum. In conclusion, we were able to synthesize **36.3** and probably the full tricyclic core **40.1** of MPC1001F, in a 25-26-step sequence, starting from *trans*-4-hydroxy-L-proline (**26.1**), but it was clear that we needed a much shorter and more efficient route to overcome the problems encountered.

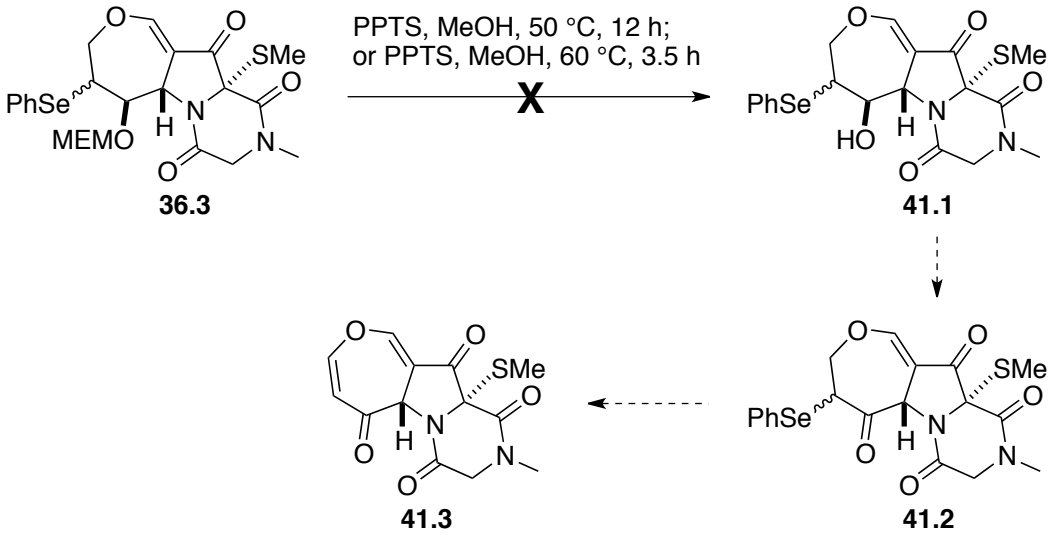
2.3. Synthetic attempts towards the tricyclic core of MPC1001F from previously synthesized late-stage intermediates

Since I was able to construct very advanced intermediates, and all the intermediate steps were optimized and the compounds properly characterized, our first attempt was to choose one of these intermediates, and design an improved route towards MPC1001F. The several unsuccessful attempts that were made in this regard will be discussed and analyzed in this section.

2.3.1. *Synthetic attempt from tetrahydrooxepin intermediate*

The very first obvious attempt started with the most advanced intermediate **36.3**. We proposed (see Scheme 41) that removal of the MEM group followed by

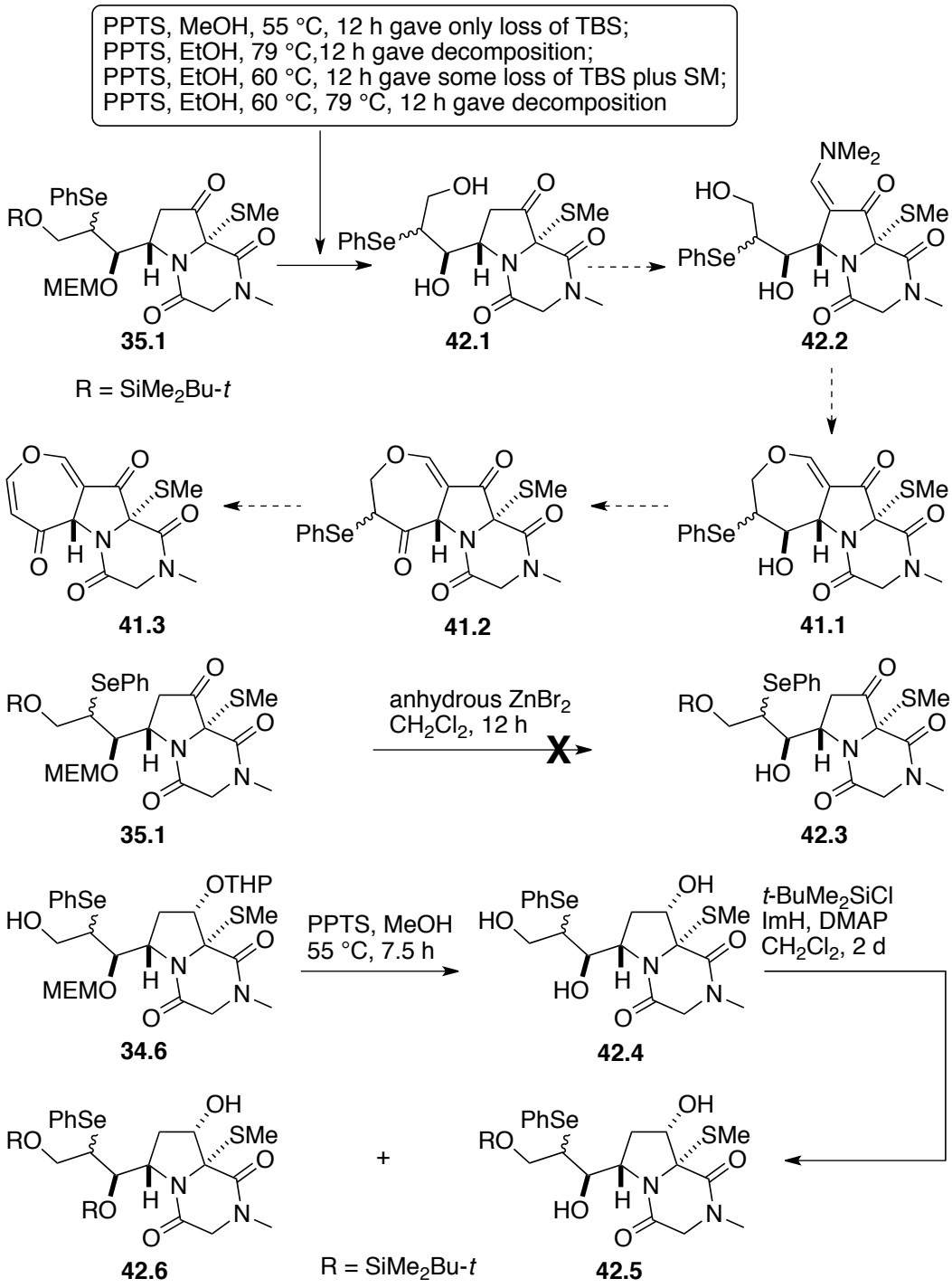
oxidation of the resulting alcohol should afford diketone **41.2**, from which the oxidative deselenylation should be very easy, as it leads to a conjugated enone system **41.3**. Unfortunately, two attempts at deprotection of the MEM ether (**36.3** → **41.1**) did not work, and only decomposition of **36.3** was observed. Before extensive studies could be carried out on this step, we ran out of starting material and decided to bring up more and find a shorter sequence to the same core.



Scheme 41. Attempts to remove MEM group from the tetrahydrooxepin **36.3**

2.3.2. *Attempts to remove MEM protecting group from other advanced intermediates*

Our next choice of intermediate was **35.1**. The plan is described in Scheme 42. Removal of both the *t*-BuMe_2Si and MEM groups should deliver the ketodiol **42.1**. Vinylogous amide formation and conjugate addition-elimination



Scheme 42. Unsuccessful attempts to remove MEM group

should then give the tetrahydrooxepin (**42.1** → **42.2** → **41.1**). Oxidation of the remaining secondary alcohol and selenoxide elimination would then produce the

target **41.3**.

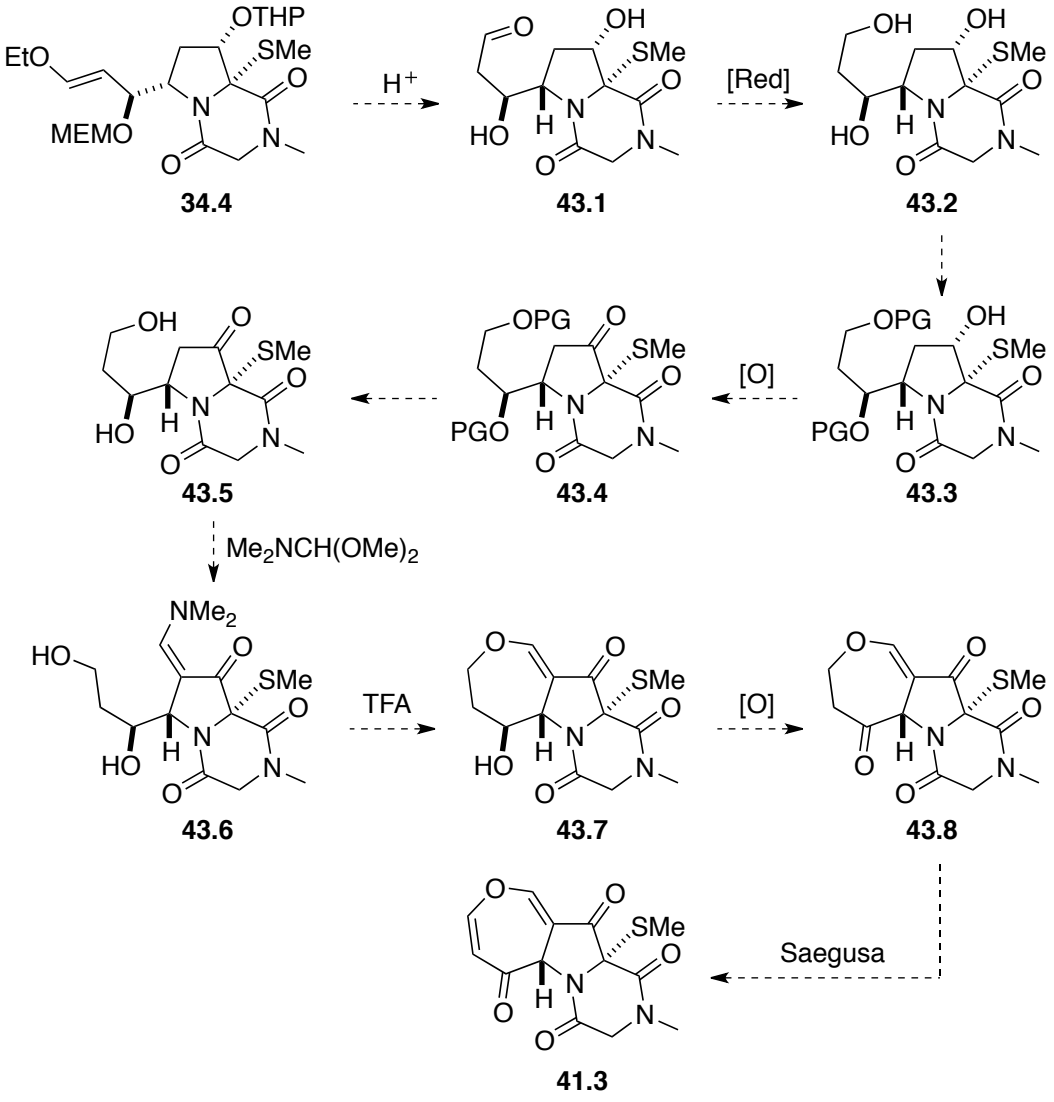
Scheme 42 shows the conditions tried to synthesize the ketodiol **42.1**. Removal of the *t*-$BuMe_2Si$ group was easy, but prolonged reaction at elevated temperatures using pyridinium *p*-toluenesulfonate and EtOH, to remove the less labile MEM group, mainly caused decomposition. An attempt to selectively remove the MEM group first, using anhydrous $ZnBr_2$ also failed (**35.1 → 42.3**) resulting in a complex mixture.

We then chose intermediate **34.6** (see section 2.2.4, Scheme 34) to study removal of the MEM group. We were actually trying to go from **34.6 → 34.7** as shown in Scheme 34 (section 2.2.4), and in one of the attempts we obtained some of the triol **42.4** as a side product (see section 2.3.3 for the proposed synthetic plan associated with a similar type of triol, **43.2**, Scheme 43). Attempted selective protection of the diol unit in the side chain, using *t*-$BuMe_2SiCl$, mainly gave monoprotected (**42.5**) and only a little of the desired diprotected product (**42.6**), and hence we aborted this route; we had also run out of this selenium-containing intermediate. In the next sections approaches avoiding selenium chemistry will be discussed.

2.3.3. *Synthetic attempts from intermediates containing the ethoxyvinyl unit*

From the discussion so far, it was obvious that the selenium route to construct the dihydrooxepin unit was unsatisfactory and we needed an alternative. We were able to make intermediate **34.4** on a multigram scale from our

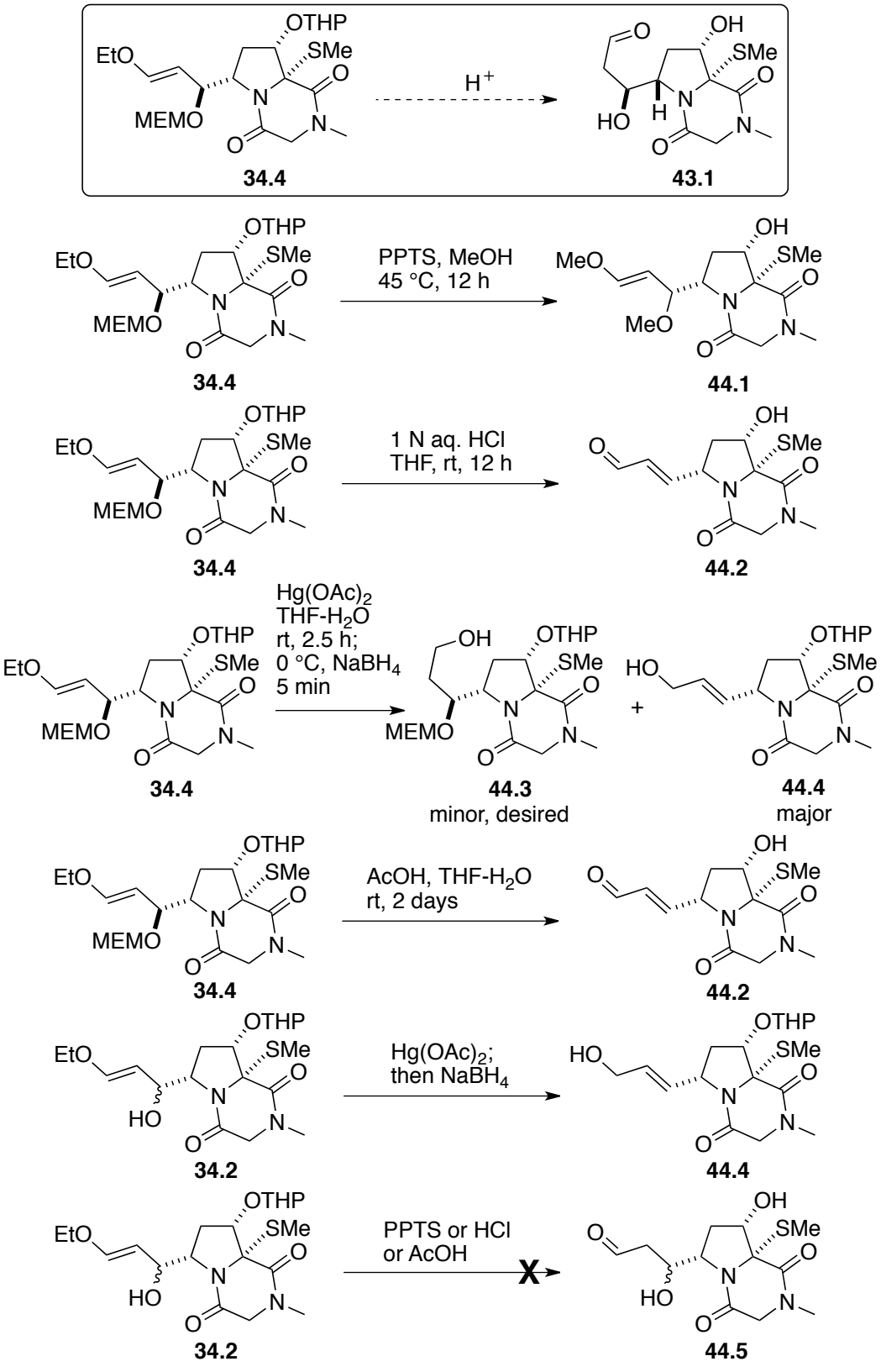
established old route (see Scheme 34). We proposed that **34.4** could be converted to the aldehyde **43.1** (see Scheme 43). Reduction of the aldehyde would generate the triol **43.2** (see Scheme 42, section 2.3.2 for related triol **42.4**, which could potentially also be subjected to this plan, as mentioned earlier). Selective



Scheme 43. New synthetic plan starting from vinyl ether **34.4**

protection of the two alcohols in the side chain, using the same protecting group should give **43.3** (see **42.6**, Scheme 42 for a related structure). Oxidation of the remaining secondary alcohol, removal of the protecting groups to generate **43.5**, installation of the enamine unit, and CF_3CO_2H-mediated cyclization should afford the tetrahydrooxepin **43.7** (cf. Scheme 40). We reasoned that 7-*endo-trig* cyclization involving the primary hydroxyl should be preferred over the 4-*exo-trig* and 5-*endo-trig* pathways involving the secondary hydroxyl. From **43.7**, oxidation of the secondary alcohol and Saegusa oxidation[65] should finish the synthesis of the tricyclic core **41.3**.

As planned, we focused on the conversion of **34.4** to aldehyde **43.1** (Scheme 44). A number of reactions were tried, as shown in Scheme 44. Use of pyridinium *p*-toluenesulfonate in MeOH gave the unwanted dimethoxy compound **44.1**, whereas aqueous hydrochloric acid and aqueous AcOH produced the enal **44.2** formed by loss of the MEMO unit, which is a characteristic reaction of these type of compounds. Inspired by the work of Walsh *et al*.,[59c] a Lewis acid mediated reaction was tried, using $Hg(OAc)_2$ and $NaBH_4$. This afforded the desired **44.3** as a minor component and the unwanted allylic alcohol **44.4** as the major product. Variable reaction times were employed at 0 °C to minimize the formation of the unwanted product, but unfortunately this method was not synthetically useful. We suspected that probably the MEMO unit is a good leaving group and hence is not even surviving the mild acidic conditions. For this reason we tried these conditions again on intermediates **34.2** (see Scheme 34) having no MEM group. The use of $Hg(OAc)_2$ gave the same unwanted allylic

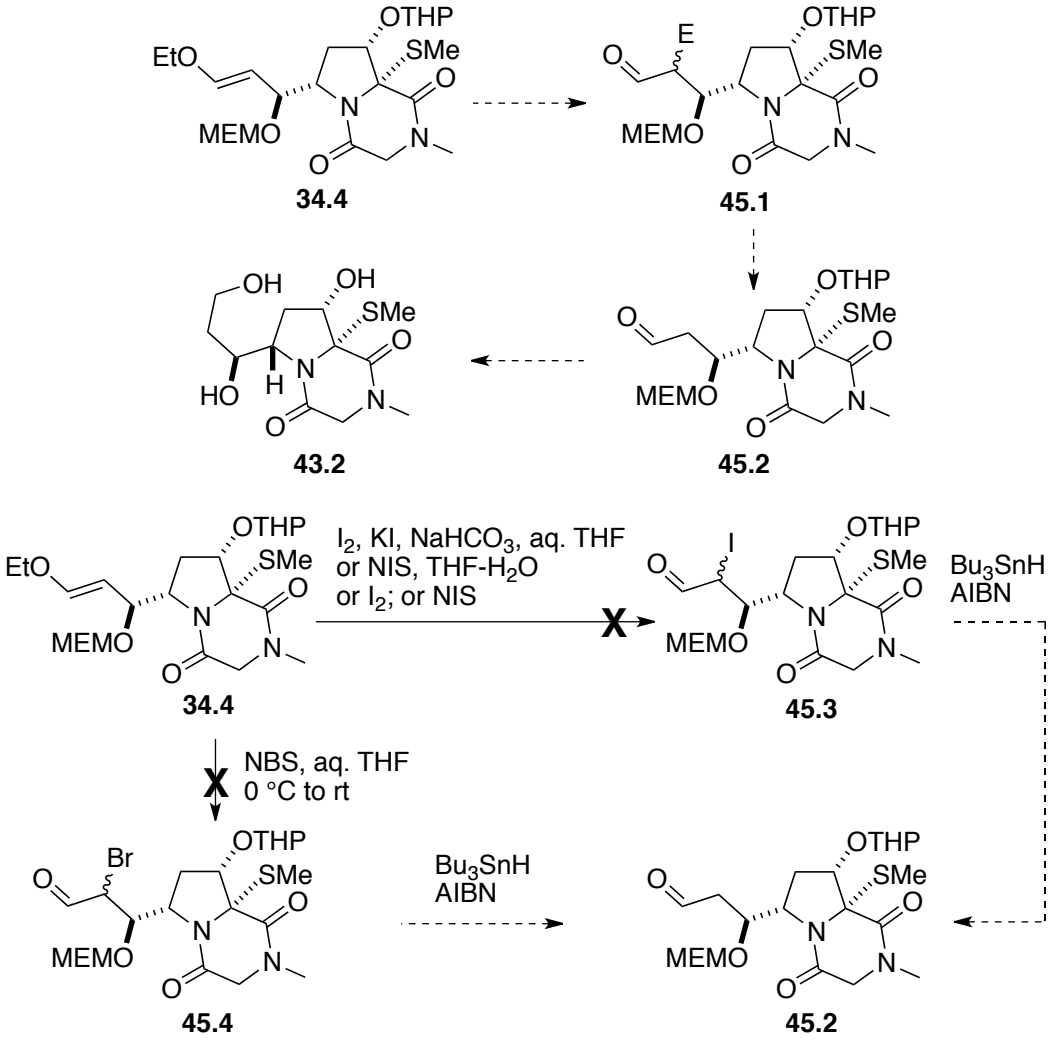


Scheme 44. Attempted modifications on vinyl ether side chain of the BC unit

alcohol **44.4** as before, and other acids like pyridinium *p*-toluenesulfonate, hydrochloric acid and AcOH caused decomposition instead of giving the desired **44.5**.

2.3.4. *Other synthetic attempts from intermediates containing the ethoxyvinyl unit*

The general plan of these attempts is summarized in Scheme 45. Since

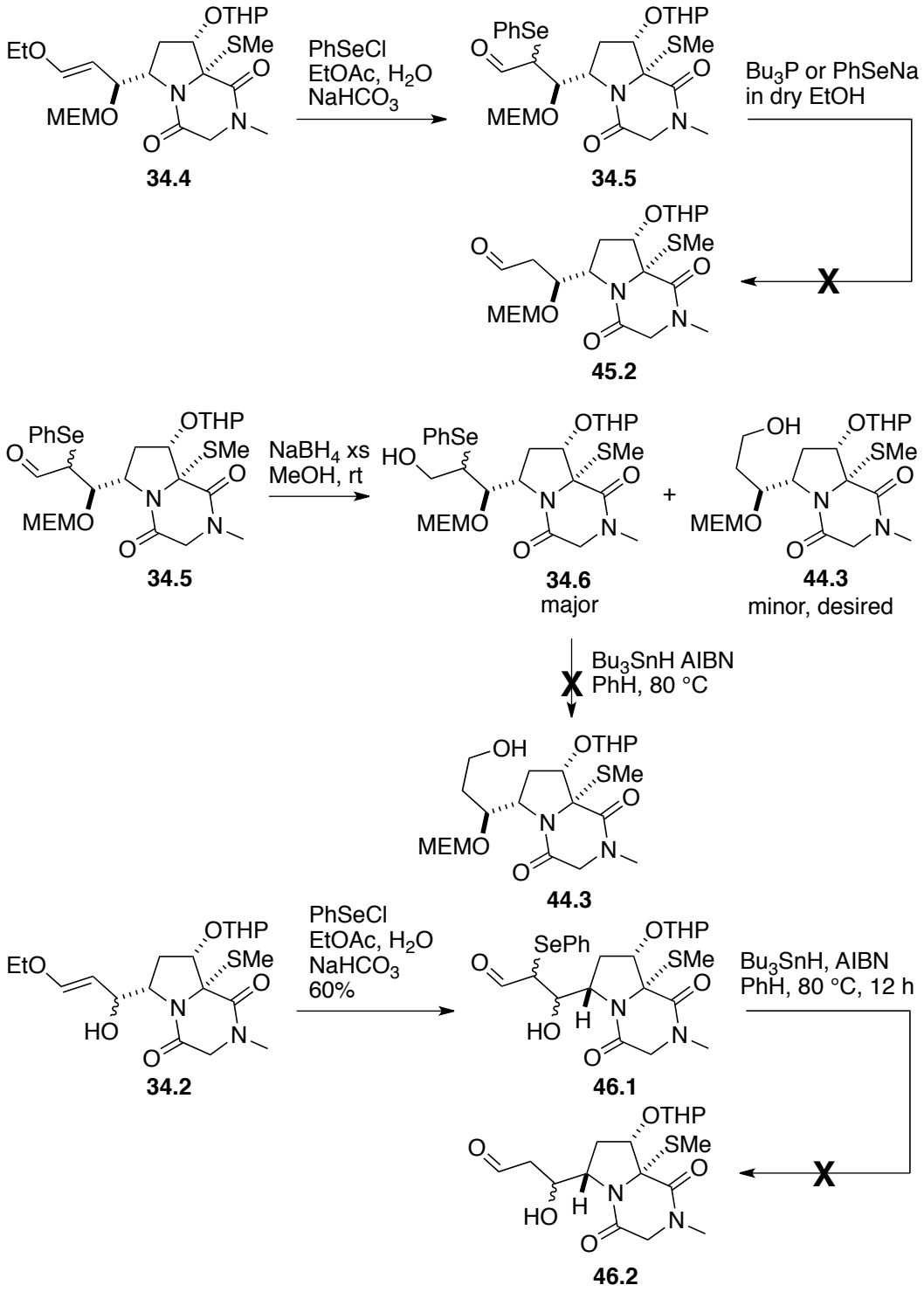


Scheme 45. Attempted electrophilic attack on the ethoxyvinyl unit

direct conversion of the ethoxyvinyl unit in **34.4** to the desired aldehyde **43.1** was unsuccessful, we planned to use some electrophiles other than PhSeCl (as was used in the previous route of section 2.2.4) to make intermediate of type **45.1** and then to remove that unit to reach aldehyde **45.2**, which can then be converted to **43.2**. As shown in Scheme 45, attempted synthesis of α-halo aldehydes **45.3** and **45.4** did not work. I_2 in KI and NBS led to decomposition, whereas NIS clearly caused the loss of the SMe group, as judged from the ^{1}H NMR of the crude reaction mixture. We proposed that these electrophiles are too strong for the SMe unit.

In search for a weaker electrophile to perform this function, we then reconsidered PhSeCl (see section 2.2.4) in the hope that we could remove the PhSe unit under mild conditions. As outlined in Scheme 46, we synthesized the α-selenoaldehyde **34.5** from **34.4**, using the procedure established earlier (see section 2.2.4, Scheme 34), and then treated the crude reaction mixture with PhSeNa (made by treating Ph_2Se_2 with $NaBH_4$ in EtOH) in order to make deselenylated product **45.2**; surprisingly, the deselenation did not work. The result was exactly the same when Bu_3P was used instead of PhSeNa. In both cases the starting compound **34.5** was recovered. As explained in section 2.2.4, during the $NaBH_4$ reduction of the α-selenoaldehyde **34.5**, we always observed formation of some deselenylated alcohol **44.3** (evident from high resolution mass spectroscopy), and hence a low temperature was employed to minimize formation of this side product. At this stage we decided to explore the possibility of employing this side reaction in a synthetically useful manner. Hence the

reduction of **34.5** was performed at room temperature in the presence of excess



Scheme 46. Further synthetic attempts to modify the ethoxyvinyl unit

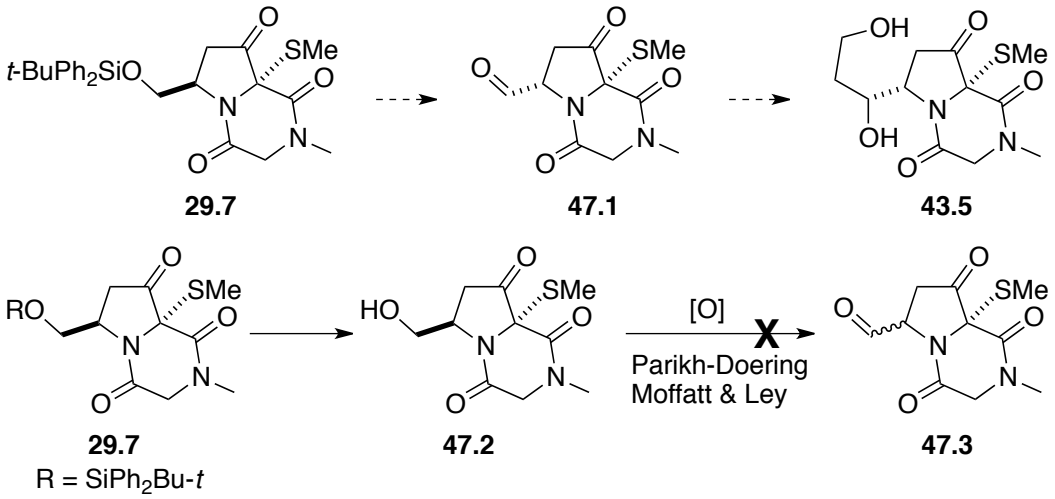
$NaBH_4$ for a long time (see Scheme 46). We indeed got some of the desired deselenylated product **44.3**, which was mixed with a lot of selenylated alcohol **34.6**; unfortunately, because of their similar polarity, they were not separable. The C-Se bond is sensitive to $NaBH_4$ only when it is α to the aldehyde and, since aldehyde reduction is faster than the C-Se bond cleavage, once all the aldehyde has been reduced, no further reaction takes place on the remaining selenylated alcohols **34.6**. Finally, we tried radical chemistry on these selenylated alcohols to remove the PhSe group[66] but this experiment (**34.6 → 44.3**) was unsuccessful and caused decomposition. Hoping that the C-Se bond will be more sensitive under radical conditions when it is α to a carbonyl, we synthesized α-selenoaldehydes **46.1** (in 60 % yield from **34.2**, see Scheme 46) and subjected them (as a mixture) to standard radical conditions in the presence of Bu_3SnH; but this approach again failed to generate **46.2** and the starting material decomposed.

2.3.5. *Attempts using no THP protecting group and a different side chain unit*

From the discussion so far, it is clear that we were in need of a replacement for the ethoxyvinyl unit, as fruitful modifications of this substructure did not work. At the same time we wanted a short concise sequence instead of the lengthy route we were using. We envisaged that if we could make the 1,4-dicarbonyl compound **47.1** (see Scheme 47), then it would be possible to convert that keto aldehyde to the keto diol **43.5** (shown in Scheme 43 in section 2.3.3) via selective reaction of the aldehyde in preference to the ketone. The added

advantage of this sequence is that it does not need any functional group interconversions on the ketone center of **29.7** and it avoids the THP protecting group steps (see Scheme 31, section 2.2.2 for use of THP group). Therefore we examined this potentially more efficient strategy (Scheme 47), starting from our BC unit **29.7**.

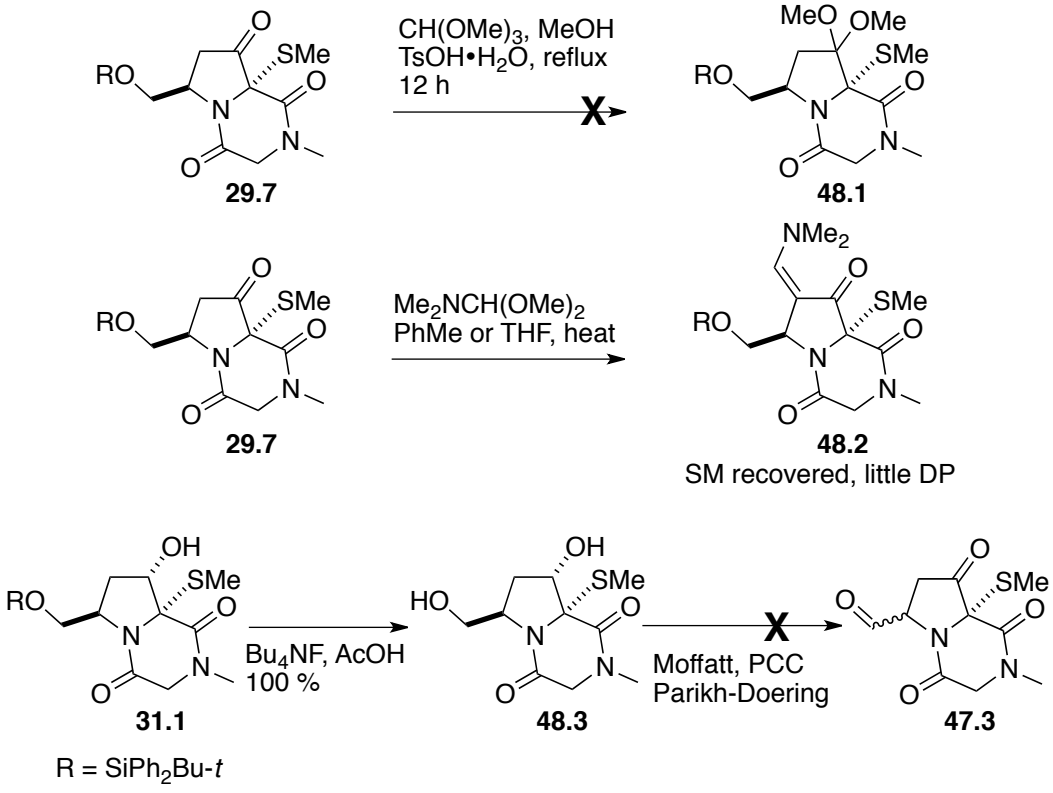
The obvious first step was to remove the *t*-$BuPh_2Si$ protecting group (Scheme 47) to make **47.2**. Surprisingly, this posed a great deal of problems, and



Reagents & Conditions for desilylation	Results
1. TBAF, THF	CM
2. TBAF, AcOH, THF	no DP
3. HF•py, THF	8% DP
4. AcCl, MeOH	CM
5. KH, 18-C-6	CM
6. $[(Me_2N)_3S\ Me_3SiF_2]$	SM recovered
7. $Bu_4NPh_3SnF_2$	SM recovered

Scheme 47. Deprotection of TBDPS ether

we were unable to carry out the deprotection. The standard conditions such as the use of Bu_4NF, Bu_4NF with AcOH, and HF•py failed to give the desired primary alcohol, with the exception of the last reagent, which gave only 8% of **47.3**. Dry HCl (AcCl in dry MeOH) and KH with 18-crown-6 ether[67a] led to decomposition. Dry conditions, using TASF (Me) i.e. $[(Me_2N)_3S\ Me_3SiF_2]$ and $Bu_4NPh_3SnF_2$,[67b] resulted in recovery of the starting material. Moreover, oxidation of the resulting primary alcohol (**47.2** → **47.3**) was also troublesome. Parikh-Doering oxidation led to decomposition, Moffatt oxidation[58] gave some product with lots of impurities, and Ley oxidation (TPAP, NMO)[52] gave only starting material. All these observations convinced us that protection of the ketone carbonyl would be

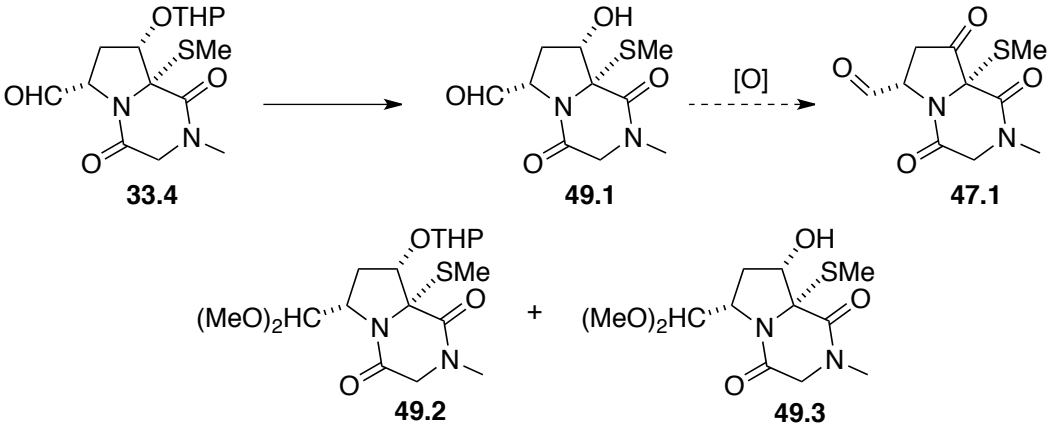


Scheme 48. Attempted modifications of the BC system without a THP group

necessary before we could do any other structural modifications. Direct ketalization using MeOH (**29.7** → **48.1**, Scheme 48) did not work, and resulted in recovery of **29.7**, presumably because of steric crowding, and prolonged heating caused some loss of the *t*-$BuPh_2Si$ group. Since we eventually needed to make a vinylogous amide (functionalize α to the ketone) we decided to construct the vinylogous amide at this earlier stage, reasoning that the enamine unit would certainly reduce the reactivity of the ketone carbonyl and thus would allow us to make the desired modifications in other parts of the molecule. Hence we attempted the conversion of **29.7** to **48.2** which, as shown in Scheme 48, gave only a trace amount of the desired product.

Our next strategy was to use **31.1** (Scheme 31, section 2.2.2) and then remove the silicon protecting group, followed by a double oxidation to get the desired keto aldehyde **47.3**. Bu_4NF buffered with AcOH gave a quantitative yield of the desired 1,4-diol **48.3** from **31.1**. Several attempts at oxidation, including Parikh-Doering and Moffatt procedures,[58] and use of PCC failed to give **47.3** from **48.3**. PCC and Moffatt conditions gave little aldehyde, but no oxidation of the secondary alcohol was observed, and no starting material was recovered. At this point we concluded that this type of 1,4-dicarbonyl compound on a pyrrolidine ring may be unstable, a characteristic that was preventing us from synthesizing this unit; hence we decided to go on with our already-established THP route (shown in section 2.2.2). Our conclusion about the stability of the 1,4-dicarbonyl system is consistent with observations made in another route, discussed later in section 2.4.1, (see **56.1** → **55.2**, Scheme 56).

Our very last attempt to make keto aldehyde **47.1** is shown in Scheme 49. We wanted to oxidize secondary alcohol **49.1** to reach **47.1**. Unfortunately, we were never able to remove the THP group from **33.4** to form aldehyde **49.1**. Several attempts were made: pyridinium *p*-toluenesulfonate in MeOH-H_2O at 50 °C gave **49.2** and **49.3**, whereas pyridinium *p*-toluenesulfonate in *t*-BuOH-H_2O gave decomposition. In aqueous THF, treatment with pyridinium *p*-toluenesulfonate resulted an incomplete reaction after 9 h at 50 °C, whereas prolonged heating resulted in a complex mixture. AcOH in aqueous THF generated very little product with some starting material after 12 h, and dilute

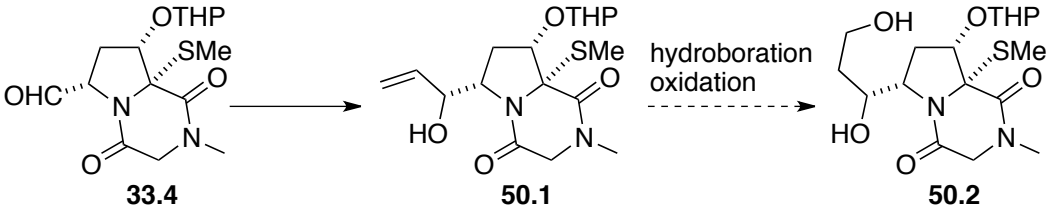


Reagents & Conditions	Results
1. PPTS, MeOH, H_2O, 50 °C, 12 h	**49.2** & **49.3**
2. PPTS, *t*-BuOH, 55 °C, 12 h	CM
3. PPTS, aq. THF, 50 °C, 9 h	SM & little DP
4. PPTS, aq. THF, 50 °C, 21 h	CM
5. AcOH, aq. THF, rt, 12 h	SM & little DP
6. AcOH, aq. THF, 60 °C, 8 h	CM
7. HCl, aq. THF	very little DP

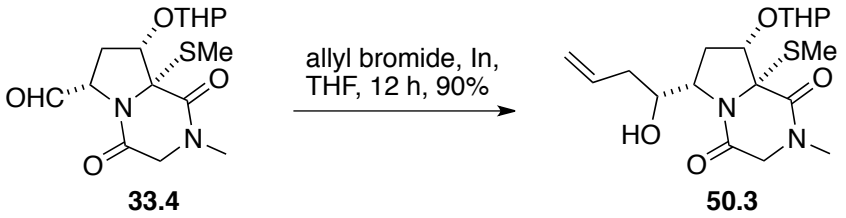
Scheme 49. Attempts to remove the tetrahydropyranyl unit

hydrochloric acid in THF gave a very poor yield of the product **49.1**.

Having decided to proceed with the THP group in place, we required a two-carbon nucleophile that could react with aldehyde **33.4**. As shown in Scheme 50, our first choice was a vinyl unit to generate **50.1**, which should serve as a precursor to the desired diols **50.2** via hydroboration-oxidation. Intermediate **50.2** can potentially be elaborated to the advanced-stage intermediate of type **43.5**. Vinylmagnesium bromide failed to give any product **50.1**, whereas vinyl-



Reagents & Conditions	Results
1. vinylcerium, –78 °C to rt, 12 h	SM
2. vinylmgnesium bromide, THF –78 °C to rt, 12 h	SM
3. vinylmagnesium bromide, $ZnCl_2$ –20 °C to rt, 12 h	SM
4. vinylmagnesium bomide, Me_2Zn THF, 0 °C to rt, 12 h	SM
5. vinylmagnesium chloride, THF –78 °C, 12 h	SM & DP



Scheme 50. Installation of the desired side chain on aldehyde **33.4**

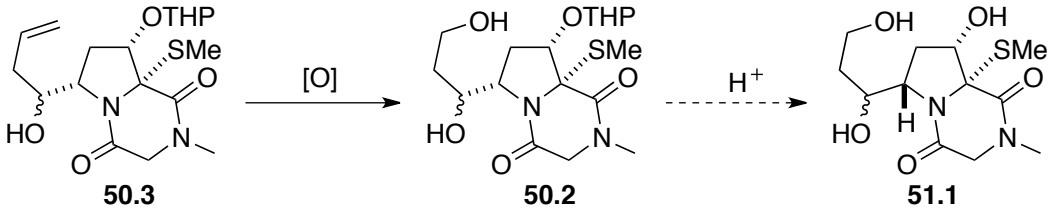
magnesium chloride led to incomplete reaction (Scheme 50). Both vinylcerium (generated from dry $CeCl_3$ and vinylmagnesium bromide)[68] and vinylzinc (generated from vinylmagnesium bromide and dry $ZnCl_2$[69a] or Me_2Zn[69b]) led to recovery of starting material. At that stage we found an excellent report[70] on an allylindium reagent, which worked beautifully to afford **50.3** from **33.4** in 90% yield (Scheme 50).

2.3.6. *Attempted modifications of the allyl side chain*

The general strategy is shown in Scheme 51. We proposed that conversion of **50.3** to the diols **50.2** is possible under oxidative cleavage conditions. Removal of the THP protecting group should afford the desired triols **51.1** as already discussed (see **43.2**, Scheme 43, section 2.3.3).

Since it is reported that oxidation of sulfur is 50 times slower than oxidation of double bonds under ozonolysis conditions,[71] we first chose to do a selective oxidative cleavage of the double bond using O_3, followed by reduction of the resulting ozonide to make **50.2**. This step was very difficult to accomplish and extensive screening of different conditions was required (see Scheme 51). We employed CH_2Cl_2-MeOH as the solvent for all of our reactions so that we could use $NaBH_4$ as the reducing agent, to break the ozonide and reduce the resulting aldehyde to an alcohol in one step. Bubbling O_3 through a solution of starting material at –78 °C until the solution turned blue, followed by reduction, resulted only in the formation of sulfoxides derived from **50.2**. Using Sudan Red

7B as indicator[72] also gave the same result. Bubbling O_3 arbitrarily for 30 sec (100 mg scale) and reduction yielded some product plus sulfoxides of **50.2** and recovered starting material. Bubbling O_3 at –100 °C mainly resulted in sulfoxides of both the starting material and **50.2**, with very little of **50.2** itself. Obviously, a controlled reaction was required to minimize or stop the formation of sulfoxides. We then decided to use the Rubin apparatus[73] with which one can add a calculated amount of O_3. This is achieved by making a saturated solution of O_3 in a known



50.3 **50.2** **51.1**

Reagents & Conditions	Results
1. O_3, CH_2Cl_2, saturated, –78 °C; MeOH, $NaBH_4$	sulfoxides of DP
2. O_3, CH_2Cl_2, saturated,Sudan Red 7B –78 °C; MeOH, $NaBH_4$	sulfoxides of DP
3. O_3, CH_2Cl_2, bubbled for 30 sec –78 °C; MeOH, $NaBH_4$	DP, sulfoxides of DP & SM
4. O_3, CH_2Cl_2, saturated, –100 °C; MeOH, $NaBH_4$	sulfoxides of SM & DP, little DP
5. 1 eqv. O_3, CH_2Cl_2, saturated, –78 °C; MeOH, $NaBH_4$	SM & DP
6. 2 eqv. O_3, CH_2Cl_2, saturated, –78 °C; MeOH, $NaBH_4$	21% & SM
7. 1 eqv. O_3, CH_2Cl_2, saturated, –78 °C; MeOH, $NaBH_4$	57% & SM
8. 1 eqv. O_3, CH_2Cl_2, slow addition –78 °C; MeOH, $NaBH_4$	little DP & mainly SM
9. 1 eqv. O_3, CH_2Cl_2, slow addition –78 °C; Me_2S	little aldehyde DP mainly SM

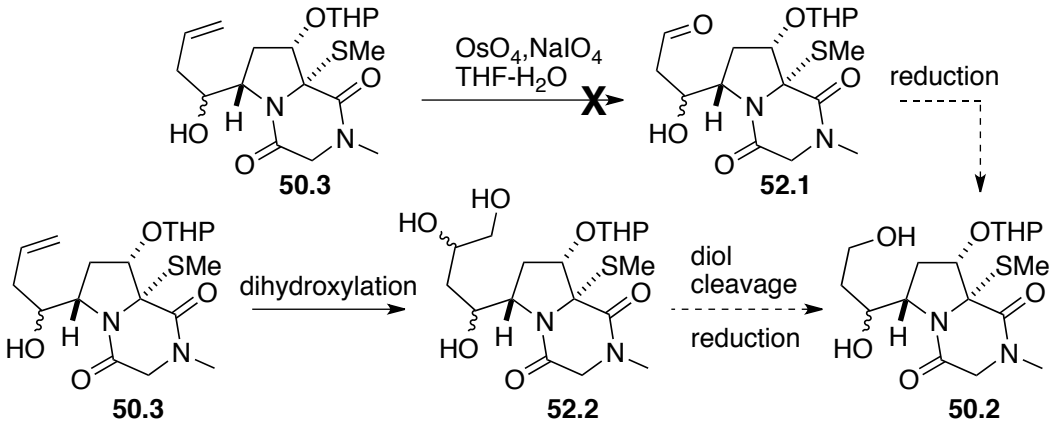
Scheme 51. Ozonolysis approaches to modify the allyl side chain

volume of CH_2Cl_2 at –78 °C (the concentration of O_3 is known) and then transferring that solution to a solution of starting material. Use of one equivalent of O_3 resulted in significant recovery of starting material plus **50.2** (and no sulfoxides), and with two equivalent of O_3 we got starting material and a 21% yield of **50.2**. Optimizing the reaction with one equivalent of O_3 on 150-200 mg scale, using $NaBH_4$ as reducing agent, we were finally able to get **50.2** in 57% yield (corrected for recovered starting material). Because of the recovery of a significant amount of starting material and the fact that these conditions failed to give a satisfactory result when run on more than 200 mg, we designed a special apparatus where one can actually control the rate of addition of the saturated solution of O_3 in CH_2Cl_2 to the solution of starting material by adjustment of a

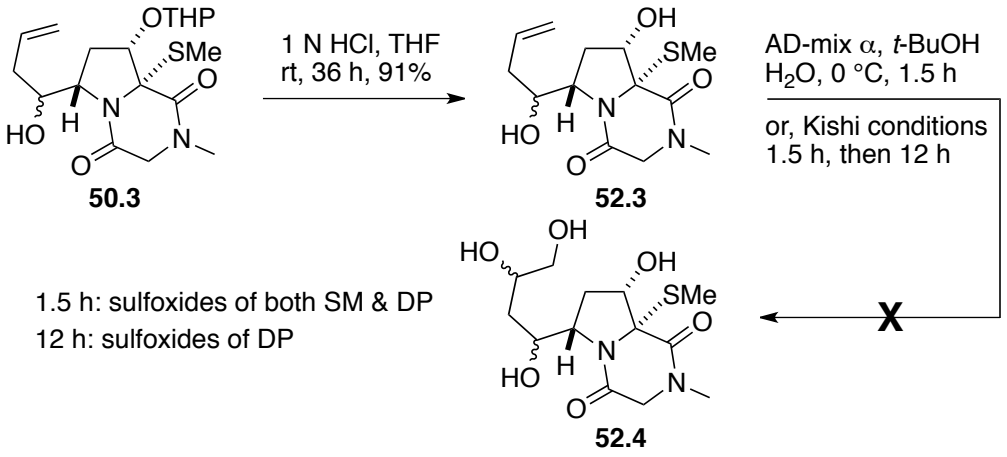
Figure 5. Special ozonolysis apparatus

vertical piston. Hence, this new apparatus was used and the rate of addition of the O_3-CH_2Cl_2 solution was controlled at a slow dropwise manner at –78 °C. Disappointingly, this experiment also led mainly to the recovery of starting material. Use of Me_2S as reducing agent instead of $NaBH_4$ also failed to improve the yield. Hence, although we were able to stop the formation of unwanted sulfoxides, the low yield of this reaction under controlled conditions led us to abandon this method.

We then explored the possibility of using the Johnson-Lemieux oxidation[74] (Scheme 52, **50.3** → **52.1**), using OsO_4-$NaIO_4$, but this resulted in decomposition. Finally, we decided to try the stepwise sequence of dihydroxylation-diol cleavage-reduction to get to the desired diol **50.2** from **50.3**, as shown in Scheme 52. Sulfides are not oxidized[75] by stoichiometric OsO_4; however, in the presence of strong co-oxidants like trialkylamine *N*-oxides, sulfides can be oxidized efficiently using both stoichiometric and catalytic OsO_4.[76] It has been shown that AD-mix reagents which contain weaker co-oxidant [$K_3Fe(CN)_6$] are less reactive towards sulfur compared to the OsO_4-NMO system.[77] Hence, various combinations of AD-mix α and β with or without methanesulfonamide were tried (see chart in Scheme 52). Only AD-mix α without methanesulfonamide resulted in some of the desired **52.2** (23%, corrected for recovered starting material) and no sulfoxides were formed, but significant amounts of starting material were recovered, even after two days. With AD-mix α and methanesulfonamide, the major products were the sulfoxides of the starting material, with little starting material, **52.2** and sulfoxides of **52.2**, within just 2 h.



Reagents & Conditions (for dihydroxylation)	Results
AD-mix α, *t*-BuOH H_2O, 0 °C, 2 days	SM plus DP, no sulfoxides DP 23% brsm
AD-mix α, *t*-BuOH H_2O, 0 °C, $MeSO_2NH_2$	2 h: sulfoxides of SM (major) little sulfoxides of DP; 12 h: SM, SM-sulfoxides (major) DP, DP-sulfoxides
AD-mix β, *t*-BuOH H_2O, 0 °C, 12 h	SM, sulfoxides of DP, little DP
AD-mix β, *t*-BuOH, H_2O $MeSO_2NH_2$, 0 °C, 12 h	SM, sulfoxides of DP
OsO_4, DABCO, $K_3Fe(CN)_6$ $MeSO_2NH_2$, *t*-BuOH, H_2O K_2CO_3, 0 °C, 30 min, (Kishi conditions)	sulfoxides of both SM & DP little DP

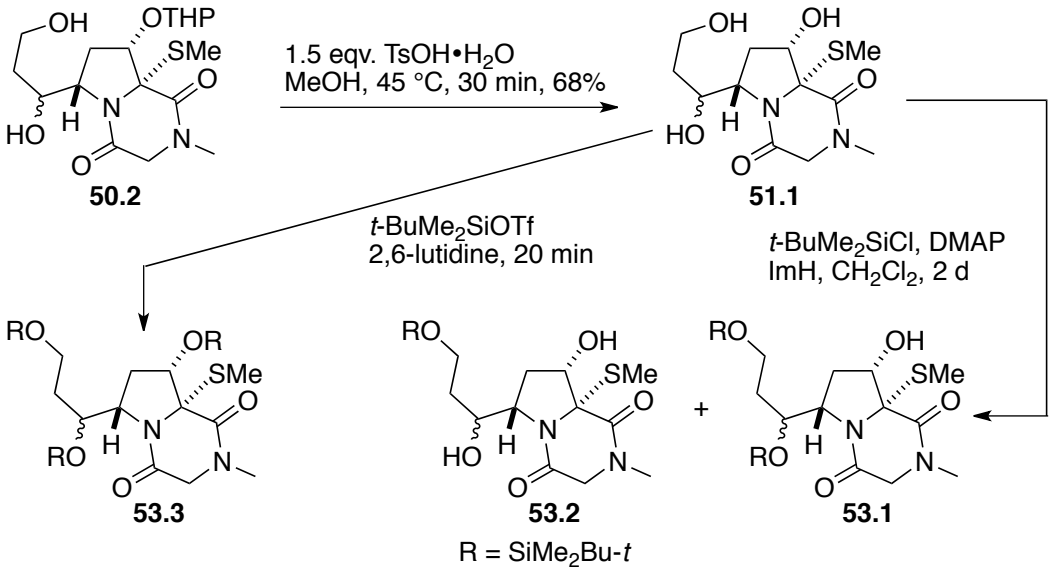


Scheme 52. Further attempted oxidative modifications of the allyl side chain

With AD-mix β, with or without methanesulfonamide, the major products were the sulfoxides of **52.2**, with some recovered starting material and hardly any of the desired product. Finally the Kishi conditions were tried, using DABCO, which resulted in formation of sulfoxides of both **50.3** and **52.2** within 30 minutes. After prolonged stirring (12 h) some sulfone derived from **52.2** was also detected by low resolution mass spectroscopy. We then decided to try all these reactions after removal of the THP group, which was achieved in 91% yield (**50.3** → **52.3**, Scheme 52). The Kishi conditions[78] applied to **52.3** (Scheme 52), gave only sulfoxides of both starting material and of **52.4**, within 1.5 h; after an overnight reaction period, the crude reaction mixture showed only sulfoxides of **52.4**. Treatment of **52.3** with only AD-mix α also led to the same result. We thus concluded that oxidative modifications on the allyl unit are not possible in the presence of the SMe group.

While optimizing the oxidative cleavage step, we also decided to explore the next few steps as described in our previous plan (see **51.1**, Scheme 51, section 2.3.6, and **43.2** → **43.3**, Scheme 43, section 2.3.3). The very next step was removal of the THP protecting group (**50.2** → **51.1**, Scheme 53). Numerous conditions were tried. Pyridinium *p*-toluenesulfonate in MeOH at 55 °C resulted in impure **51.1**. Different concentrations of aqueous hydrochloric acid were tried at room temperature, but these conditions led to incomplete reactions, and heating resulted in decomposition. An equivalent amount of TsOH•H_2O in MeOH was used at room temperature (11 days), which also resulted in incomplete reaction. Catalytic (10 mol%) TsOH•H_2O in MeOH at 45 °C (12 h) provided the same

result. Finally, 1.5 equivalent of TsOH•H_2O in MeOH at 45 °C was successful, yielding the desired triol (**51.1**) in 68% yield within just 30 min.

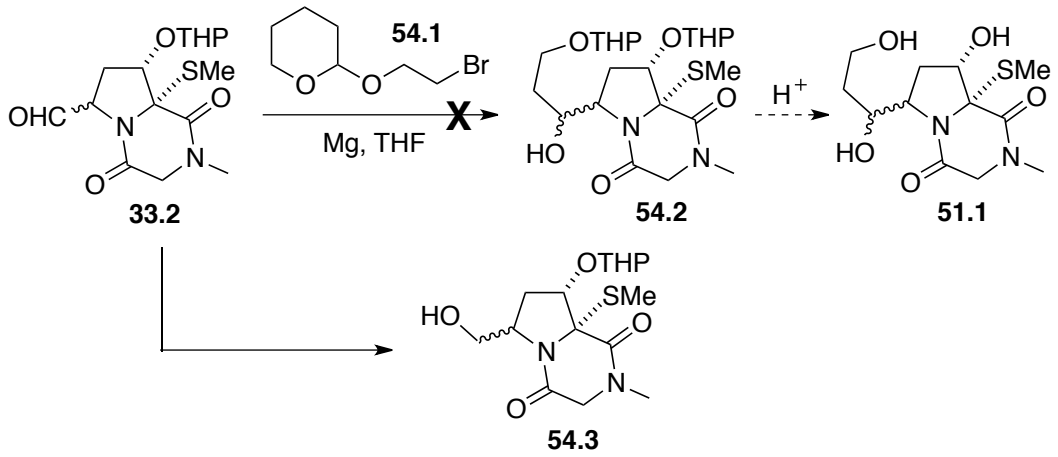


Scheme 53. Synthetic modifications of diol **50.2**

Selective protection of the diol in the side chain of **51.1** was not very straightforward. Use of *t*-$BuMe_2SiCl$ yielded mainly monoprotected product (**53.2**) with very little of the desired diprotected product (**53.1**), whereas use of a stronger silylating agent *t*-$BuMe_2SiOSO_2CF_3$, led to a trisilylated product (**53.3**). Because of the poor yield of the oxidative cleavage step (**50.3 → 50.2**), we eventually decided to abandon this route as well.

2.3.7. *Attempted route using a β-alkoxy Grignard reagent*

Based on a literature report[79] we tried to make the Grignard reagent from THP-protected 2-bromoethanol **54.1**, and then treated that with aldehyde **33.2** in the hope of making **54.2**. The latter, upon removal of THP groups, should afford the desired triol **51.1**. However, the Grignard step did not work and instead we



Scheme 54. Use of β-alkoxy Grignard reagent

isolated the reduced product **54.3**. We suspect that the reported formation of the Grignard reagent is incorrect; the reagent would be expected to expel the oxygen functionality.

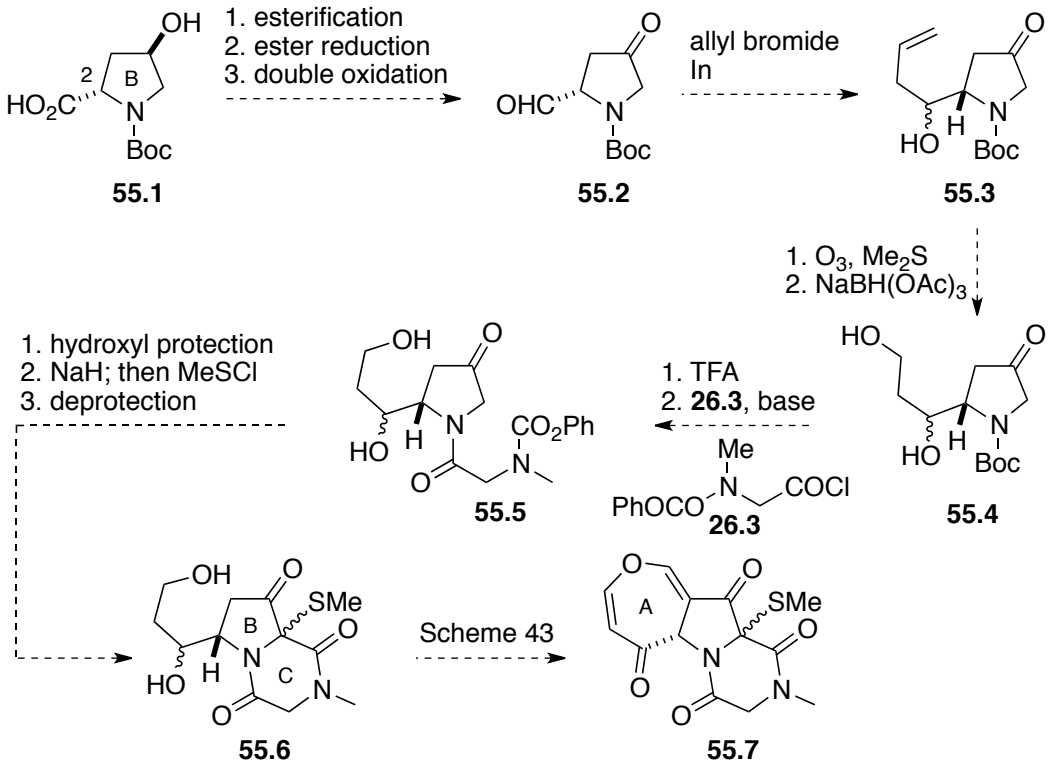
2.4. New concise enantioselective routes towards the tricyclic core

Our experience so far suggested that the allyl group is the correct choice of the side chain which acts as a precursor of the dihydrooxepin unit. We had also

optimized the method to construct the BC bicyclic system with the sulfur group, and we concluded in section 2.3.6 that no chemical modifications were possible on the allylic side chain in the presence of sulfur. Hence we needed a modified route that preserved as much as possible of our previous reactions. Clearly, we needed to install the allyl unit first, then perform the required modifications on it, and finally synthesize the diketopiperazine B ring with the SMe group. Once the BC system is made, efforts would be directed to the task of constructing the dihydrooxepin A ring, because prior research by Dr. Peng[44] revealed that the DKP ring cannot be formed onto the AB system.

2.4.1. *The first new route starting with a Boc protected amino acid*

The general plan is outlined in Scheme 55. The plan was to start with *N*-Boc-4-hydroxy-L-proline (**55.1**), and convert that to the 1,4-dicarbonyl compound **55.2**. We first wanted to check the feasibility of this route, and so we decided not to focus on the epimerization at C2, as described in section 2.2.1. Installation of the allyl group (to obtain **55.3**), ozonolysis-ozonide reduction, followed by $NaBH(OAc)_3$ selective reduction of the resulting aldehyde should afford the keto diol **55.4**. Removal of the Boc group and installation of the carbamate chain using **26.3** (see Scheme 29, section 2.2.1) should give **55.5**. Protection of the diol, NaH mediated cyclization-sulfenylation (see Scheme 30, **29.7**, section 2.2.1) and removal of the protecting groups would then afford the diketopiperazine BC ring containing the ketodiol system (**55.6**) similar to what is shown in section 2.3.3

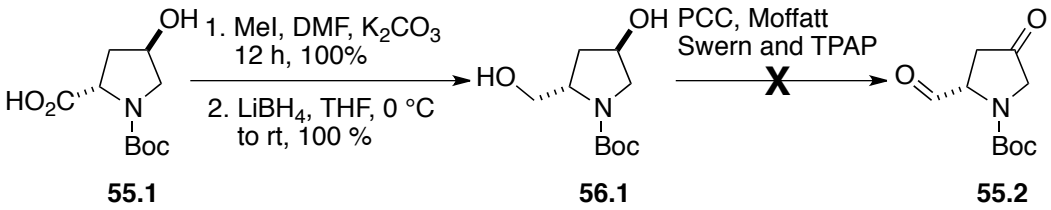


Scheme 55. First proposed concise route, using **55.1**

(**43.5**, Scheme 43). We expected that this intermediate can then be elaborated to the dihydrooxepin **55.7** (see section 2.3.3, Scheme 43, **41.3**, for related dihydrooxepin).

The Boc protected amino acid **55.1** was converted to the diol **56.1** via a simple two-step sequence involving esterification and $LiBH_4$ reduction of the ester (Scheme 56). Several oxidation attempts, which included PCC, Moffatt,[58] Swern and Ley[52] oxidation, failed to give the desired aldehyde **55.2** and resulted only in decomposition of the starting material. This observation was consistent with our conclusion described in section 2.3.5 that this type of 1,4-dicarbonyl

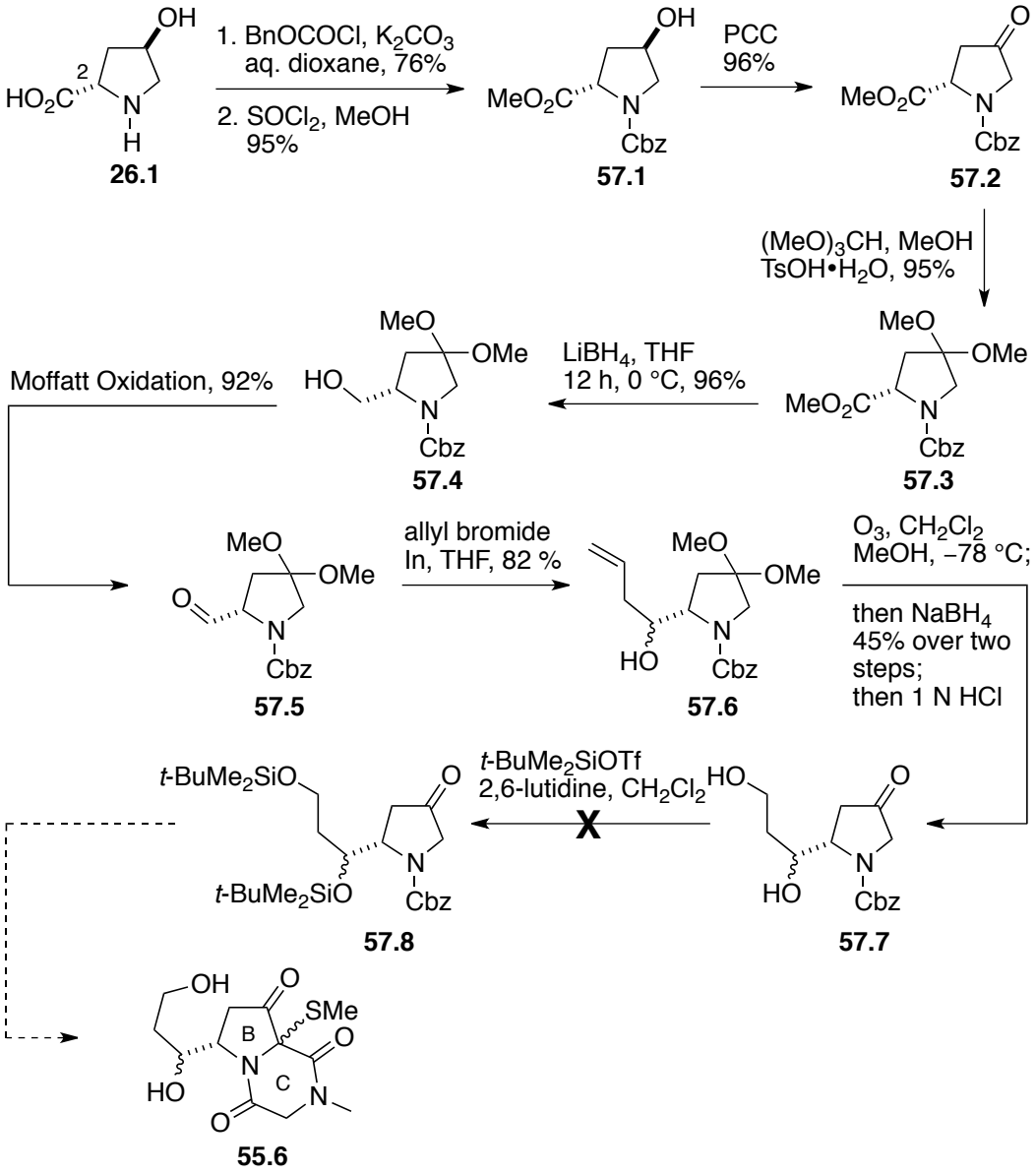
system on a pyrrolidine ring is unstable (see **47.2** → **47.3**, Scheme 47, and **48.3** → **47.3**, Scheme 48). Hence we did not pursue this route further.



Scheme 56. Failure of attempted double oxidation

2.4.2. *The second new route starting with a Cbz protected amino acid*

The second strategy was exactly similar to what we discussed in section 2.4.1. 4-Hydroxy-L-proline **26.1** was converted to ester **57.1** in a two-step sequence, Cbz protection of nitrogen and esterification. Again we ignored the epimerization at C2 for the time being. PCC oxidation of **57.1** afforded the ketoester **57.2** in 96% yield. Protection of the ketone (**57.2** → **57.3**) was necessary, as we observed in section 2.4.1 that compounds like **55.2** are unstable. DIBAL-H reduction of the ketal **57.3** to aldehyde **57.5** did not work, and so $LiBH_4$ reduction and Moffatt oxidation[58] were employed, both giving excellent yields (**57.3** → **57.4** → **57.5**). Introduction of the allyl side chain[70] went smoothly (**57.5** → **57.6**). The one-pot sequence of ozonolysis-reduction and ketal removal gave the keto diol **57.7**. Surprisingly, protection of the diol unit of **57.7** using *t*-$BuMe_2SiOSO_2CF_3$ was unsuccessful and instead gave the silyl enol ether derived from the desired doubly protected ketone **57.8**. Our next planned steps



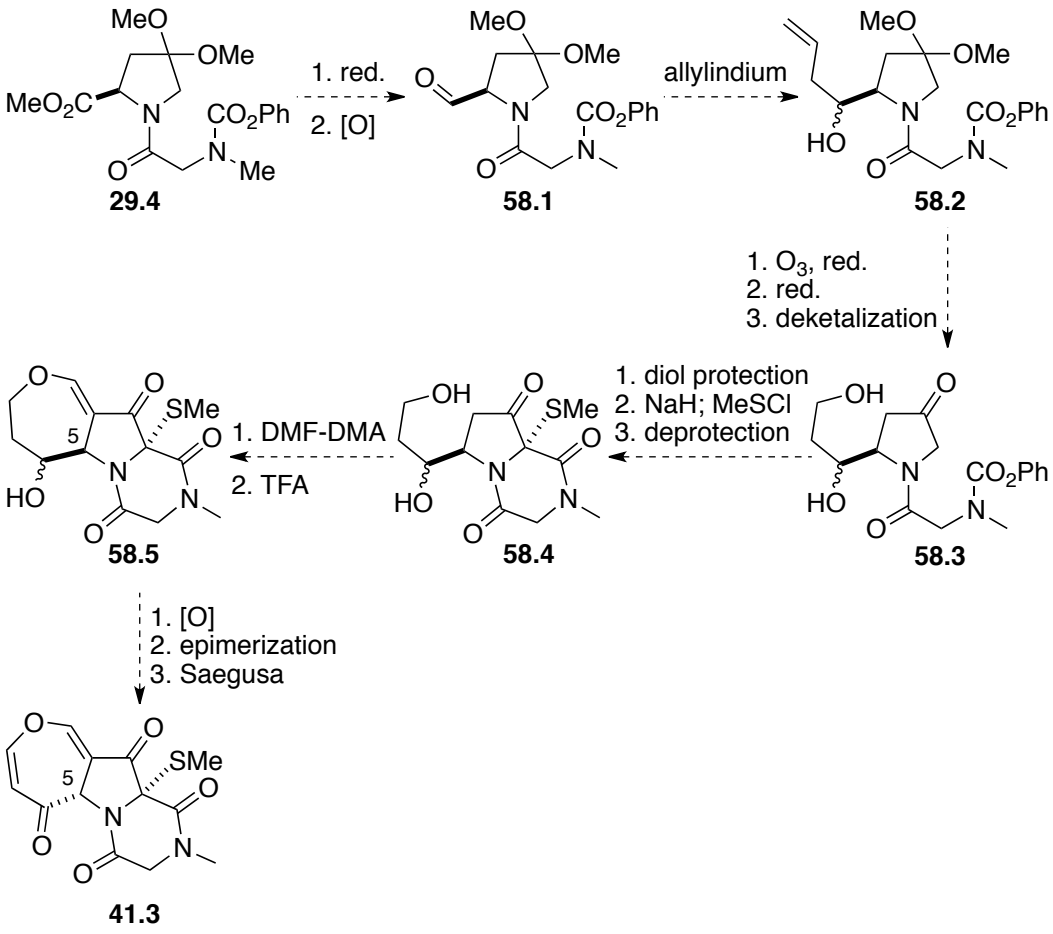
Scheme 57. Second concise approach towads the tricyclic core of MPC1001F

were to remove the Cbz group and install the carbamate side chain on nitrogen (using **26.3**). The rest of the sequence was to have been exactly the same as described in Scheme 55 (section 2.4.1). It is important to mention at this point that, while working on the above route, we were also working on a third, and potentially more efficient route (discussed in section 2.4.3). Our plan was to try

both of the routes shown in Schemes 57 and 59 at the same time and to choose the one that worked better; this turned out to be the third route, and hence we did not spend any more time optimizing this second route.

2.4.3. *Current concise enantioselective approach to the tricyclic ABC core of MPC1001F*

We decided to start with the early intermediate **29.4** (see Scheme 29,



Scheme 58. Current synthetic plan towards the ABC unit of MPC1001F

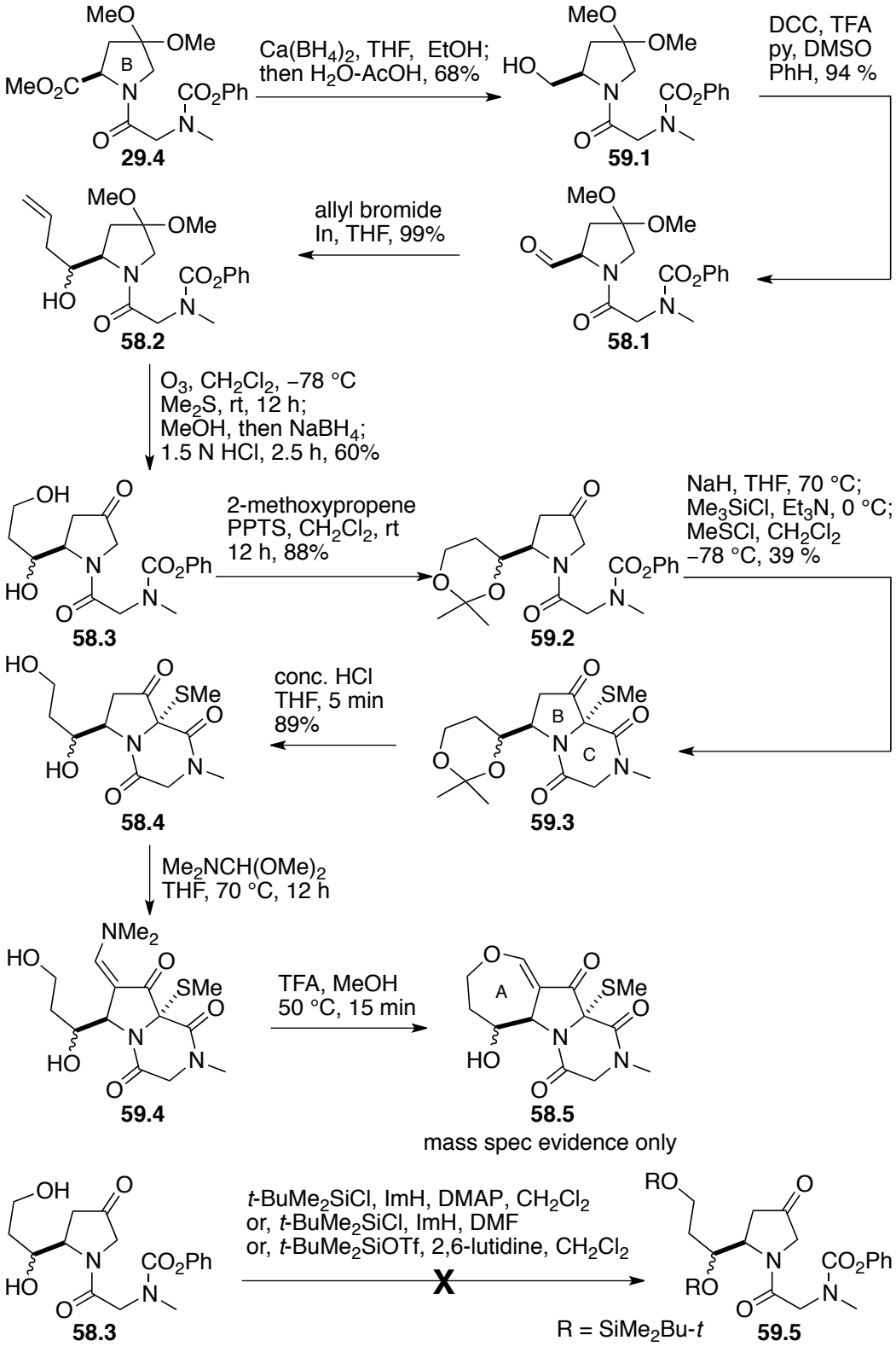
section 2.2.1) which we had made earlier. The 16-step plan towards the core is outlined in Scheme 58. Ketal **29.4** would be converted to aldehyde **58.1** by a reduction-oxidation sequence. Installation of the allyl group, followed by oxidative cleavage of the double bond, reduction and deketalization should generate the ketodiols **58.3** (see **55.5**, Scheme 55). Protection of the diols and NaH mediated cyclization-sulfenylation (see section 2.2.1, Scheme 30, **25.1 → 29.7**) and then removal of the protecting groups should produce the ketodiols **58.4** in a process similar to that mentioned in sections 2.3.3 (Scheme 43, **43.5**) and 2.4.1 (Scheme 55, **55.6**). The diols **58.4** can then be elaborated to the tetrahydrooxepin **58.5**, in the same way as shown in Scheme 43 (**43.5 → 43.7**). Intermediate **58.5** could be converted to the tricyclic core **41.3** via a three step sequence of Moffatt oxidation, epimerization and Saegusa oxidation.[65]

The first step was to perform the same type of $Ca(BH_4)_2$[47] reduction on **29.4** (see Scheme 29, **29.4 → 29.5** section 2.2.1 for related reaction), but to quench the reaction with AcOH instead hydrochloric acid so that the ketal group survives (**29.4 → 59.1**, Scheme 59). This was the desired outcome as we knew from our previous discussions (sections 2.3.5 and 2.4.1, see **47.2 → 47.3** in Scheme 47, **48.3 → 47.3** in Scheme 48 and **56.1 → 55.2** in Scheme 56) that formation of the 1,4-dicarbonyl on the pyrrolidine ring was not possible. The Moffatt oxidation,[58] which had already been proved to cause no epimerization (section 2.2.3, Table 1), when applied to **59.1** gave aldehyde **58.1** in excellent yield. Hence the stage was set to do our critical allylindium reaction[70] (see section 2.3.5, Scheme 50, **33.4 → 50.3**) which gave the desired **58.2** in almost

quantitative yield, as an inseparable mixture of diastereomers.

Extensive optimization was again required to perform the next step (**58.2 → 58.3**). A stepwise sequence of ozonolysis, reduction and deketalization gave a poor yield. Johnson-Lemieux oxidation,[74] using OsO_4-$NaIO_4$, gave mainly the dihydroxylated product instead of an aldehyde. A stepwise sequence of dihydroxylation, diol cleavage and reduction was also very low-yielding. Finally, it was found that a one-pot sequence of ozonolysis-reduction (using Me_2S), $NaBH_4$ reduction of the resulting aldehyde and dilute hydrochloric acid mediated deketalization afforded the best yield of the desired product (**58.3**) (60% over these three steps). Use of just $NaBH_4$ as reductant gave a slightly poorer yield. Compound **58.3** was water- soluble and workup involved evaporation of the aqueous layer. This yield (60% over the three steps) was obtained for a reaction done on a 200 mg scale. When the reaction was repeated on a 1-2 g scale, the yield dropped to 40-45%. Finally, use of $NaBH_4$ as a reductant for the ozonide and THF as the solvent for hydrolysis of the ketal, afforded **58.3** in 59% yield on 1-g scale.

Protection of both the hydroxyls as *t*-$BuMe_2Si$ ethers was troublesome, as observed earlier for related compounds (see section 2.3.6, **51.1 → 53.1**, Scheme 53 and section 2.4.2, **57.7 → 57.8**, Scheme 57). *t*-$BuMe_2SiCl$ and *t*-$BuMe_2SiOSO_2CF_3$ and various combinations of ImH, DMAP, DMF, CH_2Cl_2 and 2,6-lutidine were used (Scheme 59, **58.3 → 59.5**). The major product was either monoprotected ether (with *t*-$BuMe_2SiCl$) or tris-silylted enol ether (with *t*-$BuMe_2SiOSO_2CF_3$). Our strategy was to put the same protecting group on both



Scheme 59. Concise enantioselective synthesis of the ABC core

hydroxyls (necessary for the next step which involved NaH) so that they could be removed in the same step as well. Finally it was gratifying to find that protection of the diol unit in **58.3** as a ketal, using 2-methoxypropene, took place smoothly, providing ketone **59.2** in 88% yield. The same type of NaH-mediated Dieckmann-type cyclization, followed by silyl enol ether formation and then sulfenylation as was used in the very first route (section 2.2.1, Scheme 30) was applied here to reach the diketopiperazine **59.3**. The structure of this compound was confirmed by X-ray analysis (the ORTEP diagram is shown in Figure 6). The stereochemical outcome of the sulfenylation was controlled by the stereochemistry of the ketal side chain. The ^{1}H NMR spectrum of **59.3** actually showed only one diastereomer, although another minor compound having the same mass, was also isolated as an oil (but not characterized); possibly this second compound could be the other diastereomer either along the C-O bond or along the

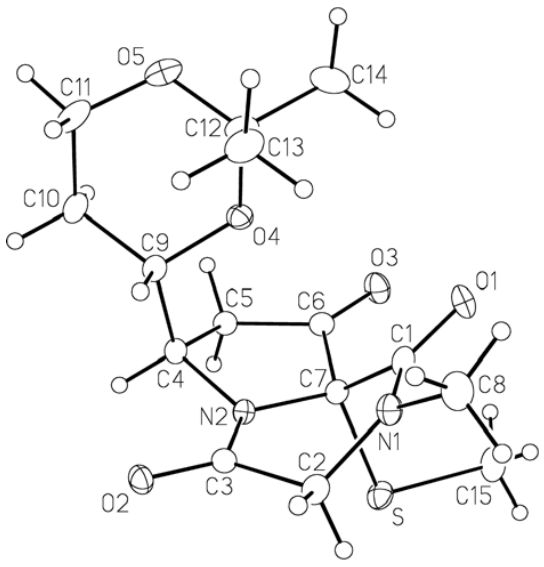


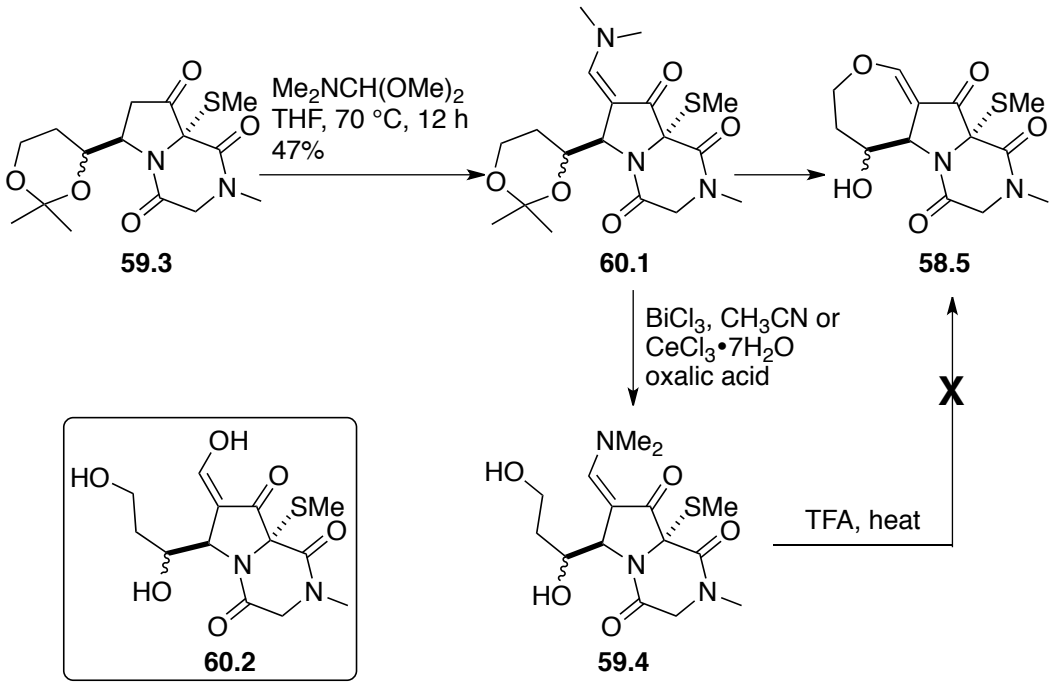
Figure 6. ORTEP diagram of **59.3**

C-S bond. We are not concerned with diastereomers along the C-O bond, as eventually that bond is converted into a double bond.

Removal of the ketal protecting group from **59.3** was straightforward giving the ketodiol **58.4** in 89% yield. Formation of the vinylogous amide **59.4** was not easy, and with dimethylformamide dimethyl acetal the reaction worked, but many impurities were also generated. Reaction between **58.4** and Bredereck's reagent[80] did not generate any of the desired product **59.4**, instead an unidentified side product resulted. Because of the very high polarity of **59.4**, it was difficult to purify. Cyclization mediated by CF_3CO_2H afforded the desired tetrahydrooxepin **58.5** in a very small scale experiment, and only low resolution mass spectral evidence was acquired. Several other attempts were made which involved use of CF_3CO_2H in PhMe at different temperatures. Some unwanted trifluoroacetylation of one of the hydroxyl groups of **59.4** was also observed. Clearly, these last two steps still require optimization. It could be possible that impurities present in **59.4** were causing problems in the CF_3CO_2H-mediated cyclization. Hence we planned to install the enamine unit on **59.3**, before removing the ketal.

The reaction **59.3** → **60.1** (Scheme 60) worked in 47% yield and the product can be purified easily. Removal of the ketal under mild conditions without affecting the enamine (**60.1** → **59.4**) was now necessary, and was achieved by using $BiCl_3$[81a] or $CeCl_3 \bullet 7H_2O$-oxalic acid,[81b] with the latter giving a cleaner reaction (as evident from low resolution mass spectroscopy). The crude reaction mixture containing **59.4** was subjected to CF_3CO_2H-mediated cyclization, but the desired process (**59.4** → **58.5**) did not work, possibly, because of the

presence of unwanted inorganic impurities. Direct treatment of **60.1** with CF_3CO_2H-water, TsOH and HCl-water to remove the ketal first, followed by conjugate addition-elimination on the vinylogous amide (**60.1 → 58.5**), was not straightforward either, and mainly showed the enamine hydrolysis product, enoldiol **60.2** (evident from low resolution mass spectroscopy). The conditions



Reagents & Conditions for **60.1 → 58.5**	Results
1. TFA, THF, H_2O, 70 °C, 15 min	**58.5** & **60.2** (major)
2. TFA, THF, H_2O, 70 °C, 12 h	**60.2**
3. 1 N HCl, THF, rt, 4 h	**60.2**
4. TFA, CH_2Cl_2, 40 °C, 12 h	CM
5. TsOH•H_2O, THF, 70 °C, 1 h	CM
6. TFA, PhMe, H_2O, 50 °C, 5 h	DP

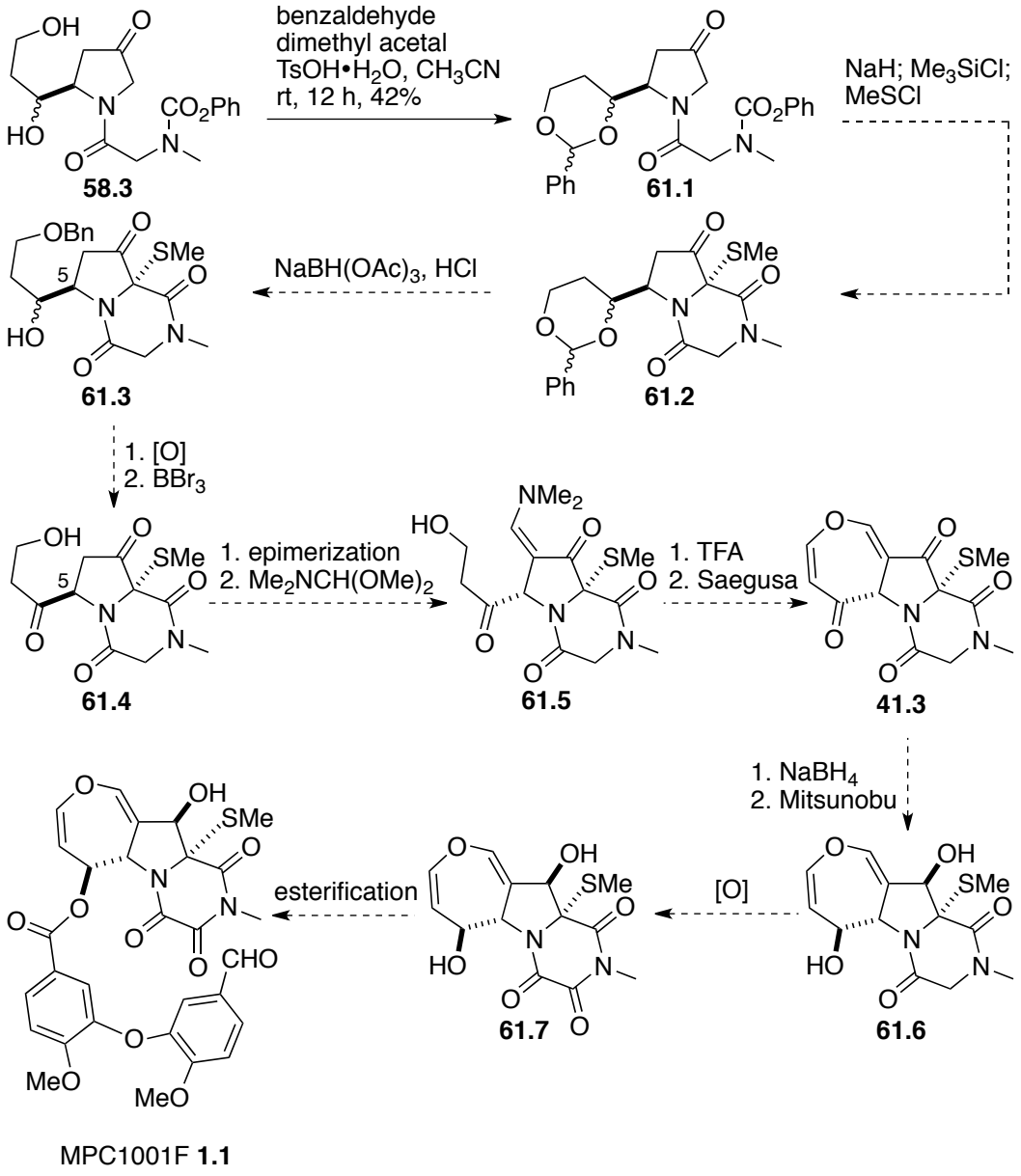
Scheme 60. Further synthetic modifications of the concise route

tried are summarized in Scheme 60. Use of PhMe as a solvent (entry 6) afforded the desired **58.5** tetrahydrooxepin in a very small scale experiment, and optimization is still in progress.

2.4.4. *Alternative modified route and future plans*

Because of the problems encountered in our current route during the construction of the A ring, we proposed an alternative pathway, which is shown in Scheme 61. Instead of protecting the diols in **58.3** as an acetonide, they were protected as a benzylidene acetal (**58.3 → 61.1**) in 42% yield. Dieckmann-type cyclization, followed by sulfenylation should give **61.2**. Selective unmasking of the secondary hydroxyl should give the benzyl ether **61.3**.[82] Oxidation of the secondary alcohol, followed by debenzylation should afford **61.4**. Epimerization at C5 and selective vinylogous amide formation under controlled conditions (the α-hydrogens in the pyrrolidinone ring are highly enolizable) should give **61.5**. CF_3CO_2H-mediated conjugate addition-elimination and Saegusa oxidation[65] would then finish the tricyclic core **41.3**. We are currently working on this route and on the third route mentioned in section 2.4.3. Once the core is synthesized, we are a few steps away from the final target, as shown in Scheme 61. Reduction of the two ketones and Mitsunobu inversions of the resulting hydroxyls (required only if the reduction gives the wrong stereochemistry of the hydroxyls) should afford **61.6**. Installation of the third carbonyl in the C ring (**61.6 → 61.7**) and attachment of the aromatic piece (the synthesis of which has already been done in

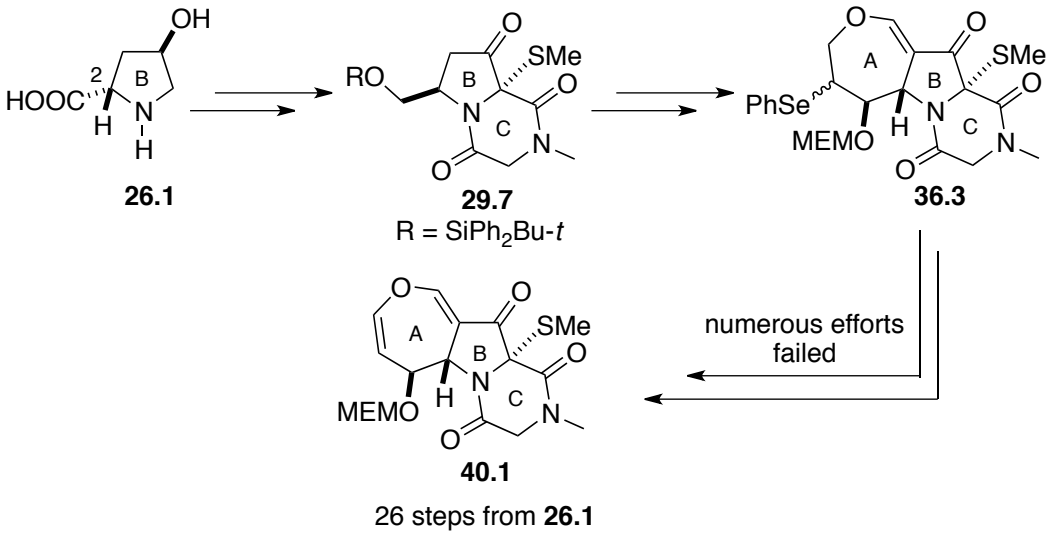
our group[44]) should finish the total synthesis of **1.1**.



Scheme 61. Future plans

3. Conclusion

The first part of this thesis explains how the enantioselective synthesis of the tricyclic core of MPC1001F was achieved along the lines summarized in Scheme 62. Starting material **26.1** was first converted to the bicyclic system **29.7**

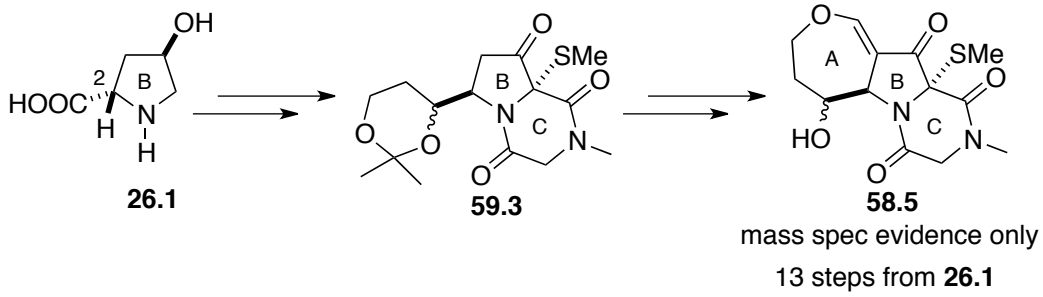


Scheme 62. Summary of attempts to synthesize the tricyclic core of MPC1001F

containing the SMe group. A one-step strategy was developed to perform the Dieckmann-type cyclization (to make the DKP ring) and sulfenylation. After a linear sequence of functional group interconversions and protection-deprotection steps, the key conjugate addition-elimination step was performed generating the tetrahydrooxepin **36.3**. Unfortunately, numerous attepts to make the dihydrooxepin **40.1** from **36.3** failed and evetually this route was abandoned.

Several other optimization studies that were carried out to overcome the challenges faced, were also mentioned in detail in this section.

In the next section of the thesis, numerous unsuccessful attempts towards the core, starting from already-synthesized intermediates from the first route, were examined. Finally, a new, short and efficient enantioselective strategy towards the same core was proposed and discussed in the final part of the thesis. This approach is now being inverstigted in order to advance our efforts to complete the synthesis of MPC1001F. As highlighted in Scheme 63, the same starting compound **26.1** was elaborated to the desired DKP unit **59.3** containing the SMe group by a short sequence. Then **59.3** was further advanced to the tetrahydrooxepin **58.5** in 13 steps from **26.1**. However only mass spectroscopic

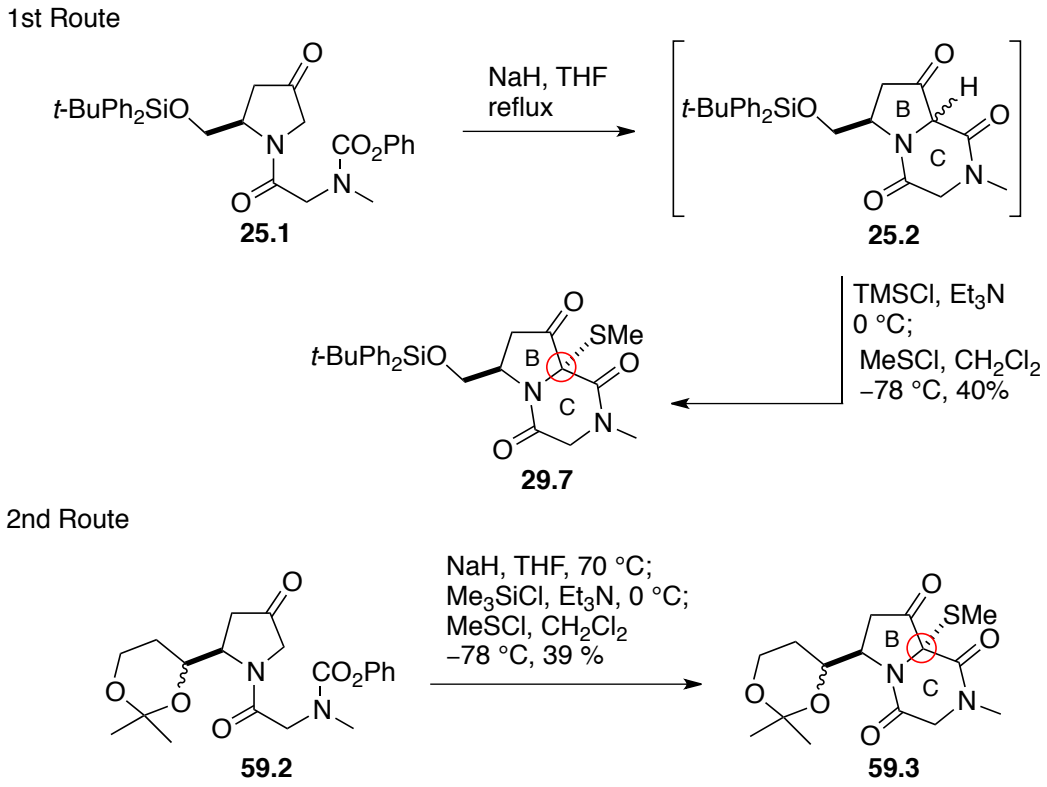


Scheme 63. Summary of the new concise route towards the ABC core

evidence for the ABC skeleton **58.5** was acquired and further optimization efforts are still in progress.

In conclusion, two major synthetic sequences were developed in this laboratory. Both routes involved the same two key steps to construct the tricyclic core of MPC1001F.

Scheme 64 highlights the NaH-mediated Dieckmann type cyclization, followed by sulfenylation, as a tool for making sulfur-containing DKP systems.

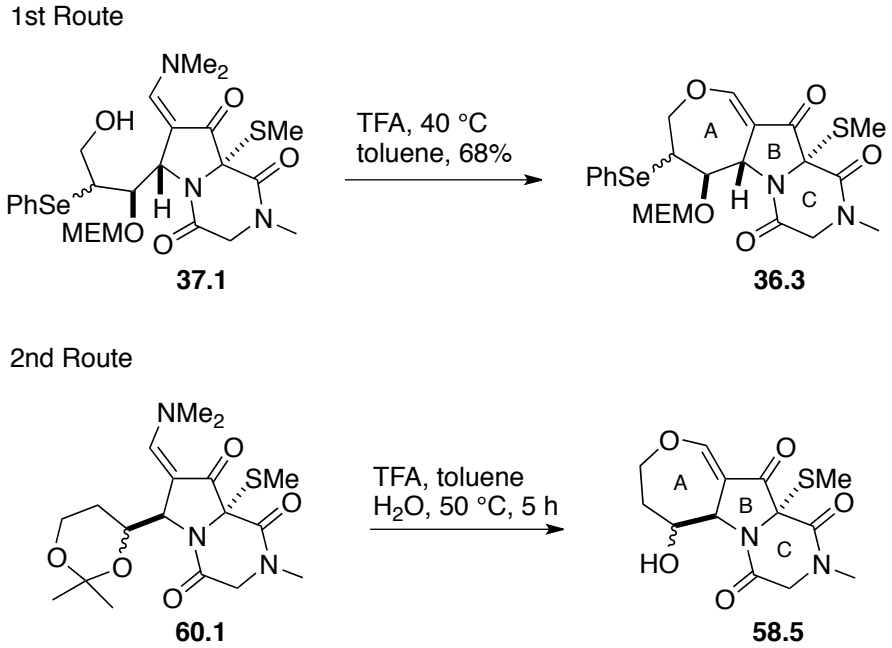


Scheme 64. NaH-mediated Dieckmann type cyclization and sulfenylation

The first enantioselective route showed the synthesis of **29.7** from **25.1** via the intermediate formation of **25.2**. In the second route the ketone **59.2** was converted to the DKP **59.3** via the same chemistry.

The conjugate addition-elimination chemistry that was employed to make the tricyclic unit of the natural product is summarized in Scheme 65. The two different vinylogous amides (**37.1** and **60.1**) were subjected to these conditions in

the presence of CF_3CO_2H to obtain the tetrahydrooxepins **36.3** and **58.5** respectively.



Scheme 65. The conjugate addition-elimination strategy

Finally, as described in Scheme 61, a modified strategy has been proposed to overcome the problems. We are hoping to complete the synthesis of tricyclic core **61.6** with proper stereocontrol, via this new route. The advanced stage intermediate **61.6** can possibly be elaborated to the natural product **1.1**.

4. Experimental Section

Unless otherwise mentioned, reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 × 42 cm) of BASF R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven (140 °C) overnight before use and cooled in a desiccator over Drierite. Large glassware was cooled under a static pressure of Ar or N_2.

Distilled solvents were used in the column chromatography. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). Dry solvents were prepared under Ar or N_2 and transferred by syringe or cannula. For drying the solvents the following methods were applied: THF, toluene and benzene were distilled from sodium and benzophenone. MeCN, CH_2Cl_2, Et_3N and pyridine were distilled from CaH_2. MeOH and EtOH were distilled from Mg.

The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, and the assignments were made by APT and HSQC spectra.

(2*R*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic acid hydrochloride (28.2).

26.1 **28.2**

trans-4-Hydroxy-L-proline **26.1** (50.938 g, 388.8 mmol) was added to a stirred and heated (50 °C) mixture of AcOH (373 mL) and Ac_2O (204 mL, 2.16 mol). The solution was refluxed (135 °C) for 7 h, cooled to room temperature and evaporated (rotary evaporator, water pump) to afford a thick yellow oil. This was dissolved in hydrochloric acid (2.0 M, 340 mL) and the solution was refluxed for 5 h. Charcoal was added carefully to the hot solution and the mixture was filtered through Celite. Evaporation of the filtrate gave **28.2** as a white solid, which was collected, washed with acetone and dried under oil pump vacuum. The material (54 g, 83%) was used for next stage.

The product **28.2** obtained from above procedure was contaminated with some starting material salt. Hence the following procedure was adopted to make diastereomerically pure **28.2**. A mixture of **26.1** (10 g, 76.33 mmol) and Ac_2O (75 mL, 793.4 mmol) was heated at 100 °C for 16 h. Evaporation of Ac_2O generated a thick yellow gel, which was then dissolved in hydrochloric acid (2.0 M, 150 mL), followed by heating at 100 °C for 8 h. The color of the reaction mixture became dark brown. Charcoal was added and the reaction mixture was filtered hot through a pad of Celite, and then the Celite bed was washed with

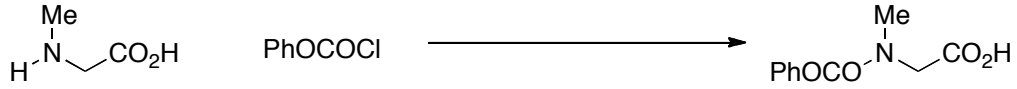
warm water (100 mL). Evaporation of the filtrate gave a greenish-yellow gel. EtOH (95%, 120 mL) was added to this gel (which caused solid formation upon dissolution of the gel) and the mixture was refluxed at 100 °C with vigorous stirring for 2 h, to produce a turbid solution. Most but not all of the solid had dissolved by this time. At this stage hexanes (50 mL) were added, which generated two layers, and this mixture was stirred and heated at 90 °C for 5 min, cooled to room temperature, put in an ice bath and left overnight. This caused crystal formation. Direct filtration was difficult because of partial solubility of the product **28.2** in EtOH, thus causing blockage in the filter funnel. Hence most of the mother liquor (light brown) was decanted and the rest was filtered which finally gave a gel-like solid. Washing with distilled acetone (200 mL), followed by air-drying, produced a white solid which was further dried under oil pump vacuum to afford **28.2** (7.57 g, 59%): mp 138-143 °C; $[\alpha]_D$ = 13.96 (*c* 0.67, MeOH); FTIR (MeOH, cast) 2100-3400 (br), 1715, 1587, 1376 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.13 (ddt, *J* = 13.6, 3.7, 1.9 Hz, 1 H), 2.29 (ddd, *J* = 13.7, 9.6, 4.3 Hz, 1 H), 3.13 (dt, *J* = 11.8, 1.5 Hz, 1 H), 3.19 (dd, *J* = 11.8, 4.1 Hz, 1 H), 3.73 (s, 3 H), 4.33-4.37 (m, 1 H), 4.47 (dd, *J* = 9.7, 3.8 Hz, 1 H), 5.47 (d, *J* = 2.2 Hz, 1 H), 9.79 (br, s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.0 (t), 52.9 (t), 53.0 (d), 68.1 (d), 169.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_5H_{10}NO_3$ 132.0655, found 132.0655. The mother liquor from the above reaction produced more solid after being kept for several days. The solid was a pale brown color and I considered it to be impure; this material was not included in the above reported yield.

Methyl (2*R*,4*R*)-4-Hydroxypyrrolidine-2-carboxylate hydrochloride (26.2).[24]

28.2 **26.2**

$SOCl_2$ (6.7 mL, 95.1 mmol) was added to a stirred and cooled (0 °C) slurry of **28.2** (13.486 g, 80.5 mmol) in dry MeOH (156 mL) contained in a three-necked flask carrying a drying tube. After 30 min the ice bath was removed and stirring was continued overnight. Evaporation of the solvent gave **26.2** as a colorless solid which was dried under oil pump vacuum at 45 °C. The material (11.75 g, 93%) was pure enough for the next stage: mp 165-168 °C; $[\alpha]_D$ = 10.16 (*c* 1.75, MeOH); FTIR (MeOH, cast) 3291, 3005, 2976, 2936, 2200-3500 (br), 1737, 1568, 1448, 1437 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.13 (ddt, *J* = 13.6, 3.7, 1.9 Hz, 1 H), 2.29 (ddd, *J* = 13.7, 9.6, 4.3 Hz, 1 H), 3.13 (dt, *J* = 11.8, 1.5 Hz, 1 H), 3.19 (dd, *J* = 11.8, 4.1 Hz, 1 H), 3.73 (s, 3 H), 4.33-4.37 (m, 1 H), 4.47 (dd, *J* = 9.7, 3.8 Hz, 1 H), 5.47 (d, *J* = 2.2 Hz, 1 H), 9.79 (br, s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.0 (t), 52.9 (t), 53.0 (d), 57.3 (d), 68.1 (d), 169.6 (s); exact mass *m*/*z* calcd for $C_6H_{11}NO_3$ (M - HCl) 145.0739, found 145.0737.

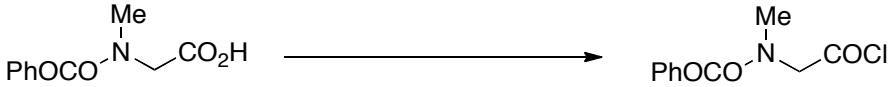
2-[Methyl(phenoxycarbonyl)amino]acetic acid (29.2).[24]



29.1 **29.2**

K_2CO_3 (75.2 g, 455.1 mmol) was added in portions to a stirred and cooled (0 °C) solution of *N*-methyl glycine (**29.1**) (40 g, 448.9 mmol) in water (453 mL), and then PhOCOCl (64 mL, 510.1 mmol) was added dropwise over ca 15 min. The ice bath was left in place but not recharged and stirring was continued overnight. The aqueous layer was washed twice with Et_2O and then acidified with concentrated hydrochloric acid. The acidic aqueous phase was extracted twice with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford **29.2** as a colorless oil (82.7 g, 88%): FTIR ($CHCl_3$, cast) 2500-3500 (br), 1723, 1477, 1456, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.07 (s, 1.5 H, carbamate rotamers), 3.17 (s, 1.5 H, carbamate rotamers), 4.14 (s, 1 H), 4.19 (s, 1 H), 7.07-7.10 (m, 1 H), 7.13-7.16 (m, 1 H), 7.17-7.22 (m, 1 H), 7.32-7.39 (m, 2 H), 11.29 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.9 (q), 36.2 (q), 50.7 (t), 121.6 (d), 121.7 (d), 125.55 (d), 125.58 (d), 129.3 (d), 151.1 (s), 151.2 (s), 154.8 (s), 155.6 (s), 174.5 (s), 174.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{11}NNaO_4$ 232.0580, found 232.0581.

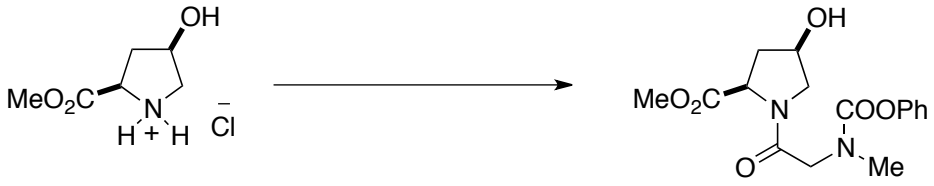
Phenyl *N*-(2-Chloro-2-oxoethyl)-*N*-methylcarbamate (26.3).[24]



29.2 **26.3**

$(COCl)_2$ (8.2 mL, 93.96 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **29.2** (18.304 g, 87.58 mmol) and DMF (0.47 mL, 6.5 mmol) in dry CH_2Cl_2 (300 mL). After 15 min the ice bath was removed and stirring was continued for an arbitrary overnight period. Evaporation of the solvent with protection from moisture gave the crude acid chloride **26.3** (dark yellow) which was used for the next step without further purification. The product was not characterized.

Methyl (2*R*,4*R*)-4-Hydroxy-1-{2-[methyl(phenoxycarbonyl)amino]-acetyl}pyrrolidine-2-carboxylate (26.4).



26.2 **26.4**

$NaHCO_3$ (84.4 g, 1004.76 mmol) was added to a stirred and cooled (0 °C) solution of amine hydrochloride **26.2** (41.5 g, 228.65 mmol) in dioxane (450 mL)

and water (400 mL). Then a solution of the above crude acid chloride **26.3** [(obtained from the corresponding acid (74.99 g, 358.80 mmol)] in dry THF (100 mL) was added dropwise over 30 min. The ice bath was left in place but not recharged and stirring was continued overnight. The dioxane-THF was evaporated under water pump vacuum and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 x 10 cm), using 1:40 MeOH-EtOAc and then 1:20 MeOH-EtOAc, gave **26.4** (67.1 g, 87%) as a white semisolid: $[\alpha]_D$ = 49.46 (*c* 0.45, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3443, 2952, 1726, 1657, 1594, 1455, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02-2.08 (m, 0.78 H), 2.21-2.29 (m, 1 H), 2.36-2.42 (m, 0.22 H), 3.03 (s, 1.2 H), 3.17 (s, 1.4 H), 3.20 (s, 0.4 H), 3.56-4.22 (m, 7 H), 4.32-4.42 (m, 1 H), 4.54-4.58 (m, 1 H), 7.06-7.11 (m, 2 H), 7.15-7.18 (m, 1 H), 7.29-7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q), 36.37 (q), 36.41 (q), 36.6 (t), 39.4 (t), 39.5 (t), 51.18 (t), 51.21 (t), 51.3 (t), 51.4 (t), 52.77 (q), 52.84 (q), 54.9 (t), 55.0 (t), 55.6 (t), 55.7 (t), 57.5 (d), 57.7 (d), 57.9 (d), 58.0 (d), 68.2 (d), 68.4 (d), 71.10 (d), 71.15 (d), 121.65 (d), 121.71 (d), 121.8 (d), 125.3 (d), 125.4 (d), 129.17 (d), 129.20 (d), 151.29 (s), 151.32 (s), 154.9 (s), 155.0 (s), 155.4 (s), 155.5 (s), 167.3 (s), 167.5 (s), 167.6 (s), 168.0 (s), 172.4 (s), 172.8 (s), 174.2 (s), 174.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{20}N_2NaO_6$ 359.1214, found 359.1213.

Methyl (2*R*)-1-{2-[Methyl(phenoxycarbonyl)amino]acetyl}-4-oxo-pyrrolidine-2-carboxylate (29.3).

26.4 **29.3**

PCC (19.468 g, 90.31 mmol) was added to a stirred and cooled (0 °C) mixture of **26.4** (10.115 g, 30.10 mmol), AcONa (2.469 g, 30.10 mmol) and 3Å molecular sieves (15.052 g, 0.5 g/mmol of **26.4**) in dry CH_2Cl_2 (350 mL). After 10 min the ice bath was removed and stirring was continued for 1.5 h. The reaction mixture was then filtered through Celite and the filter bed was washed thoroughly with CH_2Cl_2. Silica gel was added to the filtrate which was evaporated. The resulting solid was loaded onto a silica gel column (8 x 20 cm) made up with 2:1 EtOAc-hexanes, and 2:1 EtOAc-hexanes to pure EtOAc were used as eluent to afford **29.3** (8.978 g, 89%) as a white solid: mp 130-132 °C; $[\alpha]_D$ = 23.78 (*c* 1.00, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 1767, 1726, 1673, 1594, 1477, 1455, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.51 (ddd, 0.8 H, *J* = 18.9, 9.0, 2.8 Hz), 2.64 (m, 0.2 H), 2.81-2.96 (m, 1 H), 2.99 (s, 1.1 H), 3.13-3.14 (m, 1.9 H), 3.65-4.31 (m, 7 H), 4.79-4.83 (m, 0.1 H), 4.96-4.99 (m, 0.9 H), 7.03-7.10 (m, 2 H), 7.14 (q, *J* = 7.3 Hz, 1 H), 7.28-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (q), 36.0 (q), 36.2 (q), 39.4 (t), 41.1 (t), 41.2 (t), 50.3 (t), 50.5 (t),

51.3 (t), 51.5 (t), 51.6 (t), 51.7 (t), 52.6 (q), 53.0 (q), 55.3 (d), 55.4 (d), 55.9 (d), 56.1 (d), 121.5 (d), 121.6 (d), 125.25 (d), 125.30 (d), 129.1 (d), 151.1 (s), 151.2 (s), 154.6 (s), 155.2 (s), 167.4 (s), 167.59 (s), 167.64 (s), 170.4 (s), 170.7 (s), 171.3 (s), 171.4 (s), 206.2 (s), 206.4 (s), 206.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{18}N_2NaO_6$ 357.1057, found 357.1052.

Methyl (2*R*)-4,4-Dimethoxy-1-{2-[methyl(phenoxycarbonyl)amino]-acetyl}pyrrolidine-2-carboxylate (29.4).

29.3 **29.4**

TsOH•H_2O (591.3 mg, 3.11 mmol) was added to a stirred mixture of ketone **29.3** (34.16 g, 102.27 mmol) and $HCH(OMe)_3$ (13.43 mL, 122.72 mmol) in a mixture of dry MeOH (600 mL) and CH_2Cl_2 (100 mL). The mixture was refluxed for 16 h and then cooled to room temperature. Saturated aqueous $NaHCO_3$ was added, the MeOH was evaporated and the residual aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 x 10 cm), using 2:1 EtOAc-hexane, gave **29.4** (35.04 g, 90%) as a colorless oil: $[\alpha]_D$ = 78.96 (*c* 1.00, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2951, 2837,

1728, 1668, 1954, 1455, 1436, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19-2.24 (m, 0.7 H), 2.30-2.40 (m, 1 H), 2.55-2.60 (m, 0.3 H), 3.17-3.26 (m, 9 H), 3.60-3.78 (m, 5 H), 3.92-3.97 (m, 0.6), 4.14-4.31 (m, 1.4 H), 4.46-4.48 (m, 0.1 H), 4.60-4.66 (m, 0.9 H), 7.08-7.13 (m, 2 H), 7.15-7.19 (m, 1 H), 7.31-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.69 (q), 35.71 (t), 35.9 (t), 36.18 (q), 36.22 (q), 36.3 (q), 37.8 (t), 38.0 (t), 49.0 (q), 49.2 (q), 49.8 (q), 49.9 (q), 50.0 (q), 51.1 (t), 51.3 (t), 51.9 (t), 52.0 (t), 52.1 (t), 52.4 (q), 52.7 (q), 57.3 (d), 57.4 (d), 57.8 (d), 105.4 (s), 107.07 (s), 107.15 (s), 121.59 (d), 121.62 (d), 121.67 (d), 121.70 (d), 125.2 (d), 129.08 (d), 129.12 (d), 151.3 (s), 155.3 (s), 155.4 (s), 166.8 (s), 167.0 (s), 167.5 (s), 167.8 (s), 171.0 (s), 171.16 (s), 171.23 (s), 171.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{24}N_2NaO_7$ 403.1476, found 403.1470.

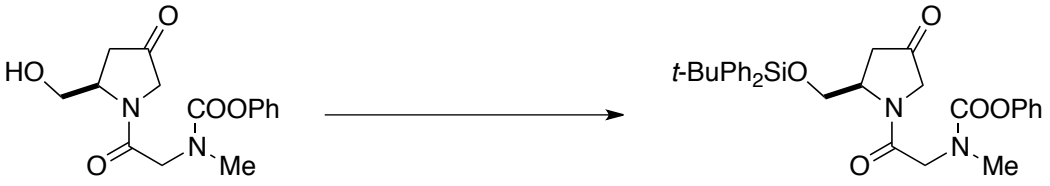
Phenyl *N*-{2-[(2*R*)-2-(Hydroxymethyl)-4-oxopyrrolidin-1-yl]-2-oxo-ethyl}-*N*-methylcarbamate (29.5).

29.4 **29.5**

Anhydrous $CaCl_2$ (11.245 g, 101.3 mmol) was added to a stirred and cooled (0 °C) solution of methyl ester **29.4** (35.0 g, 92.1 mmol) in a mixture of dry THF (110 mL) and dry EtOH (110 mL), and then $NaBH_4$ (7.669 g, 202.6

mmol) was added in one portion. Stirring at 0 °C was continued for 7 h and the mixture was acidified with hydrochloric acid (1 M, 225 mL) at 0 °C. The ice bath was left in place, but not recharged, and stirring was continued overnight. The solution was diluted with EtOAc and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 x 12 cm), using first EtOAc and then 1:20 MeOH-EtOAc, gave **29.5** (26.19 g, 93%, not dry) as a semi-solid: $[\alpha]_D = -22.02$ (*c* 1.00, CH_2Cl_2) (measured on dry material); FTIR (CH_2Cl_2, cast) 3432, 2925, 1763, 1722, 1656, 1594, 1456, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.33-2.51 (m, 1 H), 2.62-2.81 (m, 1 H), 3.04-3.24 (m, 3 H), 3.50-4.18 (m, 5.8 H), 4.30-4.37 (m, 0.28 H), 4.42-4.47 (m, 0.17 H), 4.67-4.77 (m, 0.73 H), 7.07-7.13 (m, 2 H), 7.17-7.22 (m, 1 H), 7.32-7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.6 (q), 36.8 (q), 39.3 (t), 39.4 (t), 40.8 (t), 50.6 (t), 51.8 (t), 52.2 (t), 52.8 (t), 53.1 (t), 55.9 (d), 56.1 (d), 56.4 (d), 64.2 (t), 64.6 (t), 65.1 (t), 121.7 (d), 121.8 (d), 125.5 (d), 125.6 (d), 129.31 (d), 129.32 (d), 151.26 (s), 151.29 (s), 155.0 (s), 155.8 (s), 167.48 (s), 167.51 (s), 167.8 (s), 208.5 (s), 208.6 (s), 208.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{18}N_2NaO_5$ 329.1108, found 329.1109.

Phenyl *N*-{2-[(2*R*)-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-oxo-pyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (25.1).



29.5 **25.1**

t-$BuPh_2SiCl$ (40.7 mL, 158.96 mmol) was added to a stirred solution of alcohol **29.5** (30.4 g, 99.35 mmol), imidazole (16.91 g, 248.37 mmol) and DMAP (794 mg, 6.5 mmol) in CH_2Cl_2 (500 mL). Stirring was continued for 36 h and the mixture was then diluted with CH_2Cl_2. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 x 10 cm), using 1:1 EtOAc-hexane, and recycling of the recovered **29.5**, gave **25.1** (41.95 g, 90%) as a semi-solid: $[\alpha]_D$ = –6.48 (*c* 1.00, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3048, 2956, 2931, 2859, 1766, 1726, 1667, 1593, 1473, 1449, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.48-2.56 (m, 1 H), 2.68 (dd, 0.7 H, *J* = 18.0, 9.7 Hz), 2.77-2.84 (m, 0.3 H), 2.99 (s, 0.2 H), 3.07 (s, 0.7 H), 3.16 (s, 0.6 H), 3.21 (s, 1.3 H), 3.57-3.62 (m, 1.2 H), 3.74-4.01 (m, 2.8 H), 4.14-4.38 (m, 2.1 H), 4.52-4.54 (m, 0.2 H), 4.76-4.80 (m, 0.7 H), 7.00-7.09 (m, 1 H), 7.13-7.22 (m, 2 H), 7.29-7.46 (m, 8 H), 7.50-7.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.07 (s), 19.12 (s), 26.69 (q), 26.72 (q), 26.8 (q), 36.2 (q), 36.4 (q), 36.5 (q), 36.6 (q), 39.5 (t), 41.0 (t), 41.1 (t), 50.1 (t), 50.2 (t), 51.6 (t), 51.7 (t),

52.8 (t), 53.1 (t), 53.3 (t), 55.2 (d), 55.3 (d), 55.8 (d), 56.1 (d), 65.7 (t), 65.8 (t), 66.6 (t), 66.9 (t), 121.67 (d), 121.72 (d), 121.78 (d), 121.82 (d), 125.38 (d), 125.41 (d), 125.43 (d), 127.8 (d), 127.87 (d), 127.89 (d), 128.03 (d), 128.05 (d), 129.2 (d), 129.3 (d), 129.9 (d), 130.96 (d), 130.03 (d), 130.06 (d), 130.13 (d), 130.2 (d), 130.3 (d), 132.0 (s), 132.1 (s), 132.16 (s), 132.17 (s), 132.4 (s), 132.5 (s), 132.59 (s), 132.64 (s), 135.3 (d), 135.4 (d), 135.56 (d), 135.61 (d), 135.62 (d), 151.27 (s), 151.31 (s), 151.33 (s), 151.4 (s), 154.8 (s), 154.9 (s), 155.39 (s), 155.44 (s), 166.4 (s), 166.7 (s), 167.3 (s), 208.2 (s), 208.4 (s), 208.56 (s), 208.62 (s); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{37}N_2O_5Si$ (M + H), 545.2466, found 545.2466. **Note**: The starting material **29.5** was recovered even after 36 h, and hence it was re-subjected to the same reaction conditions after isolation.

(6*R*,8a*R*)-6-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (29.7).

25.1 **29.7**

This experiment was repeated three times and the products were combined before final purification.

First run

NaH (60%w/w in mineral oil, 3.93 g, 98.27 mmol) was added to a stirred solution of ketone **25.1** (24.32 g, 44.67 mmol) in dry THF (400 mL). The reaction flask was then lowered into a pre-heated oil bath set at 70 °C and the reaction mixture was refluxed for 20 min. After 15 min, TLC monitoring (silica gel, EtOAc) showed no **25.1** left, and only a very polar spot corresponding to the cyclized product was detected (R_f = 0.1). After a total reaction time of 20 min, the mixture was cooled to room temperature and then to 0 °C. Longer heating results in decomposition. During the reaction almost all of the NaH suspension dissolved and the color of the mixture became yellow.

In a separate flask, Et_3N (9.96 mL, 71.47 mmol) was added to stirred and cooled (0 °C) Me_3SiCl (15.8 mL, 125.08 mmol) and stirring was continued for 10 min. The resulting milky solution was then added via cannula to the above reaction mixture. A brown color developed and a suspension formed. The mixture was stirred for an arbitrary period of 3.5 h at 0 °C.

In another flask, MeSCl was generated by slow addition of SO_2Cl_2 (3.2 mL, 40.2 mmol) from a syringe to a stirred and cooled (−78 °C) solution of Me_2S_2 (3.7 mL, 40.6 mmol) in dry CH_2Cl_2 (275 mL), followed by stirring for 15 min at −78 °C. The reaction mixture containing the intermediate silyl enol ether was then cooled to −78 °C and the yellow solution of MeSCl was transferred into it via a cannula, and stirring at −78 °C was continued for 30 min. The cooling bath was removed and stirring was continued for 4 h, by which time TLC (silica, 1:1 EtOAc-hexane) showed none of the cyclized intermediate remained and that the

reaction was complete. The mixture was quenched with water and extracted three times with CH_2Cl_2. A suspension remained throughout the reaction but disappeared on quenching the mixture with water. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 16 cm), using 2:1 to 1:1 EtOAc-hexanes, was done three times to afford **29.7** containing some colored impurities. After evaporating the eluate, cold (−78 °C) EtOAc was added to the impure solid product to cause precipitation of **29.7** (white), which was filtered off. The mother liquor was concentrated and the precipitation-filtration sequence was repeated several times until TLC (silica, 1:1 EtOAc-hexane) showed no **29.7** in the mother liquor.

Second run

NaH (60% in mineral oil, 5.616 g, 140.4 mmol) was added to a stirred solution of starting ketone **25.1** (34.74 g, 63.82 mmol) in dry THF (800 mL). The reaction flask was then lowered into a pre-heated oil bath set at 70 °C and the mixture was refluxed for 20 min. After 15 min, TLC monitoring (silica gel, EtOAc) showed no **25.1** left, and only a very polar spot corresponding to the cyclized product was detected (R_f = 0.1). The reaction mixture was cooled to room temperature and then to 0 °C. Longer heating results in decomposition. During the reaction almost all of the NaH suspension dissolved and the color of the mixture became yellow.

In a separate flask, Et_3N (14.2 mL, 102.11 mmol) was added to stirred and cooled (0 °C) Me_3SiCl (22.6 mL, 178.69 mmol) and stirring was continued for 10 min. The resulting milky solution was then added via cannula to the above reaction mixture. A brown color developed and a suspension formed. The mixture was stirred for and an arbitrary period of 3.5 h at 0 °C.

In another flask, MeSCl was generated by slow addition of SO_2Cl_2 (4.57 mL, 56.87 mmol) from a syringe to a stirred and cooled (−78 °C) solution of Me_2S_2 (5.17 mL, 57.44 mmol) in dry CH_2Cl_2 (500 mL), followed by stirring for 15 min at −78 °C. The rest of the procedure was the same as described above.

Third run

NaH (60%w/w in mineral oil, 2.85 g, 71.26 mmol) was added to a stirred solution of ketone **25.1** (17.63 g, 32.39 mmol) in dry THF (400 mL). The reaction flask was then lowered into a pre-heated oil bath set at 70 °C and the reaction mixture was refluxed for 20 min. After 15 min, TLC monitoring (silica gel, EtOAc) showed no **25.1** left, and only a very polar spot corresponding to the cyclized product was detected (R_f = 0.1). Immediately after developing the TLC plate (i.e. after a reaction time of 20 min), the reaction flask was raised from the heating bath and the reaction mixture was cooled to room temperature and then to 0 °C. Longer heating results in decomposition. During the reaction almost all of the NaH suspension dissolved and the reaction mixture became yellow.

In a separate flask, Et_3N (7.2 mL, 51.82 mmol) was added to stirred and cooled (0 °C) Me_3SiCl (11.5 mL, 90.69 mmol) and the mixture was stirred at 0 °C

for 10 min. The resulting milky solution was then added via cannula to the above reaction mixture. A brown color developed and a suspension formed. The mixture was stirred for an arbitrary period of 3.5 h at 0 °C.

In another flask, MeSCl was generated by slow dropwise addition of SO_2Cl_2 (2.34 mL, 29.15 mmol) from a syringe to a stirred and cooled (–78 °C) solution of Me_2S_2 (2.65 mL, 29.44 mmol) in dry CH_2Cl_2 (200 mL), followed by stirring for 15 min at –78 °C. The rest of the procedure was the same as described above.

The overall yield from the above three reactions was 28.03 g (40%): mp 152-155 °C; $[\alpha]_D$ = –4.96 (*c* 1.00, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 2931, 2858, 1764, 1727, 1472, 1427, 1410 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-1.03 (s, 9 H), 2.27 (s, 3 H), 2.61 (dd, *J* = 18.0, 2.8 Hz, 1 H), 3.02 (s, 3 H), 3.37 (dd, *J* = 18.0, 9.9 Hz, 1 H), 3.56 (dd, *J* = 10.6, 1.8 Hz, 1 H), 3.76 (d, *J* = 17.0 Hz, 1 H), 4.27 (dd, *J* = 10.6, 2.9 Hz, 1 H), 4.32-4.44 (m, 2 H), 7.33-7.48 (m, 6 H), 7.49-7.63 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 19.0 (s), 26.6 (q), 33.7 (q), 36.0 (t), 52.6 (d), 53.1 (t), 62.5 (t), 127.7 (d), 127.8 (d), 129.8 (d), 129.9 (d), 132.6 (s), 135.5 (d), 135.6 (d), 160.3 (s), 165.4 (s), 193.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{32}N_2NaO_4SiS$ 519.1744, found 519.1737.

(6*R*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-hydroxy-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (31.1).

29.7 **31.1**

$NaBH_4$ (1.663 g, 43.95 mmol) was added in portions to a stirred and cooled (0 °C) solution of **29.7** (18.18 g, 36.62 mmol) in dry MeOH (200 mL) and THF (200 mL), and stirring at 0 °C was continued for 1 h. The mixture was then quenched with saturated aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:2 to 1:1 EtOAc-hexanes, gave **31.1** (17.77 g, 97%) as a white solid: mp 163-165 °C; $[\alpha]_D$ = –13.3 (*c* 0.20, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3429, 2929, 2856, 1733, 1663, 1559, 1540, 1472, 1427 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 0.98-1.07 (s, 9 H), 2.23 (s, 3 H), 2.28 (ddd, *J* = 12.5, 7.0, 1.2 Hz, 1 H), 2.39-2.50 (m, 1 H), 2.85 (br s, 1 H), 3.03 (s, 3 H), 3.64 (dd, *J* = 10.4, 2.2 Hz, 1 H), 3.70 (d, *J* = 17.2 Hz, 1 H), 4.09 (apparent dt, *J* = 9.9, 1.8 Hz, 1 H), 4.14 (dd, *J* = 10.4, 3.9 Hz, 1 H), 4.34 (d, *J* = 17.2 Hz, 1 H), 4.98 (dd, *J* = 11.1, 7.1 Hz, 1 H), 7.33-7.48 (m, 6 H), 7.53-7.64 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 19.2 (s),

26.8 (q), 31.7 (t), 33.2 (q), 53.6 (t), 55.5 (d), 62.5 (t), 71.7 (s), 74.7 (d), 127.73 (d), 127.77 (d), 129.8 (d), 132.8 (s), 133.1 (s), 135.48 (d), 135.57 (d), 164.8 (s), 165.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{34}N_2NaO_4SiS$ 521.1901, found 521.1899.

(6*R*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (31.2).

31.1 **31.2**

TsOH•H_2O (163 mg, 0.719 mmol) was added to a stirred solution of **31.1** (17.77 g, 35.65 mmol) and 3,4-dihydropyran (9.76 mL, 106.97 mmol) in dry CH_2Cl_2 (300 mL). The pale yellowish color of the mixture changed to reddish. Stirring at room temperature was continued for 45 min, during which time the color changed to dark greenish. Et_3N (0.35 mL) was then added dropwise and the color changed to yellow. Stirring was continued for 10 min and the solvent was evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:2 EtOAc-hexanes, gave **31.2** (21.05 g, 102%, incomplete removal of solvent) as a white semisolid: $[\alpha]_D = -20.92$ (*c* 2.27, $CHCl_3$); FTIR ($CHCl_3$, cast)

3071, 3014, 2932, 2858, 1733, 1678, 1589, 1487, 1471, 1427, 1414 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.51-1.92 (m, 6 H), 2.23 (s, 2 H), 2.30 (s, 1 H), 2.34 (dd, *J* = 12.7, 7.5 Hz, 1 H), 2.49-2.61 (m, 1 H), 2.99-3.07 (m, 3 H), 3.44-3.57 (m, 2 H), 3.70 (d, *J* = 16.8 Hz, 1 H), 3.89-3.98 (m, 0.7 H), 4.01-4.18 (m, 2 H), 4.33 (apparent td, *J* = 11.2, 3.1 Hz, 0.3 H), 4.40-4.51 (m, 1 H), 4.97 (s, 0.3 H), 5.02-5.20 (m, 1.7 H), 7.32-7.47 (m, 6 H), 7.53-7.60 (m, 2 H), 7.60-7.68 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (q), 14.9 (q), 18.2 (t), 19.1 (s), 19.2 (s), 20.1 (t), 25.3 (t), 25.5 (t), 26.6 (q), 26.7 (q), 29.7 (t), 30.1 (t), 30.5 (t), 32.5 (t), 33.6 (q), 33.7 (q), 53.60 (t), 53.63 (t), 55.2 (d), 55.8 (d), 60.8 (t), 62.7 (t), 62.8 (t), 63.4 (t), 70.7 (s), 70.8 (s), 75.2 (d), 79.9 (d), 94.5 (d), 100.5 (d), 127.6 (d), 127.7 (d), 129.7 (d), 129.8 (d), 132.8 (s), 133.0 (s), 135.58 (d), 135.63 (d), 164.5 (s), 165.0 (s), 165.3 (s), 165.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{42}N_2NaO_5SiS$ 605.2476, found 605.2471.

(6*R*,8*S*,8a*R*)-6-(Hydroxymethyl)-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (33.1).

31.2 **33.1**

Bu_4NF (1 M in THF, 61.84 mL, 61.84 mmol) was added to a stirred and cooled (0 °C) solution of **31.2** (32.74 g, 56.22 mmol) in dry THF (500 mL). The ice bath was left in place but not recharged and stirring was continued for 14 h. The solvent was evaporated and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:1 EtOAc-hexanes to pure EtOAc and then 1:10 MeOH-EtOAc, gave **33.1** (16.21 g, 84%) as a white solid: mp 170-173 °C; $[\alpha]_D$ = –51.71 (*c* 1.69, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3445, 2941, 2876, 1675, 1413 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.49-1.84 (m, 6 H), 2.08-2.16 (m, 0.8 H), 2.18-2.23 (m, 2.5 H), 2.26-2.29 (s, 0.5 H), 2.33 (apparent dt, *J* = 12.5, 10.2 Hz, 0.2 H), 2.57 (apparent dt, *J* = 13.0, 10.4 Hz, 0.8 H), 3.00-3.07 (m, 3 H), 3.51-3.60 (m, 1 H), 3.61-3.67 (m, 1 H), 3.72-3.76 (m, 0.7 H), 3.76-3.82 (m, 1.3 H), 3.87 (ddd, *J* = 11.3, 8.1, 3.2 Hz, 1 H), 4.12-4.18 (m, 0.8 H), 4.18-4.24 (m, 0.2 H), 4.30 (apparent td, *J* = 11.2, 3.0 Hz, 0.2 H), 4.41-4.50 (m, 1 H), 4.65 (dd, *J* = 10.5, 7.4 Hz, 0.75 H), 4.80 (dd, *J* = 10.4, 6.9 Hz, 0.17 H), 4.86-4.90 (m, 0.17 H), 5.08-5.14 (m, 0.8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (q), 14.9 (q), 18.1 (t), 19.4 (t), 25.3 (t), 25.4 (t), 30.1 (t), 30.2 (t), 32.2 (t), 33.6 (q), 33.8 (q), 53.4 (t), 56.9 (d), 57.4 (d), 61.1 (t), 62.6 (t), 64.65 (t), 64.69 (t), 70.9 (s), 75.1 (d), 79.5 (d), 94.7 (d), 99.9 (d), 163.9 (s), 164.8 (s), 167.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{24}N_2NaO_5S$ 367.1298, found 367.1294. An X-ray structure was obtained for this compound. Crystals for X-ray analysis were obtained by dissolving a sample in EtOAc in a shortened NMR

tube which was then placed in a vial containing hexanes. The vial was closed with a stopper so that the hexanes gradually diffused into the EtOAc solution.

(8*S*,8a*R*)-2-Methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)-1,4-dioxo-octahydropyrrolo[1,2-*a*]piperazine-6-carbaldehyde (33.2).

33.1 **33.2**

DMSO (dry, 12.4 mL, 174.42 mmol) and Et_3N (dry, 12.2 mL, 87.21 mmol) were added to a stirred and cooled (0 °C) solution of **33.1** (3.0 g, 8.72 mmol) in dry CH_2Cl_2 (90 mL). Then SO_3•Py (4.164 g, 26.16 mmol) was tipped into the reaction mixture. **Note**: It is essential to add Et_3N before SO_3•Py. The color of the reaction mixture turned pale yellow. After 30 min the ice bath was removed and stirring was continued overnight during which time the color changed to dark yellow. The mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed twice with water to remove DMSO and Et_3N, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 2:1 EtOAc-hexanes to pure EtOAc, afforded **33.2** (2.491 g, 84%) as a yellowish semisolid. The ^{1}H-NMR spectrum showed both isomers of the aldehyde, the major one being the *S* isomer:

FTIR (CH_2Cl_2, cast) 2940, 2873, 1736, 1678, 1416 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48-1.88 (m, 6 H), 2.02-2.16 (m, 0.34 H), 2.19-2.28 (m, 3 H), 2.28-2.47 (m, 0.63 H), 2.50-2.68 (m, 1 H), 2.99-3.11 (m, 3 H), 3.48-3.62 (m, 1 H), 3.76-3.90 (m, 2 H), 4.21-4.32 (m, 1 H), 4.41-4.68 (m, 2 H), 4.75 (dd, *J* = 9.7, 6.7 Hz, 0.2 H), 4.83-4.91 (m, 0.2 H), 5.06 (apparent t, *J* = 3.7 Hz, 0.2 H), 5.14 (apparent t, *J* = 3.4 Hz, 0.4 H), 9.46-9.57 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 18.0 (t), 19.1 (t), 19.5 (t), 25.22 (t), 25.26 (t), 25.31 (t), 26.9 (t), 29.1 (t), 29.2 (t), 30.0 (t), 30.2 (t), 33.9 (q), 52.8 (t), 52.9 (t), 60.1 (d), 60.3 (d), 60.8 (d), 61.2 (t), 62.5 (t), 62.9 (t), 70.2 (s), 76.1 (d), 78.9 (d), 80.2 (d), 94.8 (d), 94.9 (d), 99.8 (d), 100.2 (d), 164.4 (s), 164.5 (s), 164.6 (s), 164.9 (s), 195.4 (d), 196.7 (d), 196.8 (d); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{22}N_2NaO_5S$ 365.1142, found 365.1145.

(8*S*,8a*R*)-6-(Hydroxymethyl)-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (33.1 and 33.3).

33.2 **33.1 and 33.3**

$NaBH(OAc)_3$ (4.027 g, 19 mmol) was added to a stirred solution of **33.2** (1.624 g, 4.75 mmol) in dry PhH (77 mL) contained in a round-bottomed flask

equipped with a condenser, and the flask was lowered into a pre-heated oil bath set at 55 °C. The initial white slurry turned into a milky white solution after 2 min. Heating was continued for 1.5 h and the mixture was then quenched with just sufficient MeOH to produce a clear, pale yellowish solution. TLC (silica gel, pure EtOAc, eluted two times) showed two very close spots (almost a figure eight shape) corresponding to two isomers of the reduced alcohol. Water was added to the reaction mixture which was extracted three times with EtOAc. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 9:1 EtOAc-hexanes to pure EtOAc (the less polar *S* alcohol **33.3**, which is the major component, elutes with these eluents) to 1:10 MeOH-EtOAc (more polar *R* alcohol **33.1** elutes with this eluent), gave the product (as two isomers, 1.42 g, 87% in total). A portion of the *S* alcohol **33.3** was isolated (from one of the chromatography fractions) as a white semisolid whereas isomer **33.1** was a white solid which was subjected to the Parikh-Doering oxidation as described earlier. Data for *S* alcohol **33.3**: $[\alpha]_D = -33.58$ (*c* 2.49, $CHCl_3$); FTIR ($CHCl_3$, cast) 3420, 2942, 2875, 1668, 1497, 1433, 1403 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.45-1.84 (m, 6 H), 1.97-2.04 (m, 1 H), 2.18 (s, 2 H), 2.25 (s, 1 H), 2.41 (apparent dt, *J* = 12.8, 7.4 Hz, 0.8 H), 2.45-2.53 (m, 0.2 H), 2.95-3.04 (m, 3 H), 3.48-3.55 (m, 1 H), 3.63-3.71 (m, 2 H), 3.72-3.78 (m, 1 H), 3.82 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1 H), 3.95 (dtd, *J* = 10.0, 7.5, 2.2 Hz, 1 H), 4.24 (apparent td, *J* = 11.1, 3.2 Hz, 0.2 H), 4.38-4.49 (m, 1.8 H), 4.60 (dd, *J* = 10.4, 6.8 Hz, 0.2 H), 4.76-4.88 (m, 1 H), 5.07 (apparent t, *J* = 3.5 Hz, 0.8 H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 14.7 (q), 14.9 (q), 18.1 (t), 19.3 (t), 25.3 (t), 25.4 (t), 28.8 (t), 30.1 (t), 30.2 (t), 31.4 (t), 33.6 (q), 33.8 (q), 52.9 (t), 59.5 (d), 60.0 (d), 61.2 (t), 62.6 (t), 67.4 (t), 67.5 (t), 70.4 (s), 70.5 (s), 75.1 (d), 79.6 (d), 94.7 (d), 99.9 (d), 163.9 (s), 164.5 (s), 166.8 (s), 166.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{24}N_2NaO_5S$ 367.1298, found 367.1297.

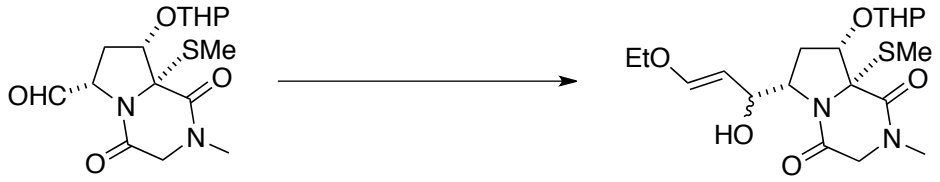
(6*S*,8*S*,8a*R*)-2-Methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)-1,4-dioxo-octahydropyrrolo[1,2-*a*]piperazine-6-carbaldehyde (33.4).

33.3 **33.4**

DCC (10.706 g, 51.89 mmol) was tipped rapidly (via a powder funnel) into a stirred solution of **33.3** (5.95 g, 17.29 mmol), pyridine (1.4 mL, 17.29 mmol) and CF_3CO_2H (0.66 mL, 8.65 mmol) in a mixture of dry DMSO (45 mL) and dry PhH (45 mL). **Note**: Pyridine has to be added before CF_3CO_2H, the substrate, PhH, DMSO, pyridine, CF_3CO_2H and then DCC were added to the reaction flask in that order. Within a few minutes dicyclohexylurea precipitated. Stirring at room temperature was continued overnight by which time the mixture had turned pale yellow. The mixture was filtered to remove dicyclohexylurea and the filtrate was washed twice with water. The combined aqueous extracts were

extracted twice with CH_2Cl_2. The filtrate and the combined organic extracts were dried (Na_2SO_4) and evaporated. More dicyclohexylurea precipitated and was filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:1 EtOAc-hexanes (dicyclohexylurea is eluted with this eluent) to pure EtOAc, gave **33.4** (5.252 g, 89%) as a white semisolid: $[\alpha]_D = -45.39$ (*c* 1.59, $CHCl_3$); FTIR ($CHCl_3$, cast) 2941, 2875, 1736, 1662, 1439, 1403 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.47-1.82 (m, 6 H), 1.99-2.11 (m, 0.5 H), 2.18-2.26 (m, 3 H), 2.27-2.33 (m, 0.5 H), 2.47-2.63 (m, 1 H), 2.97-3.08 (m, 3 H), 3.47-3.59 (m, 1 H), 3.72-3.87 (m, 2 H), 4.17-4.29 (m, 1 H), 4.41-4.52 (m, 1 H), 4.55 (dd, *J* = 10.2, 7.2 Hz, 0.8 H), 4.71 (dd, *J* = 9.8, 6.7 Hz, 0.2 H), 4.85 (apparent t, *J* = 2.6 Hz, 0.2 H), 5.11 (apparent t, *J* = 3.5 Hz, 0.7 H), 9.44-9.53 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (q), 14.6 (q), 18.0 (t), 19.1 (t), 25.2 (t), 25.3 (t), 26.9 (t), 29.2 (t), 30.0 (t), 33.9 (q), 34.0 (q), 52.7 (t), 60.3 (d), 60.8 (d), 61.2 (t), 62.5 (t), 70.1 (s), 70.2 (s), 76.0 (d), 80.1 (d), 94.9 (d), 99.8 (d), 163.9 (s), 164.5 (s), 164.55 (s), 164.8 (s), 196.7 (d), 196.8 (d); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{22}N_2NaO_5S$ 365.1142, found 365.1140. The ^1H-NMR spectrum showed that only the desired isomer of the aldehyde was present. **Note**: Before chromatography it is necessary to filter the residue through a cottonwool plug to remove as much dicyclohexylurea as possible.

(6*S*,8*S*,8a*R*)-6-[(2*E*)-3-Ethoxy-1-hydroxyprop-2-en-1-yl]-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (34.2).



33.4 **34.2**

Neat BH_3•SMe_2 (1.2 mL, 12.39 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ethoxyacetylene (dark yellow, 50%w/w in hexanes, 4.736 g, 33.78 mmol) in dry PhMe (100 mL). After 5 min the ice bath was removed and stirring at room temperature was continued for 6 h. Then the yellow reaction mixture was cooled to 0 °C and Me_2Zn (2 M in PhMe, 25.34 mL, 50.68 mmol) was added. During the addition the mixture became black. Stirring at 0 °C was continued for 30 min. A solution of **33.4** (5.252 g, 15.36 mmol) and *l*-ephedrine (143 mg, 0.865 mmol) in dry PhMe (60 mL) was then added. The ice bath was removed after 30 min and stirring at was continued for 2 days. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using pure EtOAc to 1:10 MeOH-EtOAc, gave **34.2** (four inseparable isomers, 5.116 g, 80%) as yellowish semisolid: FTIR ($CHCl_3$, cast) 3422, 2929, 1670, 1419 cm^{-1}; ^1H

NMR (498 MHz, $CDCl_3$) δ 1.20-1.35 (m, 3 H), 1.47-1.87 (m, 6 H), 2.15-2.37 (m, 4 H), 2.95-3.10 (m, 3 H), 3.47-3.61 (m, 1 H), 3.68-3.92 (m, 3.3 H), 3.92-4.05 (m, 0.7 H), 4.05-4.22 (m, 1 H), 4.28 (apparent td, J = 11.2, 2.8 Hz, 0.3 H), 4.36-4.60 (m, 1.6 H), 4.60-4.78 (m, 1 H), 4.83-4.93 (m, 0.3 H), 4.97-5.14 (m, 0.6 H), 5.51-5.60 (m, 0.3 H), 6.46-6.59 (m, 0.7 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (q), 14.6 (q), 14.9 (q), 15.1 (q), 18.1 (t), 19.4 (t), 19.5 (t), 25.2 (t), 25.4 (t), 30.0 (t), 30.1 (t), 30.2 (t), 32.7 (t), 33.6 (q), 52.8 (t), 53.1 (t), 61.1 (t), 61.2 (t), 62.3 (d), 62.7 (t), 62.8 (t), 62.9 (d), 63.8 (d), 64.5 (t), 64.9 (t), 69.6 (d), 70.5 (d), 71.03 (s), 71.07 (s), 74.8 (d), 75.4 (d), 75.9 (d), 76.1 (d), 79.3 (d), 79.8 (d), 94.6 (d), 94.7 (d), 100.1 (d), 100.2 (d), 100.3 (d), 101.8 (d), 102.4 (d), 150.09 (d), 150.16 (d), 163.8 (s), 164.3 (s), 164.48 (s), 166.5 (s), 166.6 (s), 166.9 (s), 167.0 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{30}N_2NaO_6S$ 437.1717, found 437.1717.

(6*S*,8*S*,8a*R*)-2-Methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)-6-[(9*E*)-2,5,7,11-tetraoxatridec-9-en-8-yl]octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (34.3 and 34.4).

34.2 **34.3 and 34.4**

MEMCl (1.4 mL, 12.2 mmol) was added to flask containing dry THF (4 mL) and oven-dried K_2CO_3 (1 g) and the mixture was stirred for 30 min and then let settle.

Bu_4NI (901 mg, 2.44 mmol) and *i*-Pr_2NEt (3.8 mL, 21.96 mmol) were added to a stirred suspension of oven-dried K_2CO_3 (1 g) and **34.2** (1.012 g, 2.44 mmol) in dry THF (30 mL). The supernatant liquid from the above MEMCl solution was taken up into a syringe and added dropwise to the flask containing **34.2**. The resulting stirred suspension was heated at 60 °C for 12 h by which time the color of the reaction mixture turned dark yellow. TLC (silica gel, EtOAc) showed two isomeric MEM ethers. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 9:1 EtOAc-hexanes to pure EtOAc (the less polar MEM ether **34.3** elutes with this solvent) to 1:10 MeOH-EtOAc (the more polar MEM ether **34.4** elutes with this solvent) gave the product (two MEM isomers, 1.007 g in total, 82%). Compound **34.3** is a yellow oil whereas compound **34.4** is a pale-yellowish solid. An X-ray structure was obtained for **34.4**. Less polar MEM isomer **34.3**: FTIR ($CHCl_3$, cast) 3336, 2937, 1666, 1415 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.16-1.25 (m, 3 H), 1.42-1.83 (m, 7 H), 2.05-2.21 (m, 4 H), 2.21-2.54 (m, 2 H), 2.91-3.03 (m, 3 H), 3.26-3.35 (m, 3 H), 3.39-3.52 (m, 2 H), 3.52-3.64 (m, 3 H), 3.64-3.72 (m, 2 H), 3.72-3.89 (m, 2 H), 4.28-4.51 (m, 2 H), 4.53-4.62 (m, 1 H), 4.74 (d, *J* = 7.0 Hz, 1 H), 4.82-4.88 (m, 0.8 H), 4.91 (dd, *J* = 9.5, 3.3 Hz, 0.2 H), 5.06 (apparent t, *J* = 3.4

Hz, 1 H), 6.43-6.51 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6 (q), 14.8 (q), 15.0 (q), 18.1 (t), 19.3 (t), 25.3 (t), 25.4 (t), 25.9 (t), 28.8 (t), 30.1 (t), 30.2 (t), 33.8 (q), 33.9 (q), 53.3 (t), 58.9 (q), 59.5 (d), 60.1 (d), 61.0 (t), 62.5 (t), 65.1 (t), 65.2 (t), 66.7 (t), 66.8 (t), 70.4 (d), 70.6 (d), 71.5 (s), 71.6 (s), 75.7 (d), 80.1 (d), 91.7 (t), 91.8 (t), 94.6 (d), 99.4 (d), 99.5 (d), 99.8 (d), 151.46 (d), 151.49 (d), 164.4 (s), 164.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{38}N_2NaO_8S$ 525.2241, found 525.2235.

More polar MEM isomer **34.4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.0 Hz, 3 H), 1.48-1.87 (m, 6 H), 2.07-2.20 (m, 3 H), 2.21-2.42 (m, 2 H), 2.94-3.05 (m, 3 H), 3.31-3.40 (m, 3 H), 3.47-3.66 (m, 5 H), 3.66-3.90 (m, 4 H), 3.98-4.09 (m, 1 H), 4.38 (d, *J* = 16.1 Hz, 1 H), 4.45 (dd, *J* = 10.6, 7.1 Hz, 1 H), 4.57-4.65 (m, 1 H), 4.71-4.84 (m, 2 H), 4.87-4.97 (m, 1 H), 5.12 (apparent t, *J* = 3.3 Hz, 1 H), 6.39 (d, *J* = 12.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.68 (q), 14.71 (q), 19.2 (t), 25.4 (t), 29.6 (t), 30.2 (t), 33.8 (q), 53.3 (t), 57.8 (q), 58.9 (d), 62.4 (t), 64.6 (t), 66.9 (t), 71.4 (s), 71.7 (s), 72.9 (d), 79.9 (d), 92.4 (t), 97.2 (d), 99.7 (d), 151.7 (d), 164.4 (s), 165.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{38}N_2NaO_8S$ 525.2241, found 525.2249.

(3-*R*)-3-[(6*S*,8*S*,8a*R*)-2-Methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)-1,4-dioxooctahydropyrrolo[1,2-*a*]piperazin-6-yl]-3-[(2-methoxyethoxy)-methoxy]-2-(phenylselanyl)propanal (34.5).

All the following experiments were done with the more polar MEM ether obtained in the previous step.

34.4 **34.5**

PhSeCl (601 mg, 3.14 mmol) in EtOAc (10 mL) was added slowly to a vigorously stirred biphasic mixture of **34.4** (1.433 g, 2.85 mmol) and $NaHCO_3$ (720 mg, 8.56 mmol) in water (17 mL) and EtOAc (25 mL). Stirring at room temperature was continued for 1 h. The yellow reaction mixture was then extracted twice with EtOAc, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 12 cm), using 1:1 EtOAc-hexanes to pure EtOAc, gave **34.5** (four inseparable isomers, 1.481 g, 82%) as a pale yellow semisolid: $[\alpha]_D$ = –2.87 (*c* 2.66, $CHCl_3$); FTIR ($CHCl_3$, cast) 2927, 2854, 1675, 1476, 1438, 1416 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43-1.83 (m, 6 H), 2.10-2.16 (m, 3 H), 2.18-2.31 (m, 0.5 H), 2.35 (d, *J* = 7.2 Hz, 0.5 H), 2.43 (dt, *J* = 13.1, 7.1 Hz, 0.5 H), 2.67 (dt, *J* = 13.1, 10.6 Hz, 0.5 H), 2.90-2.99 (m, 3

H), 3.29-3.35 (m, 3 H), 3.42-3.58 (m, 4 H), 3.59-3.67 (m, 1 H), 3.70-3.87 (m, 2 H), 4.17 (apparent t, J = 6.1 Hz, 0.4 H), 4.21-4.32 (m, 2.2 H), 4.35-4.47 (m, 1.3 H), 4.70-4.83 (m, 2.3 H), 4.92 (apparent t, J = 5.2 Hz, 0.78 H), 5.05 (apparent t, J = 3.5 Hz, 0.3 H), 5.08 (apparent t, J = 3.5 Hz, 0.6 H), 7.13-7.27 (m, 3 H), 7.47-7.56 (m, 1 H), 7.56-7.63 (m, 1 H), 9.22-9.31 (d, J = 3.9 Hz, 0.6 H), 9.35 (d, J = 5.7 Hz, 0.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5 (q), 14.7 (q), 19.15 (t), 19.19 (t), 25.29 (t), 25.33 (t), 30.1 (t), 30.8 (t), 31.0 (t), 33.85 (q), 33.89 (q), 51.7 (d), 53.0 (t), 53.2 (t), 53.7 (d), 57.1 (d), 57.7 (d), 58.9 (q), 59.0 (q), 62.4 (t), 68.20 (t), 68.24 (t), 71.4 (s), 71.58 (t), 71.64 (t), 72.6 (d), 79.8 (d), 79.9 (d), 96.8 (t), 97.0 (t), 99.7 (d), 99.8 (d), 126.4 (s), 126.9 (s), 128.49 (d), 128.52 (d), 128.7 (d), 129.1 (d), 129.2 (d) 135.21 (d), 135.26 (d), 135.41 (d), 135.44 (d), 164.69 (s), 164.74 (s), 165.04 (s) 165.06 (s), 191.0 (d), 191.2 (d); exact mass (electrospray) m/z calcd for $C_{27}H_{38}N_2NaO_8SSe$ 653.1406, found 653.1402.

(6*S*,8*S*,8a*R*)-6-{(1*R*)-3-Hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylselanyl)propyl}-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (34.6).

34.5 **34.6**

$NaBH_4$ (98 mg, 2.59 mmol) was added in one portion to a stirred and cooled (–42 °C, MeCN-dry ice bath) solution of **34.5** (1.481 g, 2.35 mmol) in dry MeOH (44 mL). After 6 min TLC (silica gel, EtOAc) analysis showed no **34.5** (and some PhSeSePh), and hence the reaction mixture was quenched at –42 °C with saturated aqueous NH_4Cl. The color of the mixture turned pale yellow. **Note**: The temperature and the reaction time are VERY IMPORTANT to minimize concomitant formation of deselenylated product. The reaction mixture was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 12 cm), using pure EtOAc to 1:10 MeOH-EtOAc, gave **34.6** (four inseparable isomers, 1.078 g, 72%, with a trace amount of deselenylated product detected in the mass spectrum) as a white semisolid: $[\alpha]_D$ = –59.60 (*c* 0.57, $CHCl_3$); FTIR ($CHCl_3$, cast) 3409, 2928, 2879, 1659, 1503, 1477, 1437, 1404 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.49-1.86 (m, 6 H), 2.14-2.30 (m, 3 H), 2.34-2.56 (m, 2 H), 2.89-3.09 (m, 3 H), 3.30-3.40 (m, 3 H), 3.47-3.61 (m, 4 H), 3.64-3.90 (m, 6 H), 4.29-4.53 (m, 2.2 H), 4.55-4.68 (m, 1.3 H), 4.68-4.83 (m, 1.3 H), 4.83-4.95 (m, 1.2 H), 5.04-5.19 (m, 1 H), 7.13-7.33 (m, 3 H), 7.56-7.77 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 14.6 (q), 19.1 (t), 25.31 (t), 25.35 (t), 30.10 (t), 30.14 (t), 31.8 (t), 33.84 (q), 33.89 (q), 48.6 (d), 53.1 (t), 58.6 (d), 58.95 (q), 58.98 (q), 62.3 (t), 63.6 (t), 67.8 (t), 68.1 (t), 71.5 (t), 71.6 (t), 71.8 (s), 78.2 (d), 80.3 (d), 80.6 (d), 96.4 (t), 99.83 (d), 99.87 (d), 127.4 (d), 128.94 (d), 128.97 (d), 129.0 (d), 129.3 (s), 134.2 (d), 135.2 (d), 164.4 (s), 164.49 (s), 164.51

(s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{40}N_2NaO_8SSe$ 655.1563, found 655.1563.

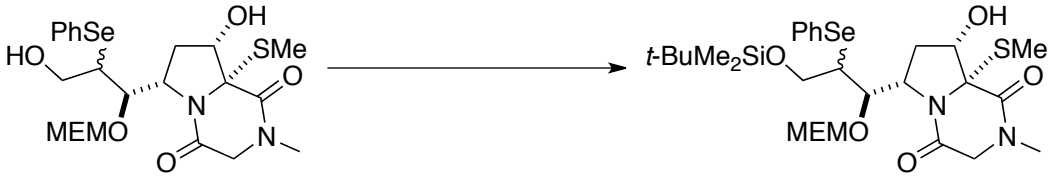
(6*S*,8*S*,8a*R*)-8-Hydroxy-6-{(1*R*)-3-hydroxy-1-[(2-methoxyethoxy)-methoxy]-2-(phenylselanyl)propyl}-2-methyl-8a-(methylsulfanyl)octahydro-pyrrolo-[1,2-*a*]piperazine-1,4-dione (34.7).

34.6 **34.7**

A catalytic amount of pyridinium *p*-toluenesulfonate (52 mg, 0.21 mmol) was added to a stirred solution of **34.6** (519 mg, 0.82 mmol) in dry MeOH (16 mL) contained in a flask equipped with a condenser, and the mixture was heated at 50 °C for 6 h. The reaction mixture was cooled and quenched with saturated aqueous $NaHCO_3$. The MeOH was evaporated and the mixture was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using pure EtOAc to 1:10 MeOH-EtOAc, gave **34.7** (two inseparable isomers, 363 mg, 81%) as a white semisolid: $[\alpha]_D$ = –46.92 (*c* 0.28, $CHCl_3$); FTIR ($CHCl_3$, cast) 3440, 2926, 2886, 1663, 1503, 1478, 1437, 1401 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.98-2.09 (m, 1 H), 2.09-2.21 (m, 3 H), 2.21-

2.45 (m, 1.5 H), 2.92-3.06 (m, 3 H), 3.28-3.39 (m, 3 H), 3.40-3.48 (m, 1.2 H), 3.49-3.58 (m, 2.8 H), 3.58-3.64 (m, 1 H), 3.64-3.79 (m, 2.5 H), 3.79-3.93 (m, 2 H), 4.24-4.34 (m, 1 H), 4.34-4.42 (m, 1 H), 4.42-4.47 (m, 0.5 H), 4.49 (d, J = 7.2 Hz, 0.6 H), 4.65-4.79 (m, 1.7 H), 4.79-4.92 (m, 1 H), 5.05-5.15 (m, 0.3 H), 7.17-7.29 (m, 3 H), 7.52-7.65 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8 (q), 13.0 (q), 30.9 (t), 31.2 (t), 33.55 (q), 33.59 (q), 47.3 (d), 48.9 (d), 53.2 (t), 57.5 (d), 58.5 (d), 58.9 (q), 59.0 (q), 62.9 (t), 63.3 (t), 67.9 (t), 68.3 (t), 71.5 (t), 71.7 (t), 73.2 (s), 75.5 (d), 75.7 (d), 79.2 (d), 82.6 (d), 96.5 (t), 97.7 (t), 127.5 (d), 127.9 (d), 128.2 (s), 129.09 (d), 129.14 (s), 129.2 (d), 134.1 (d), 135.0 (d), 163.6 (s), 163.8 (s), 165.8 (s), 165.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{32}N_2NaO_7SSe$ 571.0988, found 571.0989. No deselenylated product was detected. **Note**: The reaction time is very important as prolonged heating causes hydrolysis of the MEM group.

(6*S*,8*S*,8a*R*)-8-Hydroxy-2-methyl-8a-(methylsulfanyl)-6-[(8*R*)-12,12,13,13-tetramethyl-9-(phenylselanyl)-2,5,7,11-tetraoxa-12-silatetra-decan-8-yl]octa-hydropyrrolo[1,2-*a*]piperazine-1,4-dione (34.8).



34.7 **34.8**

t-BuMe_2SiCl (148 mg, 0.98 mmol) was added to a stirred solution of **34.7** (245 mg, 0.45 mmol), imidazole (76 mg, 1.12 mmol) and DMAP (3 mg) in dry CH_2Cl_2 (6.5 mL), resulting in formation of a white precipitate. Stirring at room temperature was continued for 2 days. The mixture was quenched with water (to form two clear phases) and extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 2:1 EtOAc-hexanes to pure EtOAc, gave **34.8** (two inseparable isomers, 647 mg, 86%) as a white semisolid: $[\alpha]_D$ = –28.64 (*c* 0.40, $CHCl_3$); FTIR ($CHCl_3$, cast) 3450, 2952, 2927, 2885, 2856, 1663, 1501, 1471, 1463, 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ –0.06-0.01 (m, 6 H), 0.79-0.87 (m, 9 H), 2.12-2.20 (m, 3 H), 2.28-2.41 (m, 2 H), 2.97-3.04 (m, 3 H), 3.32-3.37 (m, 3 H), 3.37-3.41 (m, 1 H), 3.47-3.59 (m, 3 H), 3.68-3.80 (m, 4 H), 3.81-3.89 (m, 1 H), 4.23-4.31 (m, 1 H), 4.34 (ddd, *J* = 10.0, 7.9, 1.9 Hz, 1 H), 4.57 (d, *J* = 7.0 Hz, 1 H), 4.63-4.74 (m, 1 H), 4.76-4.82 (m, 1 H), 4.82-4.88 (m, 1 H), 7.18-7.28 (m, 3 H), 7.49-7.65 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.47 (q), –5.45 (q), –5.43 (q), –5.40 (q), 11.8 (q), 12.2 (q), 18.1 (s), 25.8 (q), 25.9 (q), 30.5 (t), 31.8 (t), 33.58 (q), 33.59 (q), 48.9 (d), 53.3 (t), 57.5 (d), 58.1 (d), 58.9 (q), 62.8 (t), 64.1 (t), 68.1 (t), 68.2 (t), 71.77 (t), 71.79 (t), 73.7 (s), 73.9 (s), 75.7 (d), 76.8 (d), 79.6 (d), 97.3 (t), 97.5 (t), 127.2 (d), 127.6 (d), 128.9 (d), 129.05 (d), 129.07 (d), 129.12 (d), 129.6 (s), 129.8 (s), 133.68 (d), 133.73 (d), 134.4 (d), 162.9 (s), 163.1 (s), 166.1 (s), 166.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{46}N_2NaO_7SSeSi$ 685.1852, found 685.1856.

(6*S*,8a*R*)-2-Methyl-8a-(methylsulfanyl)-6-[(8*R*)-12,12,13,13-tetra-methyl-9-(phenylselanyl)-2,5,7,11-tetraoxa-12-silatetradecan-8-yl]octahydro-pyrrolo[1,2-*a*]piperazine-1,4,8-trione (35.1).

34.8 **35.1**

DCC (327 mg, 1.58 mmol) was tipped into a stirred solution of **34.8** (349 mg, 0.53 mmol), pyridine (43 μL, 0.53 mmol) and CF_3CO_2H (20 μL, 0.26 mmol) in a mixture of dry DMSO (3 mL) and dry PhH (3 mL). **Note**: Pyridine has to be added before CF_3CO_2H, the substrate, PhH, DMSO, pyridine, CF_3CO_2H and then DCC were added to the reaction flask in that order. Within a few min dicyclohexylurea precipitated and the reaction mixture turned pale pink. Stirring at room temperature was continued for 15 h. The reaction mixture was filtered to remove dicyclohexylurea and the filtrate was washed twice with water. The combined aqueous extracts were extracted twice with EtOAc. The filtrate and the combined organic extracts were dried (Na_2SO_4) and evaporated. More dicyclohexylurea precipitated and was filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:1 EtOAc-hexanes (dicyclohexylurea is eluted with this eluent) to 4:1 EtOAc-hexanes to pure EtOAc, gave **35.1** (two inseparable isomers, 303 mg, 87%) as a

white semisolid: $[\alpha]_D$ = –7.33 (*c* 0.12, $CHCl_3$); FTIR ($CHCl_3$, cast) 2952, 2928, 2884, 2857, 1769, 1689, 1472, 1463, 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ –0.06-0.04 (m, 6 H), 0.80-0.92 (m, 9 H), 2.32-2.38 (m, 3 H), 2.79 (dd, *J* = 18.8, 10.0 Hz, 1 H), 2.99-3.10 (m, 4 H), 3.34-3.41 (m, 3 H), 3.46 (m, 1 H), 3.57 (apparent t, *J* = 4.6 Hz, 2 H), 3.68-3.84 (m, 4 H), 3.86-3.95 (m, 1 H), 4.34-4.41 (m, 1 H), 4.46 (d, *J* = 15.8 Hz, 1 H), 4.77-4.85 (m, 1 H), 4.85-4.92 (m, 1 H), 5.01 (ddd, *J* = 9.6, 6.9, 2.2 Hz, 1 H), 7.15-7.32 (m, 3 H), 7.48-7.61 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.5 (q), –5.4 (q), 14.4 (q), 18.1 (s), 25.8 (q), 34.4 (q), 38.3 (t), 49.5 (d), 52.8 (t), 54.8 (d), 59.0 (q), 63.9 (t), 68.3 (t), 71.7 (s), 78.9 (d), 97.5 (t), 127.40 (d), 127.43 (d), 128.9 (d), 129.0 (d), 129.5 (s), 133.8 (d), 160.1 (s), 164.4 (s), 198.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{44}N_2NaO_7SSeSi$ 683.1696, found 683.1696. **Note**: Before chromatography it is necessary to filter the residue through a plug of cottonwool to remove as much dicyclohexylurea as possible.

(6*S*,8a*R*)-6-{(1*R*)-3-Hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylselanyl)propyl}-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piper-azine-1,4,8-trione (35.2).

35.1 **35.2**

A mixture of **35.1** (303 mg, 0.46 mmol), AcOH, water and THF was stirred at room temperature for 3 days. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using pure EtOAc to 1:10 MeOH-EtOAc, gave **35.2** (two inseparable isomers, 198 mg, 79%) as a white semisolid: $[\alpha]_D$ = –0.75 (*c* 2.00, $CHCl_3$); FTIR ($CHCl_3$, cast) 3402, 2925, 2892, 2854, 1762, 1676, 1578, 1559, 1477, 1435, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.32-2.39 (m, 3 H), 2.61-2.89 (m, 2 H), 2.98-3.09 (m, 3 H), 3.34-3.41 (m, 4 H), 3.41-3.50 (m, 1 H), 3.52-3.69 (m, 3 H), 3.70-3.98 (m, 4 H), 4.35 (dd, *J* = 7.6, 2.3 Hz, 1 H), 4.40-4.50 (m, 1 H), 4.75-4.84 (m, 1 H), 4.95 (d, *J* = 6.9 Hz, 1 H), 5.21 (ddd, *J* = 9.9, 7.3, 3.1 Hz, 1 H), 7.21-7.34 (m, 3 H), 7.53-7.69 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5 (q), 34.3 (q), 38.2 (t), 39.0 (t), 48.2 (d), 49.9 (d), 52.7 (t), 54.6 (d), 55.1 (d), 58.95 (q), 58.97 (q), 62.7 (t), 62.8 (t), 68.0 (t), 68.7 (s), 71.5 (t), 71.7 (t), 78.6 (d), 96.6 (t), 97.5 (t), 127.7 (d), 129.0 (s), 129.2 (d), 129.3 (d), 134.1 (d), 135.4 (d), 159.8 (s), 160.1 (s), 164.5 (s), 165.3 (s), 198.5 (s), 199.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{30}N_2NaO_7SSe$ 569.0831, found 569.0846.

(6*S*,7*Z*,8a*R*)-7-[(Dimethylamino)methylidene]-2-methyl-8a-(methylsulfanyl)-6-[(8*R*)-12,12,13,13-tetramethyl-9-(phenylselanyl)-2,5,7,11-tetraoxa-12-silatetradecan-8-yl]octahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (36.1).

35.1 **36.1**

$Me_2NCH(OMe)_2$ (10 μL, 0.075 mmol) was added to a stirred solution of **35.1** (20 mg, 0.03 mmol) in dry THF (1 mL) and the mixture was refluxed for 22 h. The pale yellow color of the initial mixture turned to dark yellow during the course of the reaction. The solvent was evaporated and flash chromatography of the residue over silica gel (0.5 x 5 cm), using pure EtOAc to 1:10 MeOH-EtOAc, gave **36.1** (5.6 mg, 26%) as a dark yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ –0.06 - –0.02 (m, 6 H), 0.78-0.92 (m, 9 H), 2.44-2.48 (m, 3 H), 2.93-3.04 (m, 4 H), 3.14-3.16 (m, 5 H), 3.38-3.41 (m, 3 H), 3.56-3.61 (m, 2 H), 3.62-3.75 (m, 3 H), 3.75-3.94 (m, 4 H), 4.36 (apparent s, 0.6 H), 4.52 (d, J = 15.4 Hz, 0.6 H), 4.86 (d, J = 6.6 Hz, 1 H), 4.93 (d, J = 6.8 Hz, 1 H), 5.37 (apparent s, 0.7 H), 7.21-7.29 (m, 3 H), 7.47 (s, 1 H), 7.54-7.57 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.5 (q), –5.3 (q), 14.4 (q), 18.2 (s), 25.9 (q), 34.5 (q), 38.9 (q), 49.0 (d), 52.1 (t), 52.8 (t), 53.6 (d), 59.0 (d), 60.4 (d), 64.8 (t), 68.08 (t), 68.14 (t), 71.8 (s), 77.9 (d), 96.4 (t), 96.9 (t), 126.7 (d), 126.9 (d), 128.8 (d), 128.9 (d), 130.1 (s), 132.5 (d), 133.4 (d),

150.1 (d), 161.8 (s), 165.1 (s), 187.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{49}N_3NaO_7SSe$ 738.2118, found 738.2114.

(6*S*,7*Z*,8a*R*)-7-[(Dimethylamino)methylidene]-6-{(1*R*)-3-hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylselanyl)propyl}-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (37.1).

35.2 **37.1**

$Me_2NCH(OMe)_2$ (21 μL, 0.160 mmol) was added to a stirred solution of **35.2** (35 mg, 0.064 mmol) in dry THF (2 mL) and the mixture was heated at 55 °C for 16 h. The pale yellow color of the initial mixture turned to dark yellow during the course of the reaction. The solvent was evaporated and flash chromatography of the residue over silica gel (0.5 x 7 cm), using pure EtOAc to 1:10 MeOH-EtOAc, gave **37.1** (23 mg, 60%) as a dark yellow oil which contained two inseparable isomers: $[\alpha]_D$ = –14.61 (*c* 0.36, $CHCl_3$); FTIR ($CHCl_3$, cast) 3359, 3056, 2927, 1682, 1590, 1477, 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.44-2.52 (m, 3 H), 3.03 (s, 3 H), 3.10-3.21 (m, 6 H), 3.36-3.42 (m, 3 H), 3.52-3.64 (m, 2 H), 3.64-3.76 (m, 3 H), 3.76-3.85 (m, 1 H), 3.86-3.95 (m, 2 H), 4.39 (apparent t, *J* = 1.7 Hz, 1 H), 4.52 (d, *J* = 16.0 Hz, 1 H), 4.83 (d, *J* = 6.4 Hz, 1 H),

5.14 (d, J = 6.4 Hz, 1 H), 5.35 (s, 1 H), 7.20-7.26 (m, 3 H), 7.41 (s, 1 H), 7.51-7.57 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (q), 14.3 (q), 14.56 (q), 14.58 (q), 29.7 (t), 34.2 (q), 34.4 (q), 34.5 (q), 35.1 (q), 46.9 (d), 48.7 (d), 49.6 (d), 52.3 (t), 52.4 (t), 52.7 (t), 52.8 (t), 55.2 (d), 56.1 (d), 58.9 (q), 59.0 (q), 60.0 (q), 64.0 (t), 67.8 (t), 67.9 (t), 68.6 (t), 68.7 (t), 69.1 (t), 71.6 (s), 71.7 (s), 80.3 (d), 83.2 (d), 95.5 (t), 95.7 (t), 96.9 (t), 127.2 (d), 128.4 (d), 128.8 (d), 129.1 (d), 129.2 (d), 129.3 (d), 129.4 (d), 129.53 (s), 129.57 (s), 133.6 (d), 133.7 (d), 133.9 (d), 134.3 (d), 135.2 (d), 136.1 (d), 150.7 (d), 160.1 (s), 161.8 (s), 163.2 (s), 163.6 (s), 164.8 (s), 185.5 (s), 185.8 (s), 187.3 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{35}N_3NaO_7SSe$ 624.1253, found 624.1254.

(1*S*,7*R*,14*R*)-14-[(2-Methoxyethoxy)methoxy]-5-methyl-7-(methylsulfanyl)-13-(phenylselanyl)-11-oxa-2,5-diazatricyclo[7.5.0.0^{2,7}]tetradec-9-ene-3,6,8-trione (36.3).

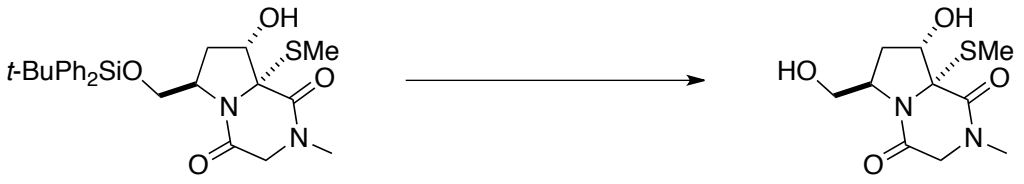
37.1 **36.3**

CF_3CO_2H (10 μL, 0.1259 mmol, an *old bottle* of CF_3CO_2H was used) was added to a stirred solution of freshly-prepared **37.1** (63 mg, 0.1049 mmol) in dry PhMe (6 mL) and the solution was heated at 45 °C for 12 h. Evaporation of the

solvent at 30-35 °C and flash chromatography of the residue over silica gel (1.5 x 6.5 cm), using EtOAc to 1:5 MeOH-EtOAc, followed by filtration of a solution of the product in EtOAc through a plug of cotton wool, gave **36.3** (39.5 mg, 68%) as a semisolid: $[\alpha]_D$ = –79.84 (*c* 0.07, $CHCl_3$); FTIR ($CHCl_3$, neat) 3055, 2925, 2890, 1733, 1679, 1621, 1477, 1437 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 2.34-2.41 (m, 3 H), 2.99-3.08 (m, 3 H), 3.34-3.43 (m, 3 H), 3.49-3.63 (m, 2 H), 3.64-3.74 (m, 2 H), 3.75-3.87 (m, 2 H), 4.14 (dd, *J* = 13.5, 3.8 Hz, 1 H), 4.30 (dd, *J* = 10.3, 4.0 Hz, 1 H), 4.36 (d, *J* = 15.9 Hz, 1 H), 4.80-4.91 (m, 2 H), 5.00 (d, *J* = 13.4 Hz, 1 H), 5.66 (dd, *J* = 10.4, 1.6 Hz, 1 H), 7.28-7.39 (m, 3 H), 7.47 (s, 1 H), 7.60-7.71 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6 (q), 34.3 (q), 48.7 (d), 52.4 (t), 56.1 (d), 59.01 (q), 59.07 (q), 62.3 (t), 67.8 (t), 69.2 (s), 71.7 (t), 83.2 (d), 95.8 (t), 106.7 (s), 127.5 (s), 128.8 (d), 129.2 (d), 129.3 (d), 129.4 (d), 136.1 (d), 157.6 (d), 160.1 (s), 163.7 (s), 185.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{28}N_2NaO_7SSe$ 579.0676, found 579.0676.

When a new bottle of CF_3CO_2H was used, the reaction did not work; however, if a trace of water was added [0.4 mL of water was added to CF_3CO_2H (4.5 mL) in PhMe (2 mL), and 0.5 mL of this stock solution was used], the reaction proceeds in 37% yield.

(6*R*,8*S*,8a*R*)-8-Hydroxy-6-(hydroxymethyl)-2-methyl-8a-(methyl-sulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (48.3).



31.1 **48.3**

Bu_4NF (1 M in THF, 0.25 mL, 0.246 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **31.1** (102 mg, 0.205 mmol) and glacial AcOH (18 μL, 0.307 mmol) in dry THF. The ice bath was left in place but not recharged and stirring was continued for 2 days. The reaction mixture remained colorless throughout. The solvent was evaporated and flash chromatography of the residue over silica gel (2 x 7 cm), using pure EtOAc to 1:40 MeOH-EtOAc, afforded **48.3** (55 mg, 107%) as a white semisolid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (ddd, *J* = 12.7, 7.2, 1.6 Hz, 1 H), 2.22 (s, 3 H), 2.41-2.51 (m, 1 H), 3.02 (s, 3 H), 3.60-3.66 (m, 1 H), 3.68-3.79 (m, 1 H), 3.79-3.85 (m, 1 H), 3.88-3.94 (m, 1 H), 4.08-4.15 (m, 1 H), 4.33-4.40 (m, 1 H), 4.74 (dd, *J* = 10.9, 7.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (q), 31.7 (t), 33.3 (q), 53.5 (t), 56.9 (d), 63.5 (t), 71.7 (s), 74.3 (d), 165.9 (s), 166.3 (s); only low resolution mass spectroscopic data was collected: *m*/*z* calcd for $C_{10}H_{16}N_2NaO_4S$ 283.3, found 283.0.

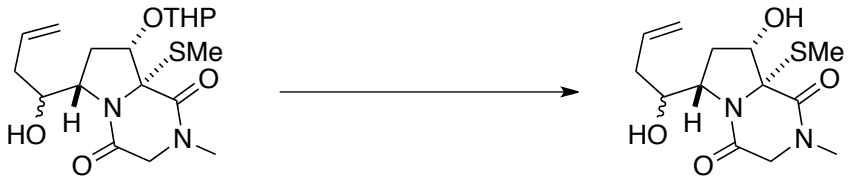
(6*S*,8*S*,8a*R*)-6-(1-Hydroxybut-3-en-1-yl)-2-methyl-8a-(methyl-sulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (50.3).

33.4 **50.3**

Indium metal (1.217 g, 10.6 mmol) was cut into small pieces (ca 5 x 10 mm) which were pressed into thin long pieces. The In pieces were dropped into stirred, dry THF (100 mL), followed by addition of allyl bromide (0.83 mL, 9.62 mmol). Stirring at room temperature was continued for 3 h, by which time most of the In had dissolved, generating a grey colored solution. Very vigorous stirring is required to ensure that almost all the In dissolves. Then a solution of **33.4** (1.645 g, 4.81 mmol) in THF (15 mL) was added dropwise and stirring was continued overnight. The solvent was evaporated to give a thick yellowish gel, which was then dissolved in EtOAc. The mixture was quenched with saturated aqueous NH_4Cl to form a white slurry with no separation of layers. The whole mixture was filtered through Celite (5 x 7 cm) and the filter bed was washed with EtOAc. The filtrate separated into two layers. The milky, white aqueous layer was extracted twice with EtOAc and the combined organic extracts and organic filtrates were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 8 cm), using 9:1 EtOAc-hexanes to pure EtOAc,

afforded **50.3** as a white semisolid (1.595 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48-1.84 (m, 6 H), 1.96-2.12 (m, 1 H), 2.14-2.22 (m, 3 H), 2.22-2.45 (m, 3 H), 2.96-3.05 (m, 3 H), 3.49-3.59 (m, 1 H), 3.67-3.82 (m, 1 H), 3.82-4.05 (m, 4 H), 4.23-4.30 (m, 0.22 H), 4.36-4.54 (m, 2 H), 4.64 (m, 0.16 H), 4.90 (br s, 0.24 H), 5.03-5.16 (m, 3 H), 5.53 (d, *J* = 2.4 Hz, 0.21 H), 5.82-6.02 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8 (q), 15.0 (q), 19.3 (t), 19.5 (t), 25.29 (t), 25.33 (t), 25.39 (t), 30.05 (t), 30.16 (t), 30.19 (t), 30.24 (t), 33.6 (q), 33.8 (q), 33.9 (q), 36.80 (t), 36.83 (t), 38.4 (t), 52.8 (t), 53.1 (t), 61.7 (d), 61.9 (d), 62.6 (t), 62.84 (t), 62.87 (t), 69.5 (d), 69.6 (d), 70.6 (s), 70.9 (s), 79.7 (d), 79.9 (d), 99.9 (d), 100.1 (d), 117.20 (t), 117.25 (t), 117.5 (t), 117.9 (t), 133.9 (d), 134.9 (d), 135.0 (d), 135.1 (d), 164.4 (s), 164.8 (s), 165.8 (s), 165.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{28}N_2NaO_5S$ 407.1611, found 407.1606.

(6*S*,8*S*,8a*R*)-8-Hydroxy-6-(1-hydroxybut-3-en-1-yl)-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (52.3).



50.3 **52.3**

Hydrochloric acid (1 N, 214 μL, 0.2135 mmol) was added to a stirred solution of **50.3** (41 mg, 0.1068 mmol) in THF (1.5 mL) and stirring at room

temperature was continued for 36 h. The solvent was evaporated and EtOAc was added. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 5 cm), using pure EtOAc to 1:10 MeOH-EtOAc, afforded **52.3** (29.1 mg, 91%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97-2.20 (m, 2 H), 2.20-2.24 (m, 3 H), 2.24-2.47 (m, 3 H), 3.02-3.09 (m, 3 H), 3.41 (br s, 1 H), 3.64 (d, *J* = 6.8 Hz, 0.67 H), 3.75-3.82 (m, 0.7 H), 3.87 (d, *J* = 17.6 Hz, 0.3 H), 3.95 (apparent td, *J* = 6.0, 3.2 Hz, 0.3 H), 4.03-4.16 (m, 2 H), 4.31-4.46 (m, 1 H), 4.53 (t, *J* = 8.9 Hz, 1 H), 5.08-5.21 (m, 2 H), 5.81-6.05 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4 (q), 13.6 (q), 28.7 (t), 30.9 (t), 33.4 (q), 33.6 (q), 37.4 (t), 38.6 (t), 52.8 (t), 53.2 (t), 61.5 (d), 61.8 (d), 69.6 (d), 72.3 (s), 75.1 (d), 75.4 (d), 117.5 (t), 117.7 (t), 133.7 (d), 134.8 (d), 164.99 (s), 165.99 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{20}N_2NaO_4S$ 323.1036, found 323.1031.

(6*S*,8*S*,8a*R*)-6-(1,3-Dihydroxypropyl)-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (50.2).

50.3 **50.2**

Rubin's apparatus[73] was used for this reaction.

CH_2Cl_2 (6.3 mL) was added from a syringe to the reaction flask of the Rubin apparatus[73] equipped with a drying tube. The apparatus was cooled to −78 °C, and a stream of ozonized oxygen was bubbled through the CH_2Cl_2 until a purple color developed. Then a solution of **50.3** (95.6 mg, 0.249 mmol) in MeOH (6 mL) was added to the second flask of the apparatus. Both joints of the apparatus were sealed with septa and the saturated O_3 solution was transferred to the solution of **50.3** by using a slow flow of Ar. The reaction mixture was then stirred for 20 min at −78 °C, followed by addition of $NaBH_4$ (47 mg, 1.245 mmol). The cooling bath was removed and stirring was arbitrarily continued overnight. The solvent was evaporated and CH_2Cl_2 was added. The mixture was then quenched with saturated aqueous NH_4Cl. The mixture was extracted twice with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using pure EtOAc to 1:10 MeOH-EtOAc, afforded **50.2** as a white semisolid (30.4 mg, 46%, corrected for recovered **50.3** (30.7 mg)]. The product was characterized by low resolution mass spectroscopy: *m*/*z* calcd for $C_{17}H_{28}N_2NaO_6S$ 411.5, found 411.2.

(6*S*,8*S*,8a*R*)-6-(1,3-Dihydroxypropyl)-8-hydroxy-2-methyl-8a-(methyl-sulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (51.1).

50.2 **51.1**

TsOH•H_2O (24.4 mg, 0.128 mmol) was added to a solution of **50.2** (33 mg, 0.085 mmol) in MeOH (2.6 mL) and the mixture was lowered into a preheated oil bath set at 50 °C and heated for 45 min. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and loaded onto a Grade III alumina column which was developed with pure EtOAc to 1:10 MeOH-EtOAc to afford **51.1** as a white solid (17.5 mg, 68%). The product was characterized by low resolution mass spectroscopy: *m*/*z* calcd for $C_{12}H_{20}N_2NaO_5S$ 327.4, found 327.2.

(2*S*,4*R*)-1-[(Benzyloxy)carbonyl]-4-hydroxypyrrolidine-2-carboxylic acid (57.1a).[83]

26.1 **57.1a**

K_2CO_3 (7.635 g, 55.24 mmol) was added to a stirred solution of **26.1** (3.29 g, 25.11 mmol) in water (20 mL) and dioxane (3.5 mL). Then CbzCl was added dropwise and vigorous stirring was continued overnight. The mixture was then extracted twice with CH_2Cl_2 and the aqueous phase was acidified with concentrated hydrochloric acid. The acidic aqueous phase was extracted twice with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product **57.1a** (4.694 g, 70%) was obtained as a colorless oil, which was used for the next step: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05-2.45 (m, 2 H), 3.57-3.71 (m, 2 H), 4.48-4.62 (m, 2 H), 5.08-5.23 (m, 2 H), 7.28-7.41 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.4 (t), 39.2 (t), 54.6 (t), 55.1 (t), 57.3 (d), 58.2 (d), 67.4 (t), 68.1 (t), 69.5 (d), 69.6 (d), 69.7 (d), 127.7 (d), 128.1 (d), 128.4 (d), 128.47 (d), 128.54 (d), 128.6 (d), 135.8 (s), 156.9 (s), 173.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{15}NNaO_5$ 288.0842, found 288.0834.

1-Benzyl 2-Methyl (2*S*,4*R*)-4-Hydroxypyrrolidine-1,2-dicarboxylate (57.1).[84]

57.1a **57.1**

$SOCl_2$ (1.55 mL, 21.25 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **57.1a** (4.69 g, 17.70 mmol) in MeOH (35 mL) contained in a three-necked flask equipped with a drying tube packed with Drierite. The ice bath

was left in place but not recharged and stirring was continued overnight. Evaporation of the solvent gave **57.1** (4.689 g, 95%) as a colorless oil which was used in the next step: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07-2.17 (m, 1 H), 2.26-2.39 (m, 1 H), 3.51-3.60 (m, 2 H), 3.63-3.74 (m, 1.5 H), 3.75-3.80 (m, 1.4 H), 4.46-4.57 (m, 2 H), 5.04-5.15 (m, 1 H), 5.15-5.25 (m, 1 H), 7.27-7.39 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5 (t), 39.3 (t), 52.1 (q), 52.4 (q), 54.7 (t), 55.3 (t), 57.7 (d), 57.9 (d), 67.3 (t), 69.6 (d), 70.3 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.6 (d), 136.3 (s), 136.5 (s), 154.5 (s), 154.9 (s), 173.0 (s), 173.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{17}NNaO_5$ 302.0999, found 302.0994.

1-Benzyl 2-Methyl (2*S*)-4-oxopyrrolidine-1,2-dicarboxylate (57.2).[85]

57.1 **57.2**

PCC (10.36 g, 48.06 mmol) was added to a stirred and cooled (0 °C) mixture of **57.1** (4.47 g, 16.02 mmol), AcONa (1.314 g, 16.02 mmol) and 3Å molecular sieves (0.5 g/1 mmol of **57.1**, 8.0 g) in dry CH_2Cl_2 (165 mL). After 10 min the ice bath was removed and stirring was continued for 1.5 h. The mixture was then filtered through Celite (5 x 7 cm) and the filter bed was washed thoroughly with CH_2Cl_2. Silica gel was added to the filtrate and the mixture was

evaporated at room temperature. The resulting solid was loaded onto a silica gel column (6 x 11 cm) made up with 2:1 EtOAc-hexanes, and 2:1 EtOAc-hexanes was used as eluent to afford **57.2** (3.934 g, 88%) as a white semisolid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (dd, *J* = 18.8, 2.7 Hz, 1 H), 2.88-3.03 (m, 1 H), 3.60-3.81 (m, 3 H), 3.90-4.06 (m, 2 H), 4.84 (d, *J* = 10.3 Hz, 0.4 H), 4.90 (d, *J* = 10.3 Hz, 0.4 H), 5.10-5.20 (m, 1 H), 5.21-5.28 (m, 1 H), 7.29-7.43 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.6 (t), 41.2 (t), 52.5 (t), 52.6 (q), 52.8 (q), 55.9 (d), 56.0 (d), 67.7 (t), 67.8 (t), 128.1 (d), 128.2 (d), 128.4 (d), 128.6 (d), 128.8 (d), 135.9 (s), 154.2 (s), 154.9 (s), 171.9 (s), 207.0 (s), 207.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{15}NNaO_5$ 300.0842, found 300.0835.

1-Benzyl 2-Methyl (2*S*)-4,4-Dimethoxypyrrolidine-1,2-dicarboxylate (57.3).

57.2 **57.3**

TsOH•H_2O (82 mg, 0.43 mmol) was added to a stirred solution of ketone **57.2** (3.934 g, 14.202 mmol) and $HCH(OMe)_3$ (1.9 mL, 17.042 mmol) in dry MeOH (70 mL). The mixture was refluxed for 16 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (4 x 8 cm), using 2:1 EtOAc-hexane, gave **57.3** (4.374 g, 95%) as a colorless oil: ^{1}H NMR

(500 MHz, $CDCl_3$) δ 2.20-2.30 (m, 1 H), 2.33-2.45 (m, 1 H), 3.17-3.27 (m, 6 H), 3.52-3.62 (m, 3 H), 3.62-3.78 (m, 2 H), 4.42 (dd, *J* = 8.4, 5.9 Hz, 0.5 H), 4.48 (dd, *J* = 8.5, 5.6 Hz, 0.5 H), 5.05-5.23 (m, 2 H), 7.28-7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.8 (t), 37.8 (t), 49.8 (q), 49.9 (q), 50.0 (q), 52.2 (t), 52.4 (q), 57.68 (d), 57.73 (d), 67.2 (t), 67.3 (t), 106.1 (s), 106.9 (s), 127.90 (d), 127.95 (d), 128.0 (d), 128.1 (d), 128.4 (d), 128.5 (d), 136.4 (s), 136.5 (s), 154.3 (s), 154.8 (s), 171.9 (s), 172.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{21}NNaO_6$ 346.1261, found 346.1251.

Benzyl (2*S*)-2-(Hydroxymethyl)-4,4-dimethoxypyrrolidine-1-carboxylate (57.4).

57.3 **57.4**

$LiBH_4$ (738 mg, 33.85 mmol) was added to a stirred and cooled (0 °C) solution of **57.3** (4.374 g, 13.54 mmol) in dry THF (35 mL). The ice bath was removed after 5 min and stirring was continued for 18 h to produce a white slurry. The reaction was quenched with water and glacial AcOH, forming a clear solution. The organic solvent was evaporated and EtOAc was added to the residual aqueous phase, which was extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of

the residue over silica gel (4 x 8 cm), using 1:1 EtOAc-hexane, afforded **57.4** (3.848 g, 96%) as a thick oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (dd, *J* = 12.7, 7.5 Hz, 1 H), 2.29 (dd, *J* = 12.0, 8.9 Hz, 1 H), 3.17-3.36 (m, 6 H), 3.42-3.55 (m, 2 H), 3.65-3.86 (m, 2 H), 4.15 (br s, 1 H), 4.19-4.24 (m, 1 H), 5.18-5.22 (m, 2 H), 7.32-7.46 (m, 5 H); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{21}NNaO_5$ 318.1312, found 318.1305.

Benzyl (2*S*)-2-Formyl-4,4-dimethoxypyrrolidine-1-carboxylate (57.5).

57.4 **57.5**

DCC (8.1 g, 39.259 mmol) was tipped (using a powder funnel) into a stirred solution of **57.4** (3.848 g, 13.04 mmol), pyridine (1.1 mL, 13.5 mmol) and CF_3CO_2H (0.5 mL, 6.576 mmol) in dry DMSO (35 mL) and dry PhH (35 mL). **Note**: The substrate, PhH, DMSO, pyridine, CF_3CO_2H and then DCC were added to the reaction flask in that order. Within few minutes dicyclohexylurea precipitated. Stirring at room temperature was continued overnight by which time the mixture turned pale yellow. The reaction mixture was filtered to remove dicyclohexylurea and the filtrate was washed twice with water. The combined aqueous extracts were extracted twice with CH_2Cl_2. The filtrate and the combined organic extracts were dried (Na_2SO_4) and evaporated. More dicyclohexylurea

precipitated and was filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (4 x 10 cm), using 1:1 EtOAc-hexanes (dicyclohexylurea is eluted with this eluent) gave **57.5** (3.523 g, 92%) as a white semisolid. Compound **57.5** was mixed with some dicyclohexylurea as both substances have the same polarity. **Note**: Before chromatography it is necessary to filter the residue through a plug of cottonwool to remove as much dicyclohexylurea as possible. Compound **57.5** was characterized by low resolution mass spectroscopy and ^{1}H NMR, and was clearly mixed with considerable amount of dicyclohexylurea.

Benzyl (2*S*)-2-(1-Hydroxybut-3-en-1-yl)-4,4-dimethoxypyrrolidine-1-carboxylate (57.6).

57.5 **57.6**

Indium metal (258 mg, 2.247 mmol) was cut into small pieces (ca 5 x 10 mm) which were pressed into thin long pieces. The In pieces were dropped into stirred dry THF (15 mL), followed by addition of allyl bromide (175 µL, 2.021 mmol). Stirring at room temperature was continued for 3 h, by which time most of the In pieces had dissolved, generating a grey colored solution. Very vigorous stirring is required to ensure that almost all the In dissolves. Then a solution of

57.5 (130 mg, 0.443 mmol) in THF (2 mL) was added dropwise and stirring was continued overnight. The solvent was evaporated to give a thick yellowish gel, which was dissolved in EtOAc. The mixture was quenched with saturated aqueous NH_4Cl to form a white slurry with no separation of layers. The mixture was filtered through Celite (2 x 5 cm) and the filter bed was washed with EtOAc. The filtrate separated into two layers. The milky white aqueous layer was extracted twice with EtOAc and the combined organic extracts and organic filtrates were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 8 cm), using 2:1 EtOAc-hexanes to 1:1 EtOAc-hexanes, afforded **57.6** as a yellow gel (121.5 mg, 82%): exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{25}NNaO_6$ 358.1625, found 358.1614.

Benzyl (2*S*)-2-(1,3-dihydroxypropyl)-4,4-dimethoxypyrrolidine-1-carboxylate (57.6a).

57.6 **57.6a**

Ozonized oxygen was bubbled through a stirred and cooled (−78 °C) solution of **57.6** (121.5 mg, 0.362 mmol) in CH_2Cl_2 (2 mL) and MeOH (1 mL) until a purple color developed. Then $NaBH_4$ (137 mg, 3.62 mmol) was added and, after 5 min, the cooling bath was removed and stirring was continued for 2 h.

The solvent was evaporated and CH_2Cl_2 was added to the residue. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:1 EtOAc-hexanes to pure EtOAc, afforded **57.6a** (55.5 mg, 45%) as a colorless semisolid. Compound **57.6a** was characterized only by low resolution mass spectroscopy: *m*/*z* calcd for $C_{17}H_{25}NNaO_6$ 362.4, found 362.3.

Phenyl *N*-{2-[(2*R*)-2-(Hydroxymethyl)-4,4-dimethoxypyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (59.1).

29.4 **59.1**

Anhydrous $CaCl_2$ (3.52 g, 31.709 mmol) was added to a stirred and cooled (0 °C) solution of methyl ester **29.4** (10.97 g, 28.868 mmol) in a mixture of dry THF (35 mL) and dry EtOH (35 mL), and then $NaBH_4$ (2.4 g, 63.425 mmol) was added in one portion. Stirring at 0 °C was continued for 8 h. The reaction mixture was then quenched at 0 °C by successive addition of water and glacial AcOH, resulting in a clear solution. Evaporation of the organic solvent resulted in a white slurry. EtOAc and saturated aqueous $NaHCO_3$ were added to the slurry,

resulting in precipitation of a calcium salt. Filtration of the biphasic mixture through Celite resulted in a clear organic phase and a milky white aqueous suspension. The layers were separated and the aqueous layer was extracted four times with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 10 cm), using EtOAc-MeOH mixtures from pure EtOAc to 1:20 MeOH-EtOAc, gave **59.1** (6.882 g, 68%) as a colorless oil: $[\alpha]_D$ = 20.28 (*c* 1.12, $CHCl_3$); FTIR ($CHCl_3$, cast) 3432, 2945, 2835, 1726, 1652, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75-1.87 (m, 1 H), 2.20-2.33 (m, 1 H), 3.04-3.12 (s, 1 H), 3.16-3.28 (m, 8 H), 3.44-3.55 (m, 1 H), 3.56-3.66 (m, 1 H), 3.67-3.77 (m, 2 H), 3.94-4.06 (m, 1 H), 4.08-4.16 (m, 1 H), 4.25-4.35 (m, 1 H), 4.54 (d, *J* = 4.8 Hz, 0.66 H), 4.60 (t, *J* = 5.0 Hz, 0.33 H), 7.06-7.17 (m, 2 H), 7.17-7.23 (m, 1 H), 7.32-7.40 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9 (t), 35.0 (t), 36.2 (q), 36.6 (q), 49.6 (q), 50.21 (q), 50.24 (q), 51.7 (t), 51.8 (t), 52.80 (t), 52.86 (t), 60.7 (d), 60.8 (d), 66.1 (t), 66.4 (t), 106.37 (s), 106.40 (s), 121.68 (d), 121.76 (d), 121.80 (d), 125.4 (d), 125.5 (d), 129.26 (d), 129.31 (d), 151.3 (s), 151.4 (s), 155.5 (s), 169.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{24}N_2NaO_6$ 375.1527, found 375.1521.

Phenyl *N*-{2-[(2*R*)-2-Formyl-4,4-dimethoxypyrrolidin-1-yl]-2-oxo-ethyl}-*N*-methylcarbamate (58.1).

59.1 **58.1**

DCC (11.7 g, 56.707 mmol) was tipped (using a powder funnel) into a stirred solution of **59.1** (6.658 g, 18.916 mmol), pyridine (1.6 mL, 19.644 mmol) and CF_3CO_2H (0.74 mL, 9.733 mmol) in a mixture of dry DMSO (45 mL) and dry PhH (45 mL). **Note**: The substrate, PhH, DMSO, pyridine, CF_3CO_2H and then DCC were added to the reaction flask in that order. Within a few minutes dicyclohexylurea precipitated. Stirring at room temperature was continued for 24 h, by which time the mixture had turned pale yellow. The reaction mixture was filtered to remove dicyclohexylurea and the filtrate was washed twice with water. The combined aqueous extracts were extracted twice with CH_2Cl_2. The filtrate and the combined organic extracts were dried (Na_2SO_4) and evaporated. More dicyclohexylurea precipitated and was filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (5 x 12 cm), using 1:1 EtOAc-hexanes (dicyclohexylurea is eluted with this eluent) to pure EtOAc, gave **58.1** (5.968 g, 90%) as a yellow oil. **Note**: Before chromatography it is necessary to filter the residue through a plug of cottonwool to remove as much

dicyclohexylurea as possible: $[\alpha]_D$ = 65.66 (*c* 0.57, $CHCl_3$); FTIR ($CHCl_3$, cast) 2942, 2836, 1725, 1662, 1594, 1454 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08-2.23 (m, 1 H), 2.27-2.46 (m, 1 H), 3.05-3.16 (m, 3 H), 3.19-3.32 (m, 6 H), 3.48 (s, 0.2 H), 3.51-3.64 (m, 0.8 H), 3.69-3.88 (m, 1 H), 4.08-4.32 (m, 2 H), 4.49 (d, *J* = 3.7 Hz, 0.3 H), 4.51 (d, *J* = 3.5 Hz, 0.3 H), 4.53 (dd, *J* = 9.2, 3.3 Hz, 0.3 H), 7.05-7.15 (m, 2 H), 7.17-7.26 (m, 1 H), 7.30-7.42 (m, 2 H), 9.42-9.54 (m, 0.8 H), 9.57 (s, 0.2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.7 (t), 33.8 (t), 36.25 (q), 36.29 (q), 36.4 (q), 36.6 (q), 48.8 (q), 49.2 (q), 50.6 (q), 50.9 (q), 51.0 (t), 51.1 (t), 51.3 (t), 52.2 (t), 52.47 (t), 52.52 (t), 63.2 (d), 63.8 (d), 105.3 (s), 106.87 (s), 106.92 (s), 121.68 (d), 121.74 (d), 121.78 (d), 125.44 (d), 125.48 (d), 125.5 (d), 129.29 (d), 129.34 (d), 151.3 (s), 151.4 (s), 154.8 (s), 155.5 (s), 167.7 (s), 167.9 (s), 199.9 (d), 200.3 (d); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{22}N_2NaO_6$ 373.1370, found 373.1363.

Phenyl *N*-{2-[(2*R*)-2-(1-Hydroxybut-3-en-1-yl)-4,4-dimethoxypyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (58.2).

58.1 **58.2**

Indium metal (3.937 g, 34.293 mmol) was cut into small pieces (ca 5 x 10 mm) which were pressed into thin long pieces. The In pieces were dropped into dry THF (200 mL), followed by addition of allyl bromide (2.7 mL, 31.176 mmol). Stirring at room temperature was continued for 3 h, by which time most of the In had dissolved, generating a grey-colored solution. Very vigorous stirring is required to ensure that almost all the In dissolves. Then a solution of **58.1** (5.456 g, 15.588 mmol) in THF (40 mL) was added dropwise and stirring was continued overnight. The solvent was evaporated to give a thick yellowish gel, which was then dissolved in EtOAc. The mixture was quenched with saturated aqueous NH_4Cl to form a white slurry with no separation of layers. The mixture was filtered through Celite (5 x 7 cm) and the filter bed was washed with EtOAc. The filtrate separated into two layers. The milky, white aqueous layer was extracted twice with EtOAc and the combined organic extracts and organic filtrates were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 9 cm), using 1:1 EtOAc-hexane to pure EtOAc, afforded **58.2** as a yellow gel (6.668 g, 99.7%): $[\alpha]_D$ = 31.48 (*c* 0.98, $CHCl_3$); FTIR ($CHCl_3$, cast) 3444, 2939, 2834, 1727, 1656, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.01-2.31 (m, 4 H), 3.04-3.11 (m, 1 H), 3.14-3.24 (m, 5 H), 3.25-3.32 (m, 3 H), 3.42 (d, *J* = 10.6 Hz, 1 H), 3.58 (d, *J* = 5.7 Hz, 1 H), 3.62-3.74 (m, 1 H), 3.94-4.10 (m, 2 H), 4.10-4.18 (m, 1 H), 4.22-4.35 (m, 1 H), 5.00-5.19 (m, 2 H), 5.79-5.97 (m, 1 H), 7.09 (d, *J* = 7.9 Hz, 0.7 H), 7.14 (d, *J* = 7.7 Hz, 1.2 H), 7.17-7.23 (m, 1 H), 7.35 (apparent q, *J* = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.6 (t), 33.0 (t), 36.2 (q), 36.6 (q), 37.4 (t), 37.6 (t), 49.21 (q), 49.23 (q), 50.59 (q), 50.63 (q), 51.91 (t), 51.97 (t),

52.8 (t), 52.9 (t), 62.1 (d), 62.4 (d), 70.1 (d), 70.8 (d), 106.63 (s), 106.67(s), 117.28 (t), 117.33 (t), 121.69 (d), 121.74 (d), 121.83 (d), 125.37 (d), 125.40 (d), 129.25 (d), 129.29 (d), 134.8 (d), 134.9 (d), 151.33 (s), 151.38 (s), 154.9 (s), 155.5 (s), 168.01 (s), 168.15 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}N_2NaO_6$ 415.1840, found 415.1831.

Phenyl *N*-{2-[(2*R*)-2-(1,3-dihydroxypropyl)-4-oxopyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (58.3).

58.2 **58.3**

Ozonized oxygen was bubbled through a stirred and cooled (–78 °C) solution of **58.2** (163 mg, 0.416 mmol) in CH_2Cl_2 (3 mL) until a purple color developed (2-3 min). Then O_2 was bubbled through this mixture for 2 min to remove the excess of O_3. Then Me_2S (0.2 mL, 2.104 mmol) was added and the cooling bath was left in place but not recharged, and stirring was continued overnight. The reaction mixture turned orange. The solvent was evaporated and MeOH (3 mL) was added. The mixture was stirred and cooled (0 °C) and $NaBH_4$ (24 mg, 0.624 mmol) was added. After 5 min the ice bath was removed and stirring was continued for 30 min. Hydrochloric acid (1.5 N) was added and

stirring was continued, the progress of the reaction being monitored by low resolution mass spectroscopy. After 1.5 h the reaction was over (it usually took 1.5-2.5 h depending on the scale). The solvent was evaporated and then the mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted three times with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and evaporated. The pH of the remaining aqueous layer (product **58.3** dissolves partially in water) was adjusted to 7 and the water was evaporated at 60 °C, using a rotary evaporator. The residue was thoroughly washed with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the combined organic residues over silica gel (1.5 x 9 cm), using pure EtOAc to 1:10 MeOH-EtOAc, afforded **58.3** (87 mg, 60%) as a yellowish semisolid. This method worked best on a scale of less than 200 mg scale, and for larger scales the yield was poor. Hence a slightly modified procedure was adopted for larger scale reactions as described below.

Ozonized oxygen was bubbled through a stirred and cooled (–78 °C) solution of **58.2** (1.002 g, 2.557 mmol) in CH_2Cl_2 (20 mL) until a purple color developed (5 min). Then O_2 was bubbled through the mixture for 5 min to remove the excess of O_3. MeOH (20 mL) and $NaBH_4$ (774 mg, 20.454 mmol) were added to the mixture at –78 °C. The cooling bath was removed and stirring was continued for 1.5 h. The solvent was evaporated to afford a thick yellowish gel which was dissolved in THF (10 mL). Hydrochloric acid (4.8 M, 10 mL) was added slowly and stirring at room temperature was continued for 14 h. The pH of this mixture was adjusted to ~7 by adding solid $NaHCO_3$ with vigorous stirring.

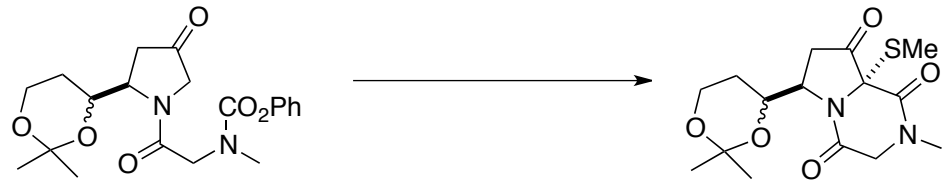
The solvent was then evaporated at 60 °C, using a rotary evaporator. The residue was thoroughly washed with CH_2Cl_2 and filtered to remove inorganic products. The filter bed was washed twice with CH_2Cl_2 and the combined organic extracts were evaporated. Flash chromatography of the residue over silica gel (3 x 8 cm), using pure EtOAc to 1:40 MeOH-EtOAc to 1:20 MeOH-EtOAc and finally 1:10 MeOH-EtOAc, afforded **58.3** (527 mg, 59%) as a white semisolid: $[\alpha]_D = -6.26$ (*c* 0.94, $CHCl_3$); FTIR ($CHCl_3$, cast) 3412 (br), 3010, 2939, 1763, 1721, 1654, 1476, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44-1.64 (m, 1.2 H), 2.42-2.69 (m, 1.3 H), 2.98-3.10 (m, 1 H), 3.11-3.32 (m, 3 H), 3.61-3.79 (m, 2.5 H), 3.80-3.98 (m, 1.5 H), 4.03-4.26 (m, 2 H), 4.27-4.33 (m, 1 H), 4.44-4.66 (m, 1 H), 7.02-7.15 (m, 2 H), 7.15-7.25 (m, 1 H), 7.29-7.43 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.1 (t), 36.2 (t), 36.4 (q), 51.8 (t), 52.7 (t), 59.3 (d), 60.1 (t), 70.3 (d), 121.70 (d), 121.74 (d), 125.5 (d), 125.7 (d), 129.37 (d), 129.39 (d), 151.2 (s), 155.9 (s), 167.2 (s), 208.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{22}N_2NaO_6$ 373.1370, found 373.1365.

Phenyl *N*-{2-[(2*R*)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-4-oxopyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (59.2).

58.3 **59.2**

2-Methoxypropene (0.23 mL, 2.336 mmol) was added to a stirred solution of **58.3** (369 mg, 1.054 mmol) and pyridine *p*-toluenesulfonate (5.5 mg, 0.022 mmol) in dry CH_2Cl_2 (5 mL), and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 8 cm), using 1:1 EtOAc-hexanes to pure EtOAc, afforded **59.2** (305 mg, 74%) as a white semisolid: $[\alpha]_D$ = 11.47 (*c* 0.89, $CHCl_3$); FTIR ($CHCl_3$, cast) 2993, 2938, 1765, 1725, 1663, 1476, 1455, 1431 cm^{-1}; ^1H NMR (498 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.19-1.42 (m, 4 H), 1.51 (m, 1 H), 1.93-2.06 (m, 0.34 H), 2.32-2.51 (m, 1 H), 2.51-2.73 (m, 1 H), 3.01-3.25 (m, 4 H), 3.57-3.69 (m, 0.37 H), 3.72-3.95 (m, 3 H), 3.95-4.17 (m, 2 H), 4.17-4.41 (m, 1 H), 4.59 (d, *J* = 9.9 Hz, 1 H), 7.02-7.21 (m, 3 H), 7.28-7.39 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0 (q), 19.3 (q), 26.8 (t), 26.9 (t), 29.4 (q), 29.44 (q), 36.2 (t), 36.3 (t), 36.4 (q), 36.5 (q), 51.6 (t), 51.9 (t), 52.5 (t), 52.7 (t), 57.5 (d), 57.6 (d), 59.02 (t), 59.05 (t), 69.7 (d), 69.8 (d), 98.3 (s), 98.4 (s), 98.8 (s), 121.6 (d), 121.7 (d), 125.3 (d), 125.4 (d), 129.22 (d), 129.26 (d), 151.3 (s), 154.9 (s), 155.4 (s), 166.7 (s), 166.95 (s), 208.2 (s), 208.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{26}N_2NaO_6$ 413.1683, found 413.1680.

(6*R*,8a*R*)-6-(2,2-Dimethyl-1,3-dioxan-4-yl)-2-methyl-8a-(methyl-sulfanyl)octahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (59.3).



59.2 **59.3**

NaH (60%w/w in mineral oil, 32.5 mg, 0.814 mmol) was added to a stirred solution of ketone **59.2** (144 mg, 0.369 mmol) in dry THF (5 mL). The reaction flask was lowered into a preheated oil bath set at 70 °C and the reaction mixture was refluxed for 20 min. After 15 min, TLC (silica, 1:20 MeOH-EtOAc) monitoring showed no **59.2** remained and only a very polar spot corresponding to the cyclized product was detected (R_f 0.1). During this time almost all of the NaH suspension dissolved and the color of the reaction mixture became yellow. The mixture was cooled to room temperature and then to 0 °C.

In a separate flask, Et_3N (81 µL, 0.581 mmol) was added to stirred Me_3SiCl (132.5 µL, 1.049 mmol) at 0 °C and stirring was continued for 10 min. The resulting milky solution was then added by syringe to the original reaction mixture. The mixture turned pale yellow and a suspension was formed. The mixture was stirred for an arbitrary period of 3.5 h at 0 °C.

In another flask, MeSCl was generated by slow dropwise addition of SO_2Cl_2 (32 µL, 0.402 mmol) to a stirred and cooled (−78 °C) solution of Me_2S_2

(37 μL, 0.406 mmol) in dry CH_2Cl_2 (3 mL), followed by stirring for 15 min. The reaction mixture containing the intermediate silyl enol ether was then cooled to −78 °C and the yellow solution of MeSCl was cannulated into it and stirring was continued overnight, the cooling bath being left in place but not recharged. The solvent was evaporated and the mixture was quenched with water. The mixture was then extracted three times with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:1 to 3:2 to 7:3 EtOAc-hexanes, afforded **59.3** (48.8 mg, 39%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25-1.33 (m, 6 H), 1.39-1.47 (m, 1 H), 1.52-1.62 (m, 1 H), 2.27 (s, 3 H), 2.78 (dd, *J* = 17.3, 2.1 Hz, 1 H), 3.07 (s, 3 H), 3.12 (dd, *J* = 17.2, 9.2 Hz, 1 H), 3.77-3.83 (m, 1 H), 3.85 (dd, *J* = 5.3, 1.8 Hz, 0.3 H), 3.88 (dd, *J* = 5.5, 1.7 Hz, 0.7 H), 3.91-3.98 (m, 1 H), 4.34 (apparent dt, *J* = 9.1, 1.9 Hz, 1 H), 4.53 (s, 0.5 H), 4.50 (s, 0.5 H), 4.60-4.66 (m, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{22}N_2NaO_5S$ 365.1142, found 365.1136.

A sample for single crystal X-ray analysis was obtained by crystallization from EtOAc-hexane by allowing hexane to diffuse into a solution of the compound in EtOAc in a closed container.

(6*R*,8a*R*)-6-(1,3-Dihydroxypropyl)-2-methyl-8a-(methylsulfanyl)octa-hydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (58.4).

59.3 **58.4**

Concentrated hydrochloric acid (20 μL) was added to a stirred solution of **59.3** (21 mg, 0.0614 mmol) in THF (1 mL). Stirring at room temperature was continued for 10 min, the acid was neutralized with the minimum amount of saturated aqueous $NaHCO_3$ and the aqueous-organic mixture was evaporated with heating, using a water bath set at 50 °C. Compound **58.4** is soluble in water. The crude residue was dissolved in the minimum amount of CH_2Cl_2 and the solution was loaded onto a silica gel column (1 x 6 cm) made up with EtOAc. The column was developed using pure EtOAc to 1:10 MeOH-EtOAc, to give **58.4** (16.5 mg, 89%) as a white solid. Only low resolution mass spectroscopic data was collected: *m*/*z* calcd for $C_{12}H_{18}N_2NaO_5S$ 325.3, found 325.0.

(6*R*,7*Z*,8a*R*)-6-(2,2-Dimethyl-1,3-dioxan-4-yl)-7-[(dimethylamino)-methylidene]-2-methyl-8a-(methylsulfanyl)octahydropyrrolo[1,2-*a*]pipera-zine-1,4,8-trione (60.1).

59.3 **60.1**

$Me_2NCH(OMe)_2$ (78 μL, 0.585 mmol) was added to a solution of **59.3** (20 mg, 0.0585 mmol) in dry THF (1 mL) and the mixture was heated at 70 °C overnight. The color of the mixture was dark yellow at this stage. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 8 cm), using pure EtOAc to 1:10 MeOH-EtOAc, afforded **60.1** (11 mg, 47%) as a pale yellow solid (containing some impurities). Only low resolution mass spectroscopic data was collected: *m*/*z* calcd for $C_{18}H_{27}N_3NaO_5S$ 420.5, found 420.1.

(1*R*,7*R*)-14-Hydroxy-5-methyl-7-(methylsulfanyl)-11-oxa-2,5-diaza-tricyclo[7.5.0.0^{2,7}]tetradec-9-ene-3,6,8-trione (58.5).

60.1 **58.5**

CF_3CO_2H (from an old bottle, 1 μL, 0.0126 mmol) and water (1 μL) were added to a solution of **60.1** (1 mg, 0.0025 mmol) in toluene (0.3 mL) and then the reaction mixture was heated at 50 °C for 5 h. TLC showed complete consumption of **60.1** and formation of a new compound, which was isolated by preparative TLC, using pure EtOAc, (R_f of the new compound was 0.3). Only low resolution mass spectroscopic data was collected for the new compound which is believed to be **58.5**: *m*/*z* calcd for $C_{13}H_{16}N_2NaO_5S$ 335.3, found 335.0.

5. Appendix : Crystallographic Experimental Details

5.1. (6*R*,8*S*,8a*R*)-6-(Hydroxymethyl)-2-methyl-8a-(methylsulfanyl)-8-(oxan-2-yloxy)octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (33.1).

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{15}H_{24}N_2O_5S$
formula weight	344.42
crystal dimensions (mm)	0.57 × 0.20 × 0.15
crystal system	monoclinic
space group	$P2_1$ (No. 4)
unit cell parameters[a]	
a (Å)	9.8302 (17)
b (Å)	9.4825 (16)
c (Å)	9.9978 (17)
β (deg)	115.4426 (18)
V (Å^3)	841.6 (2)
Z	2
ρ_{calcd} (g cm^{-3})	1.359
μ (mm^{-1})	0.219
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å]) (0.71073)	graphite-monochromated Mo Kα
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	55.88
total data collected	7364 (-12 ≤ h ≤ 12, -12 ≤ k ≤ 12, -13 ≤ l ≤ 13)
independent reflections	3870 (R_{int} = 0.0259)
number of observed reflections (*NO*)	3542 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method (*SHELXL–97*[c])	full-matrix least-squares on F^2
absorption correction method	Gaussian integration (face-indexed)

range of transmission factors	0.9679–0.8854
data/restraints/parameters	3870 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 211
Flack absolute structure parameter[d]	0.08(6)
goodness-of-fit (S)[e]	1.046 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0339
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0903
largest difference peak and hole	0.249 and –0.185 e Å^{-3}

[a]Obtained from least-squares refinement of 7375 reflections with $4.52° < 2\theta < 55.54°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[d]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. In this case the relatively large standard uncertainty indicates that the structural data alone should not be used to confirm absolute stereochemistry, but should be used in conjunction with the established stereochemistry of the precursor compound.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0490P)^2 + 0.0776P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	x	y	z	U_{eq}, Å^2
S	0.08761(5)	0.08975(5)	0.06849(5)	0.03928(13)*
O1	0.27697(14)	0.28923(13)	0.39467(14)	0.0320(3)*
O2	0.4926(2)	0.18357(17)	0.00932(17)	0.0488(4)*
O3	0.20753(14)	-0.04078(13)	0.37141(14)	0.0326(3)*
O4	0.66960(16)	0.02343(14)	0.41959(15)	0.0376(3)*
O5	0.35616(17)	-0.06703(19)	0.62566(16)	0.0501(4)*
N1	0.30405(19)	0.36816(15)	0.19335(17)	0.0335(3)*
N2	0.38674(17)	0.09934(16)	0.15525(15)	0.0304(3)*
C1	0.28848(18)	0.26666(17)	0.27864(18)	0.0265(3)*

C2	0.3296(3)	0.3383(2)	0.0625(2)	0.0419(5)*
C3	0.4118(2)	0.2004(2)	0.0728(2)	0.0376(4)*
C4	0.4606(2)	-0.04097(18)	0.1847(2)	0.0338(4)*
C5	0.3811(2)	-0.11790(18)	0.2659(2)	0.0344(4)*
C6	0.32757(19)	0.00026(16)	0.33700(18)	0.0261(3)*
C7	0.27972(19)	0.11745(16)	0.21906(18)	0.0273(3)*
C8	0.3004(2)	0.51657(18)	0.2333(2)	0.0382(4)*
C9	0.6302(2)	-0.0294(2)	0.2746(2)	0.0404(4)*
C10	0.2558(2)	-0.1327(2)	0.4978(2)	0.0395(4)*
C11	0.1150(3)	-0.1831(3)	0.5106(3)	0.0577(6)*
C12	0.0457(3)	-0.0673(4)	0.5652(4)	0.0744(10)*
C13	0.1647(4)	0.0000(4)	0.7051(3)	0.0770(10)*
C14	0.2949(4)	0.0479(3)	0.6736(3)	0.0627(7)*
C15	-0.0324(3)	0.1587(3)	0.1490(3)	0.0560(6)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2
	Distance			
S	C7	1.8598(18)	N2	C3	1.354(2)
S	C15	1.812(2)	N2	C4	1.483(2)
O1	O4[a]	2.7962(18)[b]	N2	C7	1.456(2)
O1	C1	1.232(2)	C1	C7	1.523(2)
O1	H4O[a]	1.96[b]	C2	C3	1.516(3)
O2	C3	1.222(3)	C4	C5	1.532(3)
O3	C6	1.418(2)	C4	C9	1.520(3)
O3	C10	1.438(2)	C5	C6	1.536(2)
O4	C9	1.421(2)	C6	C7	1.539(2)
O5	C10	1.383(3)	C10	C11	1.521(3)
O5	C14	1.424(3)	C11	C12	1.512(4)
N1	C1	1.337(2)	C12	C13	1.525(5)
N1	C2	1.462(3)	C13	C14	1.514(4)
N1	C8	1.468(2)			

[a]At 1–x, $^1/_2$+y, 1–z. [b]Nonbonded distance.

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle		Atom1	Atom2	Atom3
C7	S	C15		C4	C5	C6	
	102.58(9)				104.60(13)		
C6	O3	C10		O3	C6	C5	
	112.63(13)				113.47(13)		
C10	O5	C14		O3	C6	C7	
	114.78(18)				111.82(13)		
C1	N1	C2		C5	C6	C7	
	122.80(15)				103.00(13)		
C1	N1	C8		S	C7	N2	
	119.58(15)				107.59(11)		
C2	N1	C8		S	C7	C1	
	117.59(15)				108.35(11)		
C3	N2	C4		S	C7	C6	
	123.66(15)				112.83(11)		
C3	N2	C7		N2	C7	C1	
	122.54(15)				110.53(14)		
C4	N2	C7		N2	C7	C6	
	113.77(14)				102.12(13)		
O1	C1	N1		C1	C7	C6	
	123.88(15)				115.07(13)		
O1	C1	C7		O4	C9	C4	
	121.13(15)				112.20(15)		
N1	C1	C7		O3	C10	O5	
	114.95(14)				111.98(15)		
N1	C2	C3		O3	C10	C11	
	113.44(15)				107.21(17)		
O2	C3	N2		O5	C10	C11	
	123.53(19)				112.15(19)		
O2	C3	C2		C10	C11	C12	
	121.60(17)				111.7(2)		
N2	C3	C2		C11	C12	C13	
	114.87(17)				110.3(2)		
N2	C4	C5		C12	C13	C14	
	102.39(14)				108.6(2)		
N2	C4	C9		O5	C14	C13	
	111.82(15)				111.0(2)		
C5	C4	C9		O4	H4O	O1[c]	
	113.58(16)				175.1[d]		

[c]At 1–*x*, $^{-1}/_{2}$+*y*, 1–*z*. [d]Angle includes nonbonded O–H···O interaction.

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C15	S	C7	N2	-165.90(14)	C3	N2	C7	S	77.89(18)
					C3	N2	C7	C1	-40.2(2)
C15	S	C7	C1	-46.37(15)	C3	N2	C7	C6	-163.14(16)
C15	S	C7	C6	82.24(15)	C4	N2	C7	S	-100.06(14)
C10	O3	C6	C5	73.63(19)					
C10	O3	C6	C7	-170.39(14)					
C6	O3	C10	O5	63.58(19)					
C6	O3	C10	C11	-173.02(17)					
C14	O5	C10	O3	65.2(2)					
C14	O5	C10	C11	-55.4(2)					
C10	O5	C14	C13	60.0(3)					
C2	N1	C1	O1	174.94(19)					
C2	N1	C1	C7	-7.3(3)					
C8	N1	C1	O1	-3.1(3)					
C8	N1	C1	C7	174.67(16)					
C1	N1	C2	C3	-28.9(3)					
C8	N1	C2	C3	149.19(18)					
C4	N2	C3	O2	3.3(3)					
C4	N2	C3	C2	-177.45(17)					
C7	N2	C3	O2	-174.43(19)					
C7	N2	C3	C2	4.8(3)					
C3	N2	C4	C5	-173.89(16)					
C3	N2	C4	C9	64.2(2)					
C7	N2	C4	C5	4.03(19)					
C7	N2	C4	C9	-117.91(16)					

C4 N2 C7 C1
141.81(15)
C4 N2 C7 C6
18.91(17)
O1 C1 C7 S
100.78(16)
O1 C1 C7 N2 -
141.56(16)
O1 C1 C7 C6 -26.5(2)
N1 C1 C7 S -77.06(16)
N1 C1 C7 N2 40.6(2)
N1 C1 C7 C6
155.61(15)
N1 C2 C3 O2 -
150.7(2)
N1 C2 C3 N2 30.0(3)
N2 C4 C5 C6 -
25.57(18)
C9 C4 C5 C6
95.16(18)
N2 C4 C9 O4 65.3(2)
C5 C4 C9 O4 -49.9(2)
C4 C5 C6 O3
158.49(14)
C4 C5 C6 C7
37.42(18)
O3 C6 C7 S -40.78(16)
O3 C6 C7 N2 -
155.98(13)
O3 C6 C7 C1
84.25(17)
C5 C6 C7 S 81.41(14)
C5 C6 C7 N2 -
33.79(16)
C5 C6 C7 C1 -
153.56(15)
O3 C10 C11 C12 -
72.8(3)
O5 C10 C11 C12 50.5(3)
C10 C11 C12 C13 -
50.8(3)
C11 C12 C13 C14 54.1(3)
C12 C13 C14 O5 -57.6(3)

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H4O	0.6833	-0.0443	0.4782	0.056
H2A	0.3890	0.4162	0.0481	0.050
H2B	0.2312	0.3352	-0.0256	0.050
H4	0.4380	-0.0896	0.0887	0.041
H5A	0.4516	-0.1820	0.3425	0.041
H5B	0.2946	-0.1735	0.1958	0.041
H6	0.4142	0.0340	0.4290	0.031
H8A	0.1996	0.5400	0.2240	0.046
H8B	0.3246	0.5768	0.1668	0.046
H8C	0.3746	0.5320	0.3357	0.046
H9A	0.6761	-0.1237	0.2818	0.048
H9B	0.6717	0.0339	0.2226	0.048
H10	0.3068	-0.2164	0.4787	0.047
H11A	0.0403	-0.2161	0.4126	0.069
H11B	0.1411	-0.2638	0.5800	0.069
H12A	-0.0361	-0.1070	0.5866	0.089
H12B	0.0014	0.0053	0.4873	0.089
H13A	0.1211	0.0816	0.7348	0.092
H13B	0.2004	-0.0693	0.7872	0.092
H14A	0.2597	0.1216	0.5960	0.075
H14B	0.3743	0.0895	0.7644	0.075
H15A	-0.1375	0.1344	0.0854	0.067
H15B	-0.0217	0.2614	0.1577	0.067
H15C	-0.0028	0.1174	0.2475	0.067

5.2. 2-methyl-8a-(methylsulfanyl)-8-(tetrahydro-2*H*-pyran-2-yloxy)-6-(2,5,7,11-tetraoxatridec-9-en-8-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (34.4).

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{23}H_{38}N_2O_8S$
formula weight	502.61
crystal dimensions (mm)	0.51 × 0.12 × 0.06
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	7.8318 (4)
b (Å)	12.0684 (6)
c (Å)	27.3364 (15)
V (Å^3)	2583.8 (2)
Z	4
ρ_{calcd} (g cm^{-3})	1.292
μ (mm^{-1})	1.523
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	136.00
total data collected	17261 (-9 ≤ *h* ≤ 9, -13 ≤ *k* ≤ 14, -32 ≤ *l* ≤ 32)
independent reflections	4661 (R_{int} = 0.0975)
number of observed reflections (*NO*)	3012 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method (*SHELXD*[c])	direct methods/dual space
refinement method (*SHELXL–97*[d])	full-matrix least-squares on F^2
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9141–0.5081
data/restraints/parameters	4661 / 0 / 310
extinction coefficient (*x*)[e]	0.0045(6)
Flack absolute structure parameter[f]	0.01(5)

goodness-of-fit (S)[g] [all data]	1.039
final R indices[h]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0837
wR_2 [all data]	0.2290
largest difference peak and hole	0.528 and –0.411 e Å^{-3}

[a]Obtained from least-squares refinement of 3714 reflections with $6.46° < 2\theta < 132.60°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[e]$F_c^* = kF_c[1 + x\{0.001F_c^2\lambda^3/\sin(2\theta)\}]^{-1/4}$ where k is the overall scale factor.

[f]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[g]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0931P)^2 + 2.7409P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[h]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	x	y	z	U_{eq}, Å^2
S	0.4940(2)	0.31674(16)	0.32209(6)	0.0692(5)*
O1	0.4681(6)	0.5680(4)	0.38486(18)	0.0729(13)*
O2	0.4189(5)	0.1917(4)	0.47501(16)	0.0640(11)*
O3	-0.0385(5)	0.1182(4)	0.38877(19)	0.0709(13)*
O4	-0.1185(6)	-0.0349(4)	0.4355(2)	0.0723(13)*
O5	-0.3882(7)	-0.1407(4)	0.49003(19)	0.0853(16)*
O6	0.4526(6)	-0.0655(4)	0.34732(18)	0.0726(13)*
O7	0.1959(5)	0.4694(4)	0.31234(16)	0.0643(12)*
O8	-0.0279(7)	0.5902(5)	0.3296(2)	0.0872(15)*
N1	0.6071(7)	0.4340(5)	0.4274(2)	0.0632(14)*
N2	0.3393(6)	0.2928(4)	0.40882(18)	0.0532(12)*
C1	0.4902(7)	0.4691(5)	0.3956(2)	0.0566(15)*
C2	0.6234(7)	0.3168(6)	0.4403(3)	0.0631(16)*

C3	0.4512(7)	0.2604(5)	0.4434(2)	0.0570(15)*
C4	0.1571(7)	0.2540(6)	0.4070(3)	0.0605(17)*
C5	0.0897(7)	0.3150(6)	0.3626(3)	0.0636(16)*
C6	0.1968(8)	0.4208(5)	0.3589(2)	0.0563(15)*
C7	0.3766(7)	0.3799(5)	0.3729(2)	0.0523(14)*
C8	0.7351(8)	0.5098(6)	0.4471(3)	0.076(2)*
C9	0.1409(7)	0.1302(6)	0.4032(3)	0.0624(17)*
C10	-0.1009(9)	0.0080(6)	0.3881(3)	0.073(2)*
C11	-0.2431(9)	0.0208(6)	0.4648(3)	0.077(2)*
C12	-0.2904(9)	-0.0481(7)	0.5070(3)	0.077(2)*
C13	-0.4180(13)	-0.2195(8)	0.5281(3)	0.112(3)*
C14	0.2564(8)	0.0755(6)	0.3674(3)	0.0660(18)*
C15	0.3472(8)	-0.0159(6)	0.3804(3)	0.0687(18)*
C16	0.5197(9)	-0.1698(5)	0.3636(3)	0.0681(17)*
C17	0.6197(10)	-0.2221(6)	0.3229(3)	0.080(2)*
C18	0.058(3)	0.5260(12)	0.2988(4)	0.233(11)*
C19	0.0676(14)	0.5657(8)	0.2442(3)	0.109(3)*
C20	0.1682(9)	0.6678(10)	0.2486(4)	0.107(3)*
C21	0.0830(12)	0.7459(8)	0.2824(4)	0.107(3)*
C22	0.0695(11)	0.6880(9)	0.3318(4)	0.106(3)*
C23	0.5703(11)	0.4360(7)	0.2877(3)	0.087(2)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	
	Distance				
S	C7	1.831(6)	O6	C16	1.433(7)
S	C23	1.820(8)	O7	C6	1.402(7)
O1	C1	1.240(7)	O7	C18	1.331(15)
O2	C3	1.224(7)	O8	C18	1.326(12)
O3	C9	1.466(7)	O8	C22	1.406(11)
O3	C10	1.416(7)	N1	C1	1.333(8)
O4	C10	1.403(9)	N1	C2	1.463(9)
O4	C11	1.430(8)			
O5	C12	1.432(8)			
O5	C13	1.429(9)			
O6	C15	1.363(8)			

N1	C8	1.459(8)
N2	C3	1.347(8)
N2	C4	1.503(7)
N2	C7	1.469(7)
C1	C7	1.529(8)
C2	C3	1.513(8)
C4	C5	1.514(9)
C4	C9	1.504(9)
C5	C6	1.532(9)
C6	C7	1.540(8)
C9	C14	1.487(9)
C11	C12	1.472(11)
C14	C15	1.360(9)
C16	C17	1.499(9)
C18	C19	1.569(13)
C19	C20	1.468(14)
C20	C21	1.478(13)
C21	C22	1.524(12)

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle		Atom1	Atom2	Atom3
C7	S	C23		N2	C4	C5	
	103.1(3)				101.9(5)		
C9	O3	C10		N2	C4	C9	
	115.3(5)				113.1(5)		
C10	O4	C11		C5	C4	C9	
	114.2(6)				113.5(6)		
C12	O5	C13		C4	C5	C6	
	111.7(6)				105.5(5)		
C15	O6	C16		O7	C6	C5	
	113.7(6)				113.9(5)		
C6	O7	C18					
	118.1(6)						
C18	O8	C22					
	104.0(11)						
C1	N1	C2					
	121.6(5)						
C1	N1	C8					
	120.8(6)						
C2	N1	C8					
	117.2(5)						
C3	N2	C4					
	123.4(5)						
C3	N2	C7					
	123.3(5)						
C4	N2	C7					
	112.9(5)						
O1	C1	N1					
	123.8(6)						
O1	C1	C7					
	120.0(5)						
N1	C1	C7					
	116.2(5)						
N1	C2	C3					
	111.7(5)						
O2	C3	N2					
	123.9(6)						
O2	C3	C2					
	121.9(6)						
N2	C3	C2					
	114.2(6)						

O7	C6	C7			
	111.3(5)		C20	C21	C22
C5	C6	C7			
	102.5(5)		O8	C22	C21
S	C7	N2			
	108.0(4)				
S	C7	C1			
	108.0(4)				
S	C7	C6			
	113.9(4)				
N2	C7	C1			
	110.3(5)				
N2	C7	C6			
	102.3(4)				
C1	C7	C6			
	114.0(5)				
O3	C9	C4			
	101.4(5)				
O3	C9	C14			
	111.2(6)				
C4	C9	C14			
	115.8(6)				
O3	C10	O4			
	111.6(6)				
O4	C11	C12			
	110.2(6)				
O5	C12	C11			
	108.7(6)				
C9	C14	C15			
	120.4(7)				
O6	C15	C14			
	120.0(7)				
O6	C16	C17			
	109.3(6)				
O7	C18	O8			
	122.3(12)				
O7	C18	C19			
	112.4(10)				
O8	C18	C19			
	116.7(8)				
C18	C19	C20			
	101.8(11)				
C19	C20	C21			
	110.1(7)				
C20	C21	C22			
	107.0(9)				
O8	C22	C21			
	112.6(8)				

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C23	S	C7	N2	-168.3(4)	C3	N2	C4	C5	179.4(6)
C23	S	C7	C1	-49.0(5)	C3	N2	C4	C9	-58.5(9)
C23	S	C7	C6	78.8(5)	C7	N2	C4	C5	6.5(7)
C10	O3	C9	C4	-172.3(6)	C7	N2	C4	C9	128.7(6)
C10	O3	C9	C14	64.0(8)	C3	N2	C7	S	83.8(6)
C9	O3	C10	O4	70.9(8)	C3	N2	C7	C1	-34.0(8)
C11	O4	C10	O3	64.5(7)	C3	N2	C7	C6	-155.7(6)
C10	O4	C11	C12	162.8(6)					
C13	O5	C12	C11	171.7(7)					
C16	O6	C15	C14	-171.1(6)					
C15	O6	C16	C17	174.6(6)					
C18	O7	C6	C5	76.4(12)					
C18	O7	C6	C7	-168.3(11)					
C6	O7	C18	O8	39(2)					
C6	O7	C18	C19	-174.4(10)					
C22	O8	C18	O7	79.4(16)					
C22	O8	C18	C19	-66.1(18)					
C18	O8	C22	C21	61.8(10)					
C2	N1	C1	O1	177.5(6)					
C2	N1	C1	C7	-0.8(9)					
C8	N1	C1	O1	-8.8(10)					
C8	N1	C1	C7	172.8(6)					
C1	N1	C2	C3	-37.6(9)					
C8	N1	C2	C3	148.5(6)					
C4	N2	C3	O2	4.3(10)					
C4	N2	C3	C2	-175.5(6)					
C7	N2	C3	O2	176.4(6)					
C7	N2	C3	C2	-3.4(8)					

C4	N2	C7	S	-103.3(5)	57.6(11)			
C4	N2	C7	C1	138.9(5)	C19	C20	C21	C22
C4	N2	C7	C6	17.2(7)		59.9(10)		
O1	C1	C7	S	99.6(6)	C20	C21	C22	O8 -60.9(9)
O1	C1	C7	N2	-142.6(6)				
O1	C1	C7	C6	-28.1(8)				
N1	C1	C7	S	-82.0(6)				
N1	C1	C7	N2	35.8(7)				
N1	C1	C7	C6	150.3(6)				
N1	C2	C3	O2	-140.8(6)				
N1	C2	C3	N2	39.1(8)				
N2	C4	C5	C6	-28.0(6)				
C9	C4	C5	C6	-149.9(5)				
N2	C4	C9	O3	-165.3(5)				
N2	C4	C9	C14	-44.8(9)				
C5	C4	C9	O3	-49.8(7)				
C5	C4	C9	C14	70.7(7)				
C4	C5	C6	O7	159.4(5)				
C4	C5	C6	C7	39.1(6)				
O7	C6	C7	S	-39.3(7)				
O7	C6	C7	N2	-155.6(5)				
O7	C6	C7	C1	85.3(6)				
C5	C6	C7	S	82.9(5)				
C5	C6	C7	N2	-33.4(6)				
C5	C6	C7	C1	-152.6(5)				
O3	C9	C14	C15	-112.5(7)				
C4	C9	C14	C15	132.4(7)				
O4	C11	C12	O5	-70.6(7)				
C9	C14	C15	O6	179.9(6)				
O7	C18	C19	C20	-83.3(15)				
O8	C18	C19	C20	65.5(18)				
C18	C19	C20	C21	-				

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2A	0.6824	0.3102	0.4722	0.076
H2B	0.6941	0.2789	0.4154	0.076
H4	0.0955	0.2804	0.4368	0.073
H5A	-0.0327	0.3331	0.3668	0.076
H5B	0.1031	0.2693	0.3328	0.076
H6	0.1562	0.4758	0.3837	0.068
H8A	0.6957	0.5863	0.4431	0.092
H8B	0.8429	0.4997	0.4294	0.092
H8C	0.7527	0.4942	0.4819	0.092
H9	0.1580	0.0964	0.4362	0.075
H10A	-0.2131	0.0064	0.3714	0.088
H10B	-0.0213	-0.0393	0.3692	0.088
H11A	-0.3458	0.0365	0.4448	0.092
H11B	-0.1962	0.0924	0.4763	0.092
H12A	-0.1863	-0.0745	0.5240	0.092
H12B	-0.3587	-0.0040	0.5305	0.092
H13A	-0.4866	-0.2810	0.5154	0.135
H13B	-0.4793	-0.1836	0.5551	0.135
H13C	-0.3085	-0.2480	0.5401	0.135
H14	0.2668	0.1046	0.3352	0.079
H15	0.3371	-0.0452	0.4125	0.082
H16A	0.4249	-0.2193	0.3734	0.082
H16B	0.5945	-0.1582	0.3923	0.082
H17A	0.6631	-0.2942	0.3336	0.096
H17B	0.7158	-0.1740	0.3141	0.096
H17C	0.5456	-0.2321	0.2944	0.096
H18	-0.0254	0.4637	0.2953	0.280
H19A	0.1260	0.5104	0.2234	0.130
H19B	-0.0475	0.5807	0.2308	0.130
H20A	0.1806	0.7027	0.2160	0.128
H20B	0.2837	0.6500	0.2610	0.128
H21A	-0.0321	0.7651	0.2700	0.129
H21B	0.1506	0.8148	0.2854	0.129
H22A	0.1857	0.6699	0.3436	0.127
H22B	0.0168	0.7393	0.3557	0.127
H23A	0.6542	0.4117	0.2633	0.105
H23B	0.6238	0.4890	0.3101	0.105
H23C	0.4739	0.4716	0.2710	0.105

5.3. (6*R*,8a*R*)-6-(2,2-Dimethyl-1,3-dioxan-4-yl)-2-methyl-8a-(methylsulfanyl)-octahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (59.3).

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{15}H_{22}N_2O_5S$
formula weight	342.41
crystal dimensions (mm)	0.14 × 0.11 × 0.08
crystal system	monoclinic
space group	$P2_1$ (No. 4)
unit cell parameters[a]	
a (Å)	8.2786 (6)
b (Å)	9.5353 (6)
c (Å)	11.2789 (7)
β (deg)	107.900 (4)
V (Å^3)	847.25 (10)
Z	2
ρ_{calcd} (g cm^{-3})	1.342
μ (mm^{-1})	1.935
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω scans (0.8°) (5 s exposures)
data collection 2θ limit (deg)	139.80
total data collected	5392 (-10 ≤ h ≤ 9, -11 ≤ k ≤ 11, -13 ≤ l ≤ 13)
independent reflections	3124 (R_{int} = 0.0418)
number of observed reflections (*NO*)	2859 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method (*SHELXL–97*[d])	full-matrix least-squares on F^2
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.8574–0.7733
data/restraints/parameters	3124 / 0 / 210
Flack absolute structure parameter[e]	0.03(2)
goodness-of-fit (*S*)[f] [all data]	1.056
final *R* indices[g]	

R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0476
wR_2 [all data]	0.1277
largest difference peak and hole	0.387 and –0.253 e Å^{-3}

[a]Obtained from least-squares refinement of 4632 reflections with 8.24° < 2θ < 138.36°.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

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[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0768P)^2]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3)$.

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	x	y	z	U_{eq}, Å^2
S	0.09638(9)	0.25538(8)	0.41158(6)	0.0389(2)*
O1	0.3967(3)	-0.0138(2)	0.43671(19)	0.0423(5)*
O2	0.3008(3)	0.3917(2)	0.11436(18)	0.0361(5)*
O3	0.0319(3)	-0.0722(2)	0.3182(2)	0.0450(5)*
O4	0.2594(2)	-0.0360(2)	0.11987(17)	0.0331(4)*
O5	0.3155(3)	-0.1816(3)	-0.0282(2)	0.0473(6)*
N1	0.4838(3)	0.1974(3)	0.3863(2)	0.0359(5)*
N2	0.1794(3)	0.2254(2)	0.20249(18)	0.0285(5)*
C1	0.3669(3)	0.0990(3)	0.3849(2)	0.0335(6)*
C2	0.4384(4)	0.3344(3)	0.3288(3)	0.0367(6)*
C3	0.3007(3)	0.3230(3)	0.2045(2)	0.0298(6)*
C4	0.0800(3)	0.1586(3)	0.0841(2)	0.0304(6)*
C5	-0.0409(3)	0.0635(3)	0.1263(3)	0.0318(6)*
C6	0.0571(3)	0.0253(3)	0.2598(3)	0.0321(6)*
C7	0.1856(3)	0.1439(3)	0.3119(2)	0.0300(6)*
C8	0.6624(4)	0.1734(4)	0.4560(3)	0.0473(8)*
C9	0.2038(4)	0.0761(3)	0.0335(2)	0.0324(6)*
C10	0.1300(4)	0.0189(4)	-0.0976(3)	0.0404(7)*

C11	0.2640(5)	-0.0779(4)	-0.1214(3)	0.0507(9)*
C12	0.3805(4)	-0.1302(4)	0.0953(3)	0.0402(7)*
C13	0.5525(4)	-0.0585(4)	0.1200(3)	0.0487(8)*
C14	0.3886(4)	-0.2527(4)	0.1814(4)	0.0548(8)*
C15	0.1297(5)	0.1479(5)	0.5504(3)	0.0558(10)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
S	C7	1.857(3)	N2	C4	1.479(3)
S	C15	1.820(4)	N2	C7	1.446(3)
O1	C1	1.213(4)	C1	C7	1.534(4)
O2	C3	1.210(3)	C2	C3	1.514(4)
O3	C6	1.194(4)	C4	C5	1.531(4)
O4	C9	1.424(3)	C4	C9	1.535(4)
O4	C12	1.435(3)	C5	C6	1.518(4)
O5	C11	1.410(5)	C6	C7	1.541(4)
O5	C12	1.418(4)	C9	C10	1.517(4)
N1	C1	1.344(4)	C10	C11	1.529(5)
N1	C2	1.455(4)	C12	C13	1.526(4)
N1	C8	1.464(4)	C12	C14	1.507(5)
N2	C3	1.364(4)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C7	S	C15	102.42(16)	C2	N1	C8	117.4(3)
C9	O4	C12	115.9(2)	C3	N2	C4	120.7(2)
C11	O5	C12	115.2(2)	C3	N2	C7	121.3(2)
C1	N1	C2	122.3(2)	C4	N2	C7	113.8(2)
C1	N1	C8	120.1(3)	O1	C1	N1	125.0(3)

O1	C1	C7	121.8(3)
N1	C1	C7	113.2(3)
N1	C2	C3	111.5(2)
O2	C3	N2	123.1(2)
O2	C3	C2	123.0(3)
N2	C3	C2	113.9(2)
N2	C4	C5	102.1(2)
N2	C4	C9	107.8(2)
C5	C4	C9	112.7(2)
C4	C5	C6	104.5(2)
O3	C6	C5	127.1(3)
O3	C6	C7	125.3(3)
C5	C6	C7	107.3(2)
S	C7	N2	107.05(19)
S	C7	C1	109.90(18)
S	C7	C6	107.14(17)
N2	C7	C1	112.3(2)
N2	C7	C6	103.3(2)
C1	C7	C6	116.5(2)
O4	C9	C4	104.1(2)
O4	C9	C10	110.2(2)
C4	C9	C10	115.6(2)
C9	C10	C11	106.9(2)
O5	C11	C10	111.2(2)
O4	C12	O5	109.2(2)
O4	C12	C13	110.7(3)
O4	C12	C14	104.8(2)
O5	C12	C13	112.6(2)
O5	C12	C14	107.1(3)
C13	C12	C14	112.0(3)

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle
C15	S	C7	N2	-175.0(2)
C15	S	C7	C1	-52.7(2)
C15	S	C7	C6	74.8(2)
C12	O4	C9	C4	-179.1(2)
C12	O4	C9	C10	56.3(3)
C9	O4	C12	O5	-53.8(3)
C9	O4	C12	C13	70.7(3)
C9	O4	C12	C14	-168.3(3)
C12	O5	C11	C10	-57.1(3)
C11	O5	C12	O4	53.8(3)
C11	O5	C12	C13	-69.6(4)
C11	O5	C12	C14	166.8(3)
C2	N1	C1	O1	-176.0(3)
C2	N1	C1	C7	2.8(4)
C8	N1	C1	O1	-1.2(4)
C8	N1	C1	C7	177.7(3)
C1	N1	C2	C3	-41.3(4)
C8	N1	C2	C3	143.7(3)
C4	N2	C3	O2	23.4(4)
C4	N2	C3	C2	-154.7(2)
C7	N2	C3	O2	179.0(2)
C7	N2	C3	C2	0.9(4)
C3	N2	C4	C5	-178.1(2)
C3	N2	C4	C9	62.9(3)
C7	N2	C4	C5	24.6(3)
C7	N2	C4	C9	-94.4(3)
C3	N2	C7	S	81.1(3)
C3	N2	C7	C1	-39.6(3)
C3	N2	C7	C6	-166.0(2)
C4	N2	C7	S	-121.7(2)
C4	N2	C7	C1	117.6(2)
C4	N2	C7	C6	-8.8(3)
O1	C1	C7	S	97.0(3)
O1	C1	C7	N2	-144.0(3)
O1	C1	C7	C6	-25.1(4)
N1	C1	C7	S	-81.9(2)
N1	C1	C7	N2	37.1(3)
N1	C1	C7	C6	156.0(2)
N1	C2	C3	O2	-139.6(3)
N1	C2	C3	N2	38.5(3)
N2	C4	C5	C6	-29.6(3)
C9	C4	C5	C6	85.8(3)
N2	C4	C9	O4	68.3(3)
N2	C4	C9	C10	-170.7(2)
C5	C4	C9	O4	-43.7(3)
C5	C4	C9	C10	77.3(3)
C4	C5	C6	O3	-159.6(3)
C4	C5	C6	C7	25.9(3)
O3	C6	C7	S	-73.0(3)
O3	C6	C7	N2	174.2(3)
O3	C6	C7	C1	50.6(4)
C5	C6	C7	S	101.7(2)
C5	C6	C7	N2	-11.2(3)
C5	C6	C7	C1	-134.8(2)
O4	C9	C10	C11	-53.5(3)
C4	C9	C10	C11	-171.2(3)
C9	C10	C11	O5	54.4(3)

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2A	0.5401	0.3786	0.3164	0.044
H2B	0.3983	0.3952	0.3852	0.044
H4	0.0160	0.2301	0.0226	0.036
H5A	-0.1471	0.1136	0.1225	0.038
H5B	-0.0694	-0.0215	0.0736	0.038
H8A	0.6777	0.0760	0.4850	0.057
H8B	0.6964	0.2368	0.5278	0.057
H8C	0.7327	0.1913	0.4017	0.057
H9	0.3031	0.1373	0.0366	0.039
H10A	0.1034	0.0966	-0.1588	0.048
H10B	0.0243	-0.0338	-0.1052	0.048
H11A	0.2170	-0.1235	-0.2037	0.061
H11B	0.3638	-0.0217	-0.1232	0.061
H13A	0.5418	0.0203	0.0622	0.058
H13B	0.6351	-0.1260	0.1076	0.058
H13C	0.5910	-0.0238	0.2059	0.058
H14A	0.2760	-0.2956	0.1627	0.066
H14B	0.4255	-0.2199	0.2680	0.066
H14C	0.4696	-0.3221	0.1697	0.066
H15A	0.0848	0.1967	0.6100	0.067
H15B	0.2514	0.1310	0.5885	0.067
H15C	0.0708	0.0581	0.5274	0.067

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