The Development of a Convergent and Efficient Enantioselective Synthesis of the Bengamides *via* a Common Polyol Intermediate

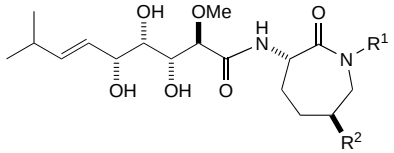
by **Robert K. Boeckman Jr.***, **Tammy J. Clark**, and **Brian C. Shook**

Department of Chemistry, University of Rochester, Rochester, New York, 14627-0216
(phone: +1(585)275-4229; fax: +1(585)756-0210; e-mail: rkb@rkbmac.chem.rochester.edu)

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

An efficient, general synthetic route to the bengamide family of antitumor agents from a common polyol thioester is described. Consecutive aldol condensations afford the protected polyol thioester side chain suitable for coupling to the bengamides. A novel chiral-phase-transfer-catalyzed enantioselective alkylation affords the properly functionalized caprolactams required for the synthesis of more-complex members of the bengamide family. Use of the methyl 2-naphthyl ether protecting group, compatible with the boron *Lewis* acids required for enantioselective aldol condensation, allows direct access to all the bengamides.

1. Introduction. – Marine organisms have proven rich sources of novel, small-to-medium-size organic molecules [1]. Natural products of marine origin possess a broad array of biological activities, many of which are unique relative to materials isolated from terrestrial organisms, including plant, animal, and microbial sources [1]. Particularly noteworthy is a structurally diverse array of substances exhibiting antitumor activity, including, to name a few, bryostatin 1, halichonrin B, discodermolide, and the bengamides [1]. Some of these substances possess macrocyclic rings with complex functional arrays capable of binding to cellular proteins and interfering with critical processes, such as mitosis. Even acyclic structures, *e.g.*, discodermolide and the bengamides, a family of *N*-acyl-α-aminocaprolactams derived from a common polyol acid (certain representatives bearing an additional OH group esterified with a fatty acid), are also capable of interfering with mitosis [2][3].



1 R^1 = Me, R^2 = $O_2C(CH_2)_{12}Me$
2 R^1 = CH_3, R^2 = OH
3 R^1 = H, R^2 = H

Some 24 natural bengamides have now been isolated, principally from *Jaspis* sponges found in coral reefs near the Fiji Islands and Australia, and their preliminary biological activites have been reported [3][4]. Among this group, bengamide B (**1**) exhibits a unique profile in the *NCI* (*National Cancer Institute*) panel of 60 cell lines

compared to standard antitumor agents, arresting growth at both G1/S and G2/M restriction points [2]. The antiproliferative activity of a number of the natural bengamides and synthetic analogues have now been carefully evaluated and compared to standard antiproliferative agents [3][5]. Several bengamides display activities with IC_{50} values for *in vitro* growth inhibition of 10–100 nM, bengamide B (**1**) appearing the most promising of this group [3][5]. Notably, bengamides bearing myristate esters on the caprolactam subunit are >100 times more potent *in vitro* than, *e.g.*, bengamide Z (**2**). This difference probably arises from the poor cellular uptake of **2**, since it has been demonstrated that **1** is converted to **2** intracellularly, which may suggest that the latter is the agent actually responsible for the antiproliferative effects [2][3][5]. Recent work has been reported toward identification of the biological target(s) of the bengamides [6]. Furthermore, an analogue of bengamide B (**1**) is currently undergoing clinical trials as a therapeutic agent against drug-resistant solid tumors [7].

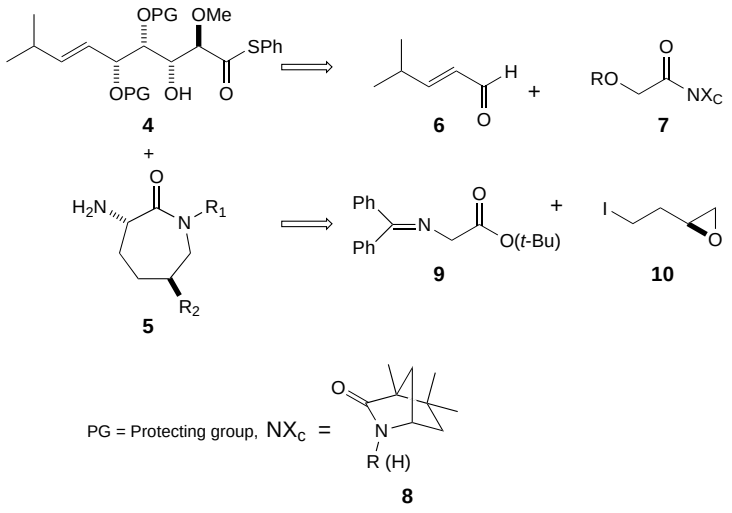
The continuing interest in bengamide analogues as clinical candidates for cancer chemotherapy has led to a substantial amount of effort being devoted to the development of methods for their synthesis. A number of total syntheses of the bengamides have been reported, especially of the structurally fairly simple bengamide E (**3**) [8]. These studies are based on methods for the assembly of the polyol acid side-chain common to all the bengamides. Several interesting approaches based on carbohydrates and other starting materials from the chiral pool have been recorded, along with novel approaches by methods for acyclic stereocontrol. Among the most efficient of these routes, those reported by *Mukai et al.* require a lengthy route from tartaric acid or optical resolution leading to enantiomerically enriched bengamide E [9], while that of *Marshall* and *Luke* requires the construction of an enantiomerically pure allylstannane *via* an asymmetric reduction and subsequent condensation with a derivative of (*R*)-glyceraldehyde [10].

Two of the three existing syntheses of bengamide B (**2**) are quite lengthy [11]. The most efficient route to date is that reported recently by *Kinder et al.*, which employs a sensitive carbohydrate-derived γ-lactone aldehyde from which the required olefin is elaborated in modest yield by a *Takai* olefination [12]. This route is especially efficient, since coupling to the amino caprolactam subunit can be accomplished directly with the γ-lactone playing the active ester component. Most prior syntheses had taken advantage of standard peptide-bond-forming methods that require multiple steps or amination of esters with dimethylaluminum amides [11][12].

2. Results and Discussion. – Herein, we report a full account of our studies towards the development of an efficient, enantioselective, general route to the bengamide family of polyol amides [13]. Since all the bengamides share a common polyol acid, we sought to develop a single short sequence to access the major structural subtypes of the bengamides, which differ only in the nature of the lactam coupling partner. In common with all of the previous syntheses, our retrosynthesis begins by disconnecting the side chain **4** and caprolactam **5** subunits (*Scheme 1*). Construction of the polyol side chain was envisaged through an initial *syn* asymmetric aldol reaction starting from (*E*)-4-methylpent-2-enal (**6**) and the α-functionalized acetimide **7**, bearing the chiral auxiliary **8** (4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one) derived from camphoric acid [14], followed by either an asymmetric acylation/reduction sequence or an *anti* aldol

reaction. Surprisingly, none of the previous syntheses involved the readily available synthon **6** as a potential starting material, except for that of *Marshall* and *Luke* who employed it for the construction of their enantiomerically enriched allyl stannane unit [10]. The α-amino ε-caprolactam present in bengamide E is commercially available, however, the functionalized caprolactams present in, *e.g.*, bengamides B and Z had to be synthesized. Installation of the two stereogenic C-atoms of **5** was envisioned *via* an enantioselective alkylation of **9** with the functionalized oxirane **10**. An alternative synthesis of the caprolactam moiety **5**, starting from hydroxylysine, was recently reported [12].

Scheme 1

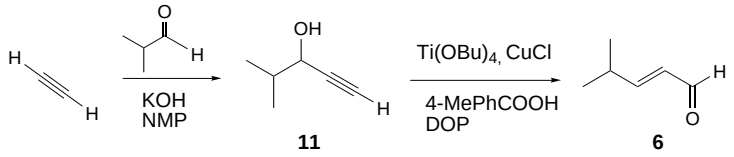


2.1. *Synthesis of the Polyol Side Chain*. Because the aldehyde **6** is commercially available only in small quantities and since we required access to larger amounts of this material, we developed an economical and efficient large-scale synthesis of this compound (*Scheme 2*). Condensation of isobutyraldehyde with an excess of acetylene in *N*-methylpyrrolidinone (NMP)[1]) in the presence of KOH according to *Chodkiewicz* [15] afforded the propargyl alcohol **11** in 81% yield. Rearrangement of **11** at 140° in dioctyl phthalate (DOP), by means of a catalytic system based on Ti^{IV} and Cu^{I} originally described by *Chabardes* [16], provided **6** in 86% yield in an (*E*)/(*Z*) ratio of $> 98:2$ (*Scheme 2*). A variety of high-boiling solvents could be used, but DOP facilitates the isolation of **6** by fractional distillation at reduced pressure. The residual mixture (containing the catalyst) could be repeatedly re-used by recharging with alcohol **11**, which makes the process amenable to the development of a continuous process.

We initially investigated the use of a 4-methoxybenzyl (PMB) ether for the protection of the OH group in **7**. However, preliminary experiments demonstrated that PMB ethers are too labile under the conditions of the boron aldol reaction. Thus, we chose the more robust benzyl (Bn) ether as the protecting group. Our preparation of

[1]) For abbreviations, see *Exper. Part.*

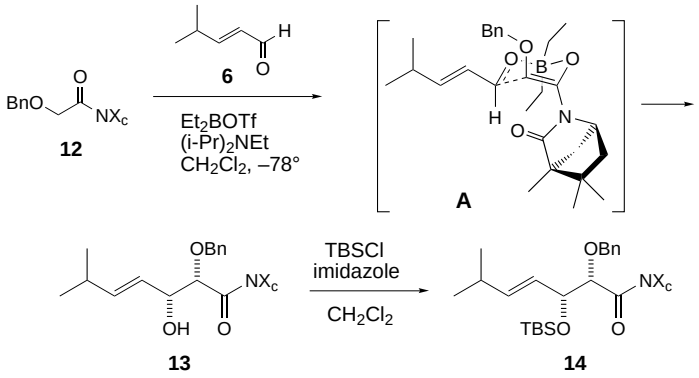
Scheme 2



For abbreviations, see text and *Exper. Part*

the required polyol sidechain **4** began with acylation of the Li salt of **8** [14] (prepared by treatment of **8** with BuLi) with benzyloxyacetyl chloride at $-78° \rightarrow 0°$ to give the desired imide **12** in 89% yield (*Scheme 3*). The latter was treated with Et_2BOTf (Tf = trifluoromethylsulfonyl) in the presence of $(i\text{-}Pr)_2NEt$ at $-78°$ in CH_2Cl_2 under standard conditions. This furnished the (*Z*)-configured boron enolate, which was condensed with **6** *via* the chair-like six-membered transition state **A** to afford the desired *syn* aldol product **13** in a diastereoisomer ratio (dr) $>24:1$ [14]. Without purification, **13** was immediately silylated with (*t*-Bu)Me_2SiCl (TBSCl) under standard conditions, providing **14** in 80% overall yield from **12**.

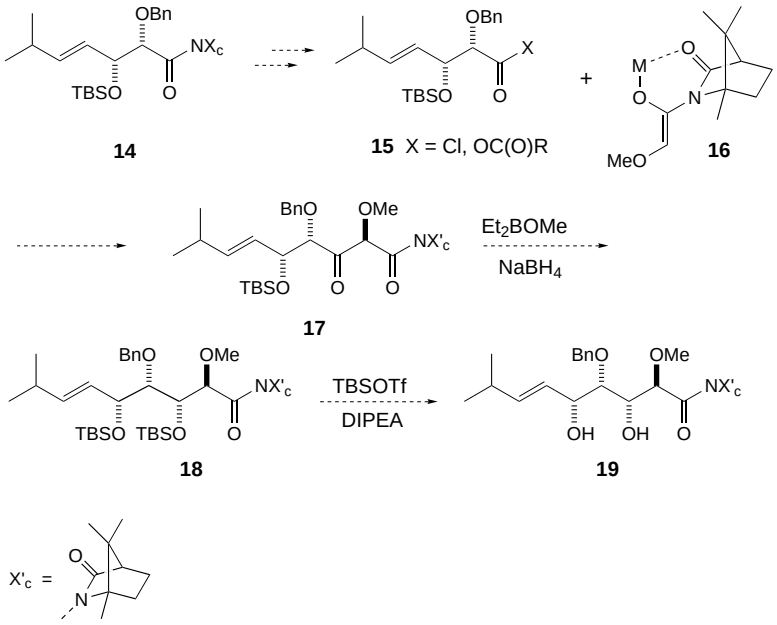
Scheme 3



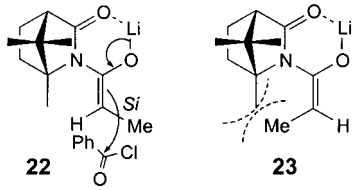
The *syn* configuration of the aldol adduct **13** arises from control over rotamer population about the enolate C–N bond in the transition state **A**. Calculations of possible transition-state structures employing low-order semi-empirical molecular-orbital theory were consistant with the observed stereochemical outcome. The lowest-energy transition-state structure had the B–O bond of the enolate *anti* to that of the lactam C=O group, thereby minimizing dipole interactions, with subsequent approach of the aldehyde to the sterically less-encumbered face of the enolate, *i.e.*, *syn* to the CH_2 bridge, affording the (2*S*,3*R*)-diastereoisomer in very high stereoselectivity [13][17]. The steric bulk and rigidity of the camphor-derived auxiliary **8** and the aforementioned dipole/dipole interactions result in a highly organized transition state with excellent control over bond-rotamer populations.

According to our original concept (*Scheme 4*) for the creation of the 2,3-*anti*-3,4-*syn* stereotriad present in **4**, we sought to employ an auxiliary-directed asymmetric acylation followed by a chelation-controlled reduction. Conversion of the *syn*-adduct **14** to the corresponding acyl halide or mixed anhydride **15** followed by reaction with the enolate **16** was expected to afford the β-keto imide **17**, which could be transformed to the desired polyol sidechain **19** by two additional steps. Before committing major effort to this route, we decided to first look at a model system.

Scheme 4



Camphor-derived auxiliaries are effective chiral controllers, as seen in the boron-mediated *syn* aldol reaction **12** → **13**. Selective formation of the (*Z*)-enolate **16** by deprotonation and metallation of **20**, was anticipated based on our prior studies regarding the alkylation of glycolates [18]. The (*Z*)-enolate **22** is favored kinetically over the corresponding (*E*)-enolate **23** owing to 'allylic strain' in the latter. Electrophiles approach the less-hindered α-face (*Si*-face) of the enolate, avoiding C(7) with its two Me groups (see *Figure*) [18].



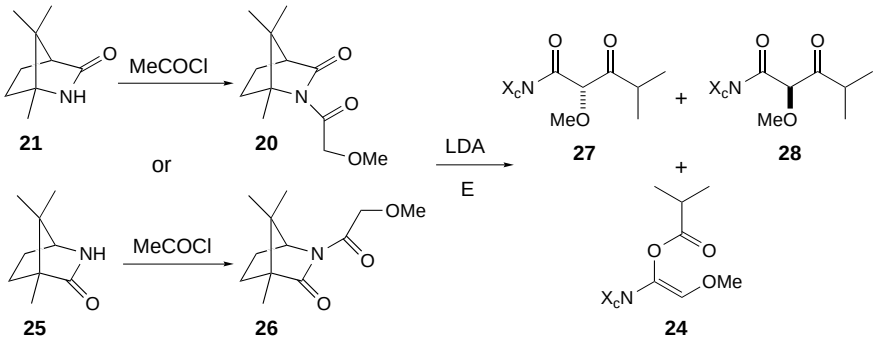
Figure

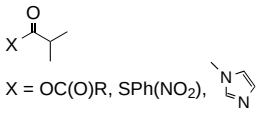
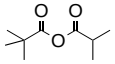
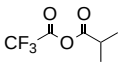
We chose (1*R*,4*S*)-2-(2-methoxyacetyl)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**20**) as a model for asymmetric acylation (*Table*). Initial attempts with pivaloyl chloride resulted in exclusive *O*-acylation and formation of the enol ester **24** in 87% yield (*Table*, *Entry 1*). Often, with less-reactive electrophiles, *C*-acylation is favored over *O*-acylation (matching the softness of the enolate). However, when a thioester was used at $-78°$, the starting material was recovered (*Table*, *Entry 2*). Upon warming to $-30°$, **20** decomposed to **21** *via* ketene formation. Keeping the temperature below $-40°$ was, therefore, essential to avoid decomposition. We next explored various other acyl electrophiles like activated thioesters [19], acyl imidazolides, and mixed anhydrides (*Table*, *Entry 4*), however, each of these experiments resulted in the recovery of the starting material. Changing the counterion from Li to Na did not improve the reactivity, in contrast to alkylation [18], suggesting that the Me group adjacent to the N-atom of **20** is, perhaps, bulky enough to hinder the approach of electrophiles.

Next, we tested the isomeric camphor-derived auxiliary **25**, where the Me group is adjacent to the C=O rather than to the N-atom. Reaction of **26** with electrophiles led to a more-reactive (*Z*)-enolate, resulting in a 3:2 mixture of *C*- *versus* *O*-acylation. However, no stereoselectivity was observed under these conditions, and the two *C*-acylation products **27** and **28** were formed in equal amounts (*Table*, *Entry 5*). When one equiv. of Et_2Zn was added prior to the acid chloride to, hopefully, create a more-covalent enolate –O bond, stereoselectivity increased to 3:1, but, surprisingly, the regioselectivity decreased, resulting in a 3:2 ratio in favor of *O*-acylation, which could be the result of facile ligand exchange in the ate complex (*Table*, *Entry 6*). It is known that Li enolate aggregation is favored in nonpolar solvents [21]. We, therefore, conducted the reaction in a 6:1 mixture of toluene/THF. Use of the less-polar medium had a dramatic effect on the product ratio. In toluene/THF, nearly exclusive *C*-acylation was observed. A concommitant increase in stereoselectivity with a ratio of **27**/**28** to 4:1 (*Table*, *Entry 7*) also occurred. Presumably, aggregation effectively blocks the enolate O-atom, resulting in a highly regioselective reaction. Various mixed anhydrides gave similar results when toluene was used as the solvent (*Table*, *Entries 8* and *9*). Although we were able to obtain the desired *C*-acylation products **27** and **28** with moderate stereoinduction, the dr could not be further increased.

We then chose to explore the even more direct *anti* aldol route (*Scheme 5*). Beginning with **14**, cleavage of the auxiliary NX_c group with EtSLi at $-40°$ provided the corresponding thioester **29** (95%) along with recovered **8** (93%). Compound **29** was selectively reduced at $-78°$ with $(i\text{-}Bu)_2AlH$ (DIBAL) to afford a mixture of the monothiohemiacetal **30** and the desired aldehyde **31**. No overreduction of **30** was observed, not even in the presence of excess DIBAL. More surprisingly, **30** was sufficiently stable to partly survive aqueous workup and chromatography. The origin of this phenomenon lies in the tendency of aldehydes bearing electron-withdrawing α-substituents to exist as stable hydrates. Fortunately, conversion of **30** to the required aldehyde **31** was conveniently achieved by briefly warming the mixture to 85° at *ca.* 20 torr on a rotary evaporator. The resulting, somewhat sensitive aldehyde **31** was then immediately subjected to a variant of the chelation-controlled *Gennari–Mukaiyama* aldol reaction with the phenylthioketene acetal **32** [22], which can be obtained as *ca.* 10:1 mixture of the corresponding (*E*)- and (*Z*)-isomers by treatment of *S*-phenyl 2-

Table

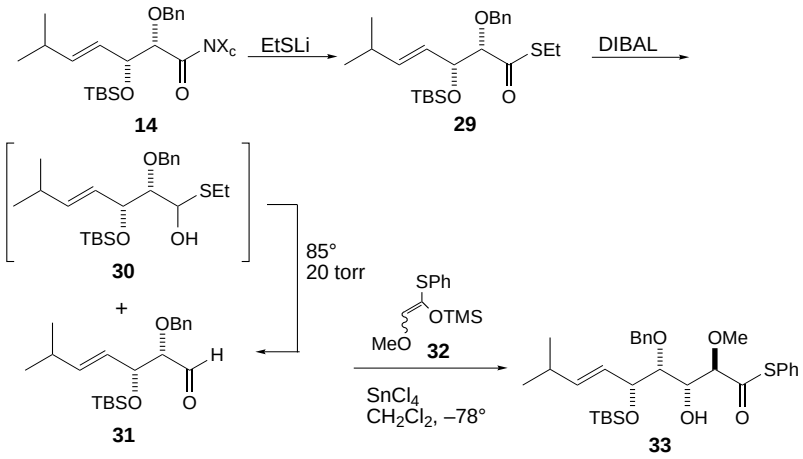


Entry	Imide	Electrophile (E)	Solvent(s)/Additives	*T* [°]	Product Ratio[a]) **27**/**28**/**24**	Yield [%]
1	**20**		THF	– 78	0 : 0 : 100	87
2	**20**		THF	– 78	no reaction	–
3	**20**		THF	– 30	enolate decomposition to **21**	–
4	**20**	 X = OC(O)R, SPh(NO_2),	THF	– 60	no reaction	–
5	**26**		THF	– 78	30 : 30 : 40	90
6	**26**		THF/Et_2Zn	– 78	33 : 11 : 56	88
7	**26**		THF : $PhCH_3$ (1 : 6)	– 78	77 : 19 : 4	94
8	**26**		$PhCH_3$	– 45	71 : 29 : 0	94
9	**26**		$PhCH_3$	– 45	77 : 23 : 0	77

[a]) The abs. configurations of **27** and **28** were determined by chelation-controlled $ZnBH_4$ reduction and esterification to *syn*-oriented methyl 3-hydroxy-2-methoxy-4-methylpentanoate followed by chemical correlation [20].

methoxythioacetate with Me_3SiOTf and Et_3N [23][24]. The (*E*)/(*Z*) ratio of **32** is somewhat variable. However, fortunately, the stereoselectivity of the aldol condensation with **31** is independent of the isomer ratio of **32** [22]. Addition of **31** at $-78°$ to the preformed Sn^{IV} enolate (prepared by treatment of freshly distilled **32** in CH_2Cl_2 with a 1.0M solution of $SnCl_4$ in heptane for 40 min and followed by stirring at $-78°$ for 4 h) afforded, after workup and purification, the desired 2,3-*anti*-3,4-*syn* aldol product **33** in 73% yield with a dr of 11.5:1.

Scheme 5

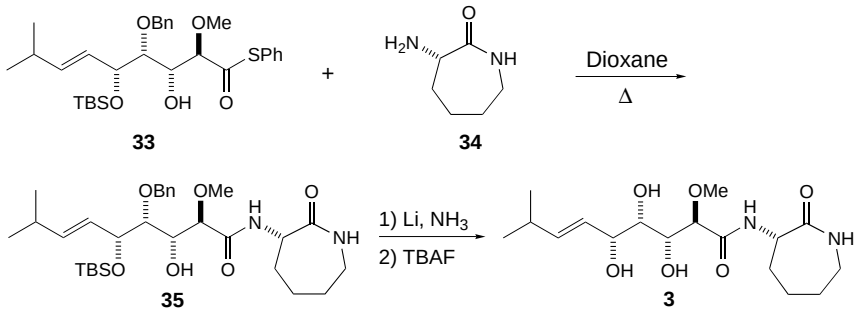


It is important to note that similar condensations reported by *Mukai et al.* [9], who used the related *S*-(*tert*-butyl) hemithioacetal, afforded significantly lower dr values of *ca.* 7:1. We, by the way, observed this phenomenon in the *Gennari–Mukaiyama* aldol reaction performed with a variety of chiral aldehydes.

Verification of both the relative and absolute configuration of the polyol sidechain was easily accomplished by conversion to (+)-bengamide E (**3**, 3-aminohexahydrobenzazepin-3-one). Treatment of **33** with the commercially available (−)-α-amino-ε-caprolactam **34** in dioxane at reflux provided **35** in 98% yield (*Scheme 6*). Conversion to **3** was then accomplished by cleavage of the benzyl ether with Li/NH_3 under *Birch* conditions followed by cleavage of the silyl ether with tetrabutylammonium fluoride (TBAF) in THF, affording pure (+)-bengamide E (**3**) in 67% overall yield for both steps. Synthetic (+)-bengamide E was identical in all respects to an authentic natural sample [12].

2.2. *Synthesis of the Substituted ε-Caprolactam Subunits.* Having confirmed the relative and absolute configuration of the key intermediate **33**, we then turned our attention to the development of a general route to the functionalized α-amino-ε-caprolactam units present in the more-complex bengamides B (**1**) and Z (**2**). Several routes to these intermediates have been described, but none are ideal [11][12]. The most practical to date is that of *Kinder et al.* [12], which affords the required lactam(s) in seven steps starting from commercial, albeit expensive, (5*R*)-5-hydroxy-L-lysine. We sought to develop a route that could be readily adapted to the synthesis of all naturally

Scheme 6

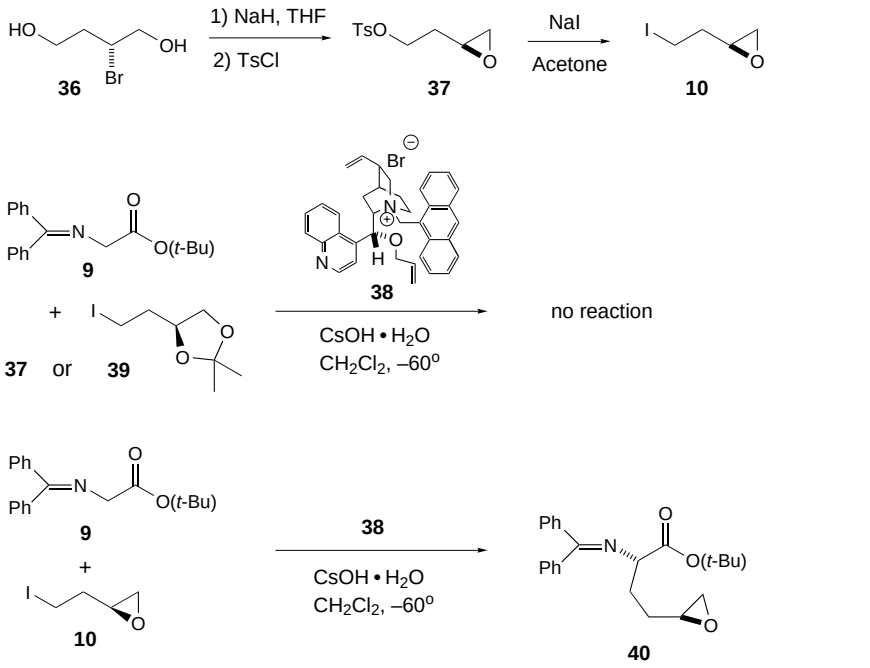


occurring lactam subunits (and synthetic analogues thereof) from a common reaction sequence. We chose to disconnect the caprolactam to the commercial iminoglycine ester **9** and the chiral epoxide **10** (Scheme 1) and to control the sense of asymmetry at the α-amino acid center by using an appropriate chiral phase-transfer catalyst (PTC) and either of the enantiomers of **10**. This should, in principle, allow one to access all four diastereoisomers of **5** with or without an alkyl group at the lactam N-atom. *Corey et al.* described a useful cinchonidine-derived catalyst for this purpose [25]. However, the use of only a few bifunctional electrophiles, such as 1-chloro-4-iodobutane, has been described in this context [26].

The epoxide **10** is obtained from (2*R*)-2-bromobutane-1,4-diol (**36**), which is readily available in two steps and 70% overall yield from D-aspartic acid (*Scheme 7*) [27]. Treatment of **36** with excess NaH in THF followed by *in situ* tosylation afforded **37** in 89% yield. The OTs function of **37** was replaced then by a iodo group under standard *Finkelstein* conditions, providing **10** in 93% yield.

With **10** in our hands, we then examined the key asymmetric alkylation of **9** by means of PTC. The key step consists of treating **9** with an appropriate bifunctional electrophile and $CsOH \cdot H_2O$ in the presence of 10 mol-% of the 9-anthracenylmethyl-substituted cinchonidinium bromide derivative **38** in CH_2Cl_2 at $-60°$ [25][26]. We initially examined the coupling with **39**, however, surprisingly, both **39** and **37** were unreactive. Fortunately, the iodoethyloxirane **10** reacted smoothly under the above conditions to afford the desired ester **40**. Essential for this transformation was to finely pulverize $CsOH \cdot H_2O$ under Ar gas and to use an efficient overhead stirrer to achieve acceptable reaction rates. Under near-optimal conditions, we found that **9** undergoes complete conversion to **40** in the presence of as little as 1.3 equiv. of the substrate **10**, 5 equiv. of finely powdered $CsOH \cdot H_2O$, and 10 mol-% of the phase-transfer catalyst **38** in CH_2Cl_2 at $-60°$ for 18 h, **40** being formed in 83% yield as a single diastereoisomer (dr $>96\%$ according to 400 MHz ^{1}H-NMR analysis). After aqueous workup, the residual epoxide **10** was removed *in vacuo* with a *Kugelrohr* apparatus. The chiral catalyst was recovered from the aqueous phase (as the chloride salt) by extraction with CH_2Cl_2 (85%) and re-used. Compound **40**, which proved unstable to chromatography, did not require further purification and was used as obtained. This application of the *Corey* phase-transfer alkylation constitutes a significant extension of the scope of this

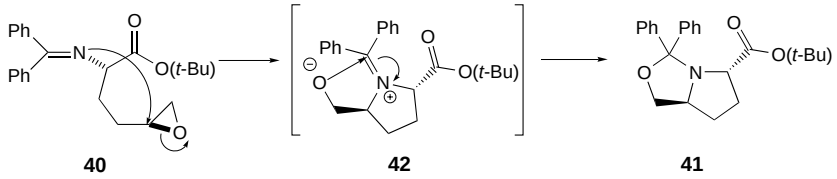
Scheme 7



methodology and highlights its versatility and potential with respect to other bifunctional electrophiles.

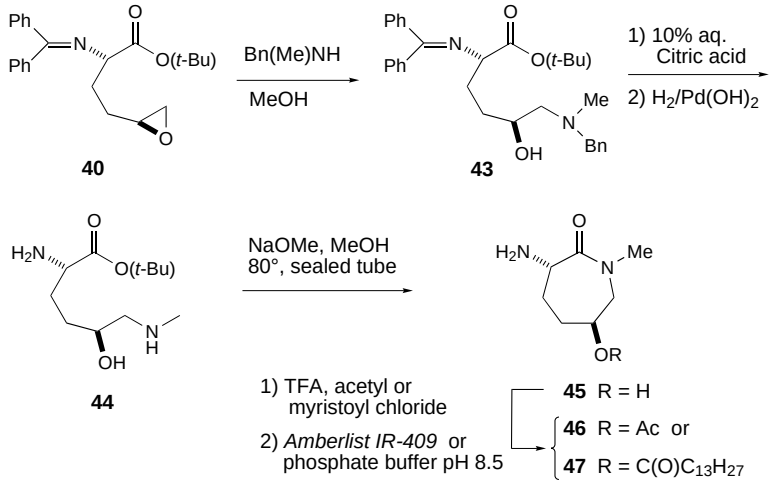
The introduction of a terminal N-function by nucleophilic cleavage of the oxirane ring in **40** was not expected to be problematic. Unfortunately, primary amines, including methanolic $MeNH_2$, were insufficiently nucleophilic to this end. Also, the use of even very mild *Lewis* acids to activate the oxirane resulted in the bicyclic proline ester **41**, presumably by cyclization of the iminium ion **42** (*Scheme 8*).

Scheme 8



We overcame this limitation by using more-nucleophilic *secondary* amines. Treatment of **40** with *N*-benzyl-*N*-methylamine (8 equiv.) in MeOH at room temperature for 13 h provided **43** in 98% yield (*Scheme 9*). Hydrolysis of the imino function of **43** was effected with 10% aqueous citric acid/THF 1:1 [28], and debenzylation by hydrogenation (1 atm) over 5 mol-% of *Pearlman*'s catalyst in EtOH [29], affording **44** in 86% overall yield. Treatment of **44** with MeONa in MeOH at 85° (sealed tube)

Scheme 9

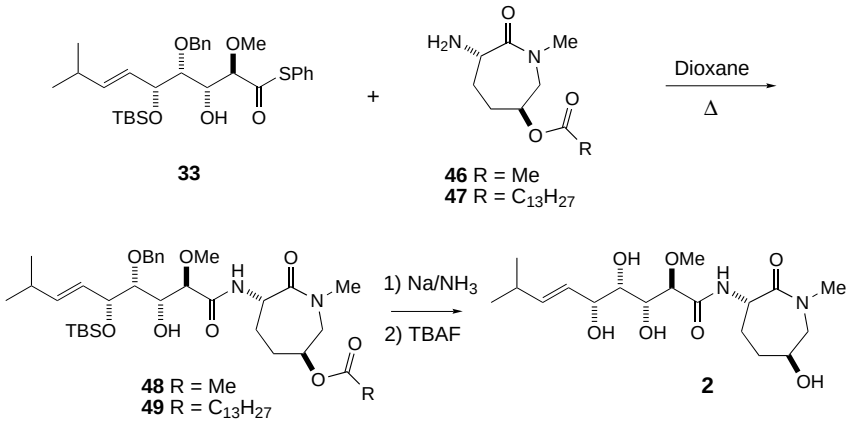


provided the desired caprolactam **45**, presumably *via* initial intramolecular cyclization to the corresponding six-membered lactone followed by ring expansion (O → N acyl migration) *via* a bicyclic ortho amide intermediate [30][31]. The resulting hydroxy lactam **45** was selectively *O*-acylated by treatment with either acetyl or myristoyl chloride in the presence of excess trifluoroacetic acid (TFA) as solvent, affording the key lactam subunits **46** and **47** after liberation of the free base by treatment with *Amberlyst IR-400* resin or pH 8.5 phosphate buffer [32]. The selective *O*-acylation was achieved by irreversible protonation of the α-amino group in the strongly acidic medium [32].

The synthetic route presented to the lactam subunits **46** and **47** features several noteworthy elements: *1*) complete stereoselectivity and high overall yield, requiring purification at only three stages (**37**, **43**, and **46** or **47**); *2*) the possibility for structural variation at several stages, *e.g.*, through the use of different bifunctional electrophiles (instead of **10**) or alkyl groups on the lactam N-atom and the acyl group on the secondary alcohol; and *3*) the economy of our method, which is based on inexpensive starting materials and reagents.

2.3. *Synthesis of (+)-Bengamide Z* (**2**). Another attractive feature of the above sequence is the possibility to directly use the side-chain synthon, the phenyl thioester **33** in the fragment coupling with the lactams **46** or **47** without further activation. Only the route developed by *Kinder et al.* is also based on direct coupling by cleavage of a γ-lactone [12]. To prevent side reactions upon condensing **33** with the unprotected caprolactam **45**, the corresponding acetate **46** was used instead. Condensation of **33** and **46** (1.05 equiv.) in refluxing dioxane afforded the desired coupled product **48** in 94% yield (*Scheme 10*). Deblocking was then conducted in two steps. First, **48** was reduced with Na/NH_3, resulting in concommitant removal of both the benzyl and the acetate groups, the latter presumably by aminolysis, affording the corresponding silyl-protected intermediate in 73% yield. Second, without purification, desilylation with Bu_4NF

Scheme 10



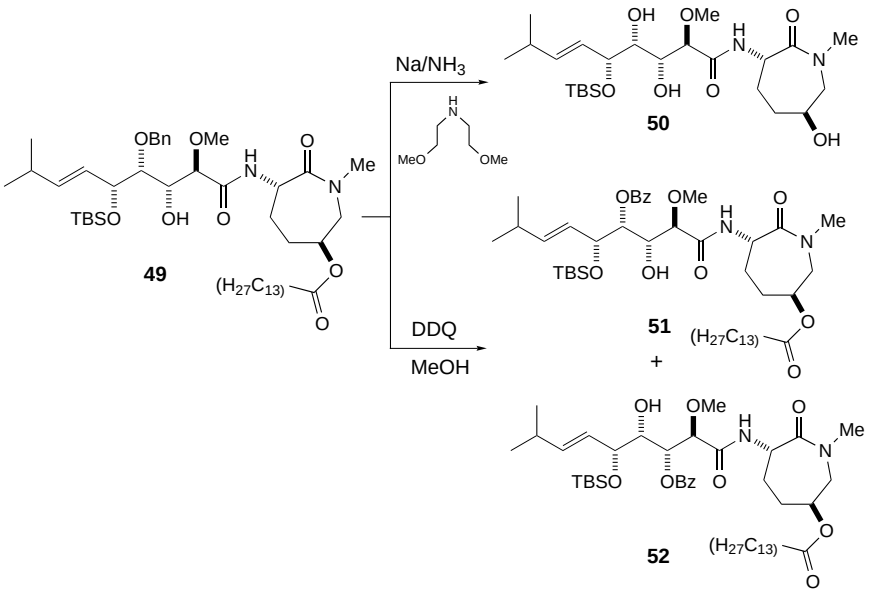
(TBAF) afforded (+)-bengamide Z (**2**) in 74% yield. This compound was identical in all respects to natural (+)-bengamide Z [12].

2.4. *Synthesis of (+)-Bengamide B* (**1**). The coupling of **33** with **47** (1.05 equiv.) in refluxing dioxane was highly efficient, affording **49**, a protected bengamide B derivative, in 98% yield. Regrettably, in spite of considerable effort, the selective removal of the benzyl ether in the presence of the myristoyl ester could be effected under neither reductive nor oxidative conditions. For example, with diethanolamine as a sodium amide scavenger during Na/NH_3 reduction, cleavage was successful for branched esters but failed for the less-hindered myristoyl ester, affording **50** (*Scheme 11*). Also, attempts at selective re-esterification of **50** were, surprisingly, not successful [3][5][12]. Attempts to remove the benzyl group in **49** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) resulted in a mixture of the regioisomeric benzoates **51** and **52**, respectively, largely independent of the amount of DDQ employed. This result can be explained by a more-rapid oxidation of the hemiacetal intermediate than oxidation of the starting benzyl ether or hydrolysis of the hemiacetal to the desired alcohol. Unfortunately, selective cleavage of the benzoyl group in **51** and **52** in the presence of the myristoyl ester also proved unfeasible, as expected based upon a literature precedent [33].

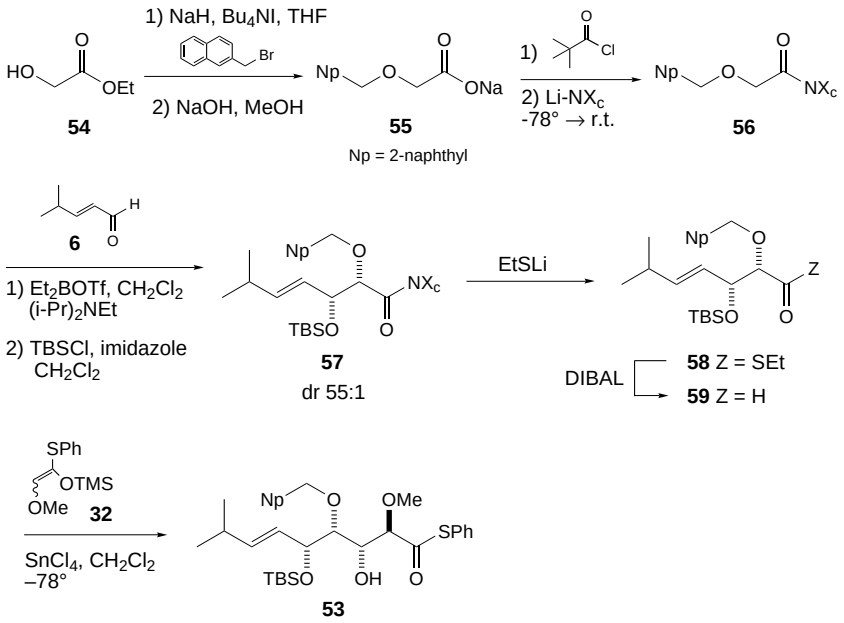
These disappointing results led us to consider using a more labile OH protecting group, namely the *para*-methoxybenzyl (PMB) function. However, based on preliminary experiments, PMB ethers are not stable to the *Lewis* acid conditions of the boron-enolate aldol reaction. A careful evaluation of the options uncovered during a literature survey led us to select the 2-naphthylmethyl ether protecting group [34], since it is stable to *Lewis* acids (particularly in the α-position of a C=O group) and can be readily removed under mild oxidative conditions, *e.g.*, DDQ in aqueous MeOH [34].

The key-2-naphthylmethyl-protected phenyl thioester **53** was prepared in analogous fashion to **33** (*Scheme 12*). The chiral imide **56** was prepared from ethyl glycolate (**54**) in three steps. Treatment of **54** with NaH and 2-(bromomethyl)naphthaline in the presence of a catalytic amount of Bu_4NI afforded the corresponding ether in 80% yield.

Scheme 11



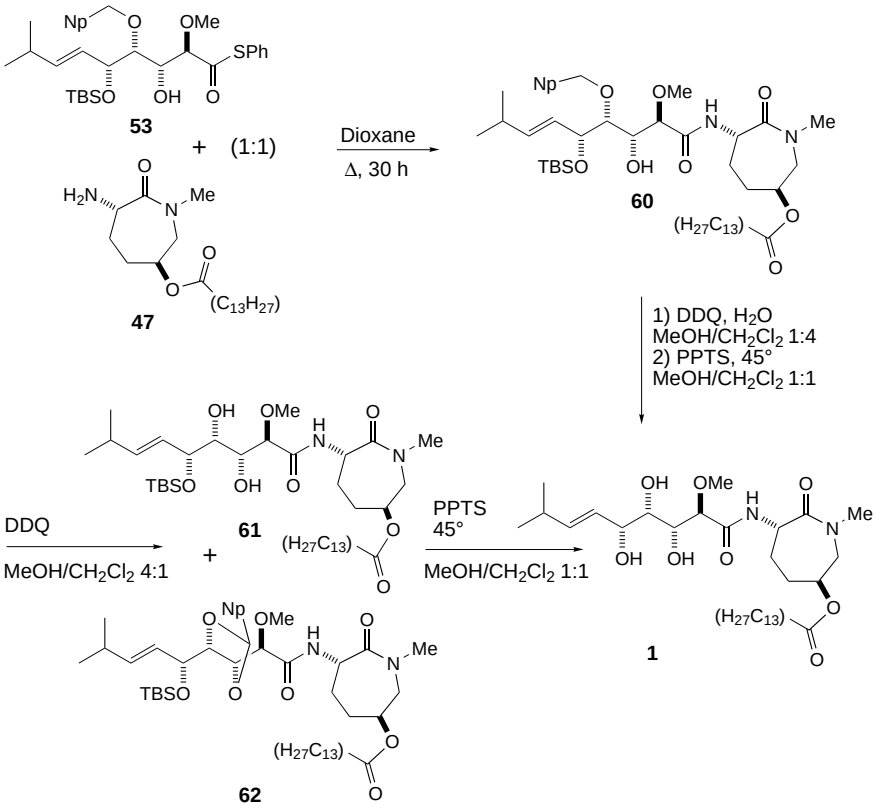
Scheme 12



Exposure of this material to NaOH in anhydrous MeOH led to the solid Na salt **55** in 97% yield, which was activated with pivaloyl chloride in THF and reacted with the *N*-Li salt of **8** to afford **56** in 71% yield (55% for three steps, unoptimized). We were pleased

to observe that generation of the Z-configured boron enolate from **56** upon exposure to Et_2BOTf and $(i\text{-}Pr)_2NEt$ proceeded smoothly with no evidence of cleavage of the naphthylmethyl protecting group. Condensation with the unsaturated aldehyde **6** afforded the expected β-hydroxy imide, which was *in situ* protected as the TBS ether by treatment with $(t\text{-}Bu)Me_2SiCl$ and imidazole to afford the protected *syn*-product **57** in 75% overall yield (dr 55 : 1). The bulkier 2-naphthylmethyl group apparently enhances the stereoselectivity of the aldol reaction compared to the benzyl group. The chiral auxiliary of **57** was then cleaved with EtSLi to the intermediate thioester **58**, which was directly reduced with DIBAL to the sensitive aldehyde **59** in 91% overall yield. Finally, **59** was treated with the preformed Sn^{IV} enolate derived from **32** to give predominantly the expected *anti*-configured aldol product **53** (dr $>8:1$) in 62% yield (unoptimized). As expected, coupling of an equimolar mixture of **56** and **47** in dioxane afforded the corresponding amide **60** in 69% yield (*Scheme 13*).

Scheme 13



Unlike benzyl ethers, 2-naphthylmethyl ethers are readily oxidized by DDQ [33][34]. Thus, we were very pleased to find that treatment of **60** with DDQ in aqueous $MeOH/CH_2Cl_2$ 4 : 1 produced a 1 : 1 mixture of the dihydroxy compound **61** and the corresponding acetal **62**. The latter arises from trapping of the intermediate oxonium

ion by the proximal OH group (*Scheme 13*). Upon use of higher ratios of MeOH/CH_2Cl_2 or more H_2O, the reaction rate decreased without affecting the product ratio. When the reaction was performed in MeCN, acetal **62** was obtained exclusively in 79% yield. Fortunately, treatment of the above mixture with 5 equiv. of pyridinium toluene-4-sulfonate (PPTS) in MeOH/CH_2Cl_2 1:1 at 45° cleaved both the acetal and the silyl ether, affording (+)-bengamide B (**1**) in 76% overall yield. Indeed, subsequent experiments demonstrated that both steps could be conducted in one pot. Thus, treatment of **60** with DDQ in CH_2Cl_2/MeOH 4:1 for 2 h, followed by adjustment to CH_2Cl_2/MeOH 1:1, addition of PPTS (5 equiv.), and heating to 45° for 10 h, afforded (+)-bengamide B (**1**) in 89% yield.

3. Conclusions. – The efforts described herein have resulted in the development of a highly efficient and flexible synthetic route to the bengamide family of marine polyol amide antiproliferative agents. The optimal sequence affords enantiomerically pure (+)-bengamide B (**1**) from D-aspartic acid and 4-methylpent-2-enal (**6**), with a longest linear sequence of 12 steps (18 total steps). The same basic route affords bengamide Z (**2**) with a longest linear sequence of 13 steps (19 total steps) from the same starting materials, and also bengamide E (**3**) in 9 steps.

We thank Dr. *Kenneth W. Bair*, Dr. *Frederick R. Kinder*, and *Richard W. Versace* for their assistance and the *Novartis Institute for Biomedical Research* and the *NIH* (GM-30345) for generous financial support.

Experimental Part

General. – Abbreviations: Bn: benzyl (= phenylmethyl), Bz: benzoyl (= phenylcarbonyl), DDQ: 2,3-dichloro-4,5-dicyanobenzo-1,4-quinone, DIBAL: diisobutylaluminium hydride, DIPEA: diisopropylethylamine, DMF: dimethylformamide, DOP: dioctylphthalate, dr: diastereoisomer ratio, HMPA: hexamethylphosphortriamide, HPLC: high-performance liquid chromatography, LDA: lithium diisopropylamide, LHMDS: lithium hexamethyldisilazane, NMP: *N*-methylpyrrolidinone, NP: 2-naphthyl, NX_c: 4,5,5-trimethyl-3-oxo-2-azabicyclo[2.2.1]heptan-2-yl (chiral auxiliary 1), NX_c': 1,7,7-trimethyl-3-oxo-2-azabicyclo[2.2.1]heptan-2-yl (chiral auxiliary 2), PMB: 4-methoxybenzyl, PPTS: pyridinium toluene-4-sulfonate, PTC: phase-transfer catalysis, TBAF: tetrabutylammonium fluoride, TBS: (*tert*-butyl)dimethylsilyl, Tf: trifluoromethanesulfonyl, THF: tetrahydrofuran, TMS: trimethylsilyl, Ts: tosyl (=(4-methylphenyl)sulfonyl).

All reactions performed in org. solvents were conducted in flame-dried glassware under Ar gas atmosphere and with magnetic stirring, unless otherwise noted. Air-sensitive reagents and solns. were transferred *via* syringe (unless otherwise noted) and introduced through rubber septa. Solids were introduced under positive pressure of Ar gas. Temp. refer to the heating bath, unless otherwise noted. The term '*in vacuo*' refers to removal of solvents with a *Büchi* rotary evaporator attached to a water aspirator (15–30 Torr) followed by pumping to constant weight (at <1 Torr). Flash chromatography (FC) was performed with the indicated solvent system on *EM Reagents* silica gel *60* (230–400) mesh, or on basic alumina (*Baker*). Analytical thin-layer chromatography (TLC) was performed with glass plates (0.25 mm) precoated with silica gel *60 F-254* (*EM Reagents*). Visualization was effected by either short-wavelength UV, exposure to I_2 vapor, or dipping in the indicated stain followed by heating on a hot plate for *ca.* 10 s. Reagent-grade solvents were used without purification for all extractions and workup procedures. Deionized H_2O was used for all extractions and for preparing aq. solns. Commercial solid reagents were used as received (unless otherwise indicated). Solvents and commercial liquid reagents for reactions were dried and/or purified according to published procedures by distillation: THF and Et_2O from Na/benzophenone ketyl; (i-Pr)$_2$NH, Et_3N, (i-Pr)$_2$EtN, DMF, HMPA, CH_2Cl_2, and toluene from CaH_2. FT-IR Spectra are reported in cm^{-1}, with polystyrene as a standard. ^1H- and ^{13}C-NMR Spectra were recorded at 300 or 400 MHz; chemical shifts δ are reported in ppm downfield relative to Me_4Si (solvent calibration); coupling constants *J* are expressed in Hz. Low- and high-resolution (HR-)mass spectra (MS) are expressed in *m*/*z*.

4-Methylpent-1-yn-3-ol (**11**). A three-necked 250-ml round-bottom flask was equipped with a mechanical stirrer, a septum with outlet to an oil bubbler, and a stopper with a glass tube for addition of acetylene. The flask was charged with powdered KOH (45.7 g, 0.82 mol) and dry NMP (90 ml). The mixture was cooled to $-40°$, stirring was initiated, and scrubbed acetylene (passed through conc. H_2SO_4 and through a drying tube of KOH) was rapidly bubbled into the suspension until saturated. The inlet tube was removed, adequate outlets were provided for relief of pressure, and isobutyraldehyde (18.5 ml, 0.20 mol) was added in one portion. The mixture was allowed to warm to r.t. over 2 h and was quenched by slowly pouring it on ice (175 g). The flask was rinsed with 60 ml of Et_2O. The phases were separated, and the aq. phase was extracted 3 × with 40 ml portions of Et_2O. The combined org. phases were washed successively with 90 ml of H_2O (3 ×) and 120 ml of sat. brine, dried ($MgSO_4$), and carefully concentrated *in vacuo* to afford 17.4 g (87%) of **11** of a colorless oil, which provided spectral data identical to those reported in [15]. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.20 (*m*, 1 H); 2.48 (*d*, $J = 2.3$, 1 H); 1.91 (*sept.*, $J = 5.7$, 1 H); 1.81 (br. *s*, 1 H); 1.03 (*dt*, $J_1 = 7.1$, $J_2 = 2.3$, 6 H).

*(*E*)-4-Methylpent-2-enal* (**6**). A 50 ml round-bottom flask was charged with **11** (16.5 g, 0.168 mol), 3.9 g of *p*-toluic acid (0.0290 mol), 0.33 g of CuCl (0.0034 mol), 0.81 ml of $(BuO)_4Ti$ (0.0023 mol), and 20 ml of dioctyl phthalate (DOP) under Ar. The flask was equipped with a reflux condenser and heated to 150°. The progress of the reaction was monitored by GC[2]), and complete disappearance of **11** was observed after 5 h. The mixture was cooled to r.t. and purified by *Kugelrohr* distillation (100° at 4 torr) to afford 13.4 g (81%) of **6** ($(E)/(Z) > 98:2$). The spectral data were identical to those reported in [35]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.51 (*d*, $J = 7.8$, 1 H); 6.81 (*d*, $J_1 = 15.7$, $J_2 = 6.4$, 1 H); 6.07 (*ddd*, $J_1 = 15.7$, $J_2 = 7.8$, $J_3 = 1.3$, 1 H); 2.60 (*sept.*, $J = 6.7$, 1 H); 1.11 (*d*, $J =$ 6.7, 6 H).

*(1S,4*S*)-4,5,5-Trimethyl-2-{[(phenyl)methoxy]acetyl}-2-azabicyclo[2.2.1]heptan-3-one* (**12**). A soln. of 6.5 g of (*1R,4S*)-2-aza-4,5,5-trimethylbicyclo[2.2.1]heptan-3-one (**8**) [14] (42 mmol) in 60 ml of THF was cooled to $-20°$, and 30.2 ml of a 1.53M soln. of BuLi in hexanes (46 mmol) was added. The mixture was warmed to 0° and stirred for 45 min, then cooled to $-78°$. A soln. of 10.15 g (8.7 ml, 55 mmol) of (benzyloxy)acetyl chloride in 40 ml of THF was added, and the mixture was allowed to warm to $-20°$. After 14 h, the mixture was quenched with 15 ml of sat. aq. NH_4Cl soln. and diluted with 30 ml of AcOEt and 40 ml of H_2O. The phases were separated, and the aq. layer was extracted twice with 30 ml of AcOEt. The combined org. phases were washed successively with 40 ml of H_2O (2 ×), 40 ml of sat. brine, dried ($MgSO_4$), and concentrated to afford a white solid, which was recrystallized from hexanes to provide 11.3 g (89%) of **12**. M.p. 66–68°. $[\alpha]_D^{25} = +6.7$ ($c = 0.70$, CH_2Cl_2). IR (neat): 1743, 1704. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.43–7.28 (*m*, 5 H); 4.71 (*s*, 1 H); 4.69 (*s*, 2 H); 4.58 (*s*, 3 H); 1.91 (*dd*, $J_1 = 10.4$, $J_2 = 0.8$, 1 H); 1.80–1.65 (*m*, 3 H); 1.14 (*s*, 3 H); 1.09 (*s*, 3 H); 0.91 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.1; 169.3; 128.4; 128.1; 127.9; 73.4; 70.5; 57.4; 54.0; 44.7; 42.1; 38.1; 26.3; 25.7; 9.7. HR-MS: 302.1744 ($[M+1]^+$, $C_{18}H_{23}NO_3$; calc. 302.1756).

Diethylboron Trifluoromethanesulfonate. A 50-ml 3-necked round-bottom flask suited for short path distillation (vented by a 3-way stopcock to Ar and aspirator vacuum with drying tube) was charged with 48 ml of a 1.0M soln. of Et_3B (4.71 g, 48 mmol) in hexane, and the contents were cooled to 0°. Dropwise, with stirring, was added 4.1 ml of neat trifluoromethanesulfonic acid (6.90 g, 46 mmol) at 0° over 20 min, and stirring of the resulting orange soln. was continued at 0° for 1 h. The hexane was distilled off at 0°, and the residual diethylboron trifluoromethanesulfonate was purified by distillation at 14 Torr (b.p. 55–60°) [36]. *Caution: this reagent is extremely pyrophoric*. Upon completion of the distillation, the apparatus was carefully vented with Ar, and the product was stored neat in a flask bearing a 3-way *Teflon* stopcock (to allow for removal of material *via* gas-tight syringe under Ar). The compound is stable under Ar for several weeks at $-5°$.

*(1S,4S)-2-{(2*S*,3*R*,4*E*)-3-Hydroxy-6-methyl-2-[(phenyl)methoxy]hept-4-enoyl}-4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**13**). A soln. of 3.8 g of **12** (13 mmol) in 75 ml of CH_2Cl_2 was cooled to $-78°$ and treated with 4.4 ml of DIPEA (3.27 g, 25 mmol). Then, 2.61 ml of diethylboron triflate (2.92 g, 13.4 mmol) was added dropwise[3]). The mixture was warmed to 0° and stirred for 1 h, and then cooled to $-78°$ again. Aldehyde **6** (7.0 g, 62 mmol) was added dropwise, and the mixture was warmed to $-50°$ and stirred for 9 h. The mixture was quenched at $-50°$ by addition of 17 ml of a 3:1 mixture of pH 7 phosphate buffer and MeOH, followed by slow addition of 17 ml of a 3:1 mixture of MeOH and 30% aq. H_2O_2. The biphasic system was warmed to 0° and stirred for 1 h, the phases were separated, and the aq. phase was extracted three times with 15 ml of CH_2Cl_2. The combined org. phases were washed successively with 40 ml each of H_2O and sat. brine, dried ($MgSO_4$), filtered

---

[2]) Parameters: *HP-5*-crosslinked 5% PHME siloxane column; 30 m × 0.32 mm × 0.25 μm film thickness; column pressure: 108 kPa, initial temp.: 50°, initial time: 2 min, rate: 3°/min.; **11**: t_R 3.92 min.; **6**: t_R 4.90 min.

[3]) It is likely that Bu_2BOTf, which is easier to handle, could also be used.

and concentrated to afford 4.3 g (85%) of **13** as a white solid, which was used without further purification. IR (neat): 3477, 2960, 2871, 1744, 1696, 1345. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 (*m*, 5 H); 5.78 (*ddd*, $J_1 = 15.6$, $J_2 = 6.1$, $J_3 = 1.0$, 1 H); 5.55 (*ddd*, $J_1 = 15.6$, $J_2 = 6.3$, $J_3 = 1.4$, 1 H); 4.95 (*d*, $J = 3.4$, 1 H); 4.70 (*d*, $J = 11.8$, 1 H); 4.50 (*d*, $J = 11.8$, 1 H); 4.37 (br. *s*, 1 H); 2.52 (br. *s*, 1 H); 2.32 (*m*, $J = 6.8$, 1 H); 1.89 (*d*, $J = 10.4$, 1 H); 1.78 (*dd*, $J_1 = 13.0$, $J_2 = 2.8$, 1 H); 1.68 (*d*, $J = 10.5$, 1 H); 1.63 (*d*, $J = 2.7$, 1 H); 1.14 (*s*, 3 H); 1.08 (*s*, 3 H); 1.01 (*dd*, $J_1 = 6.8$, $J_2 = 2.7$, 6 H); 0.83 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.7; 169.8; 140.1; 137.1; 128.4; 128.2; 128.0; 125.5; 81.1; 73.7; 72.8; 57.5; 54.7; 44.8; 41.5; 38.1; 30.6; 26.3; 25.8; 22.2; 21.9; 9.9. HR-MS: 400.2474 ($[M+1]^+$, $C_{24}H_{34}NO_4$; calc. 400.2488).

*(1*S*,4*S*)-2-{(2*S*,3*R*,4*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-2-[(phenyl)methoxy]hept-4-enoyl}-4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**14**). A 100 ml round-bottom flask was charged with 3.5 g of **13** (8.8 mmol), 1.8 g of 1*H*-imidazole (26 mmol), 2.0 g of TBSCl (13 mmol), and 12 ml of DMF (just enough to dissolve all the reagents)[4]). The resulting soln. was stirred at r.t. for 13 h, by which time consumption of **13** was complete (TLC analysis). The mixture was diluted with 80 ml of CH_2Cl_2 and quenched with 15 ml of sat. aq. NH_4Cl soln. The resulting mixture was diluted with an additional 6 ml of H_2O, the phases were separated, and the aq. phase was extracted with 15 ml of CH_2Cl_2 (3×). The combined org. phases were washed successively with 20 ml of aq. 0.5M HCl soln., 20 ml of H_2O (2×), 20 ml of sat. aq. $NaHCO_3$ soln., and 20 ml of sat. brine. After drying ($MgSO_4$), the org. phase was filtered and concentrated to a soft white solid. The volatile Si-containing impurities were removed via *Kugelrohr* distillation (80°, 4.5 torr), and the crude product was purified by FC (SiO_2; AcOEt/hexanes 1:15) to afford 3.6 g (94%) of **14** as a white solid. M.p. 98–100°. $[\alpha]_D^{25} = -1.6$ ($c = 3.1$, CH_2Cl_2). IR (neat): 2959, 1745, 1696. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.35–7.23 (*m*, 5 H); 5.64 (*dd*, $J_1 = 16.0$, $J_2 = 6.5$, 1 H); 5.52 (*ddd*, $J_1 = 15.6$, $J_2 = 7.2$, $J_3 = 1.0$, 1 H); 5.02 (*d*, $J = 4.9$, 1 H); 4.67 (*d*, $J = 12.4$, 1 H); 4.58 (*s*, 1 H); 4.57 (*d*, $J = 12.4$, 1 H); 4.52 (*d*, $J = 4.9$, 1 H); 4.42 (*d*, $J = 4.9$, 1 H); 2.28 (*m*, $J = 6.7$, 1 H); 1.84 (*d*, $J = 12.1$, 1 H); 1.72–1.70 (*m*, 1 H); 1.60–1.58 (*m*, 1 H); 1.29–1.26 (*m*, 1 H); 1.12 (*s*, 3 H); 1.06 (*s*, 3 H); 0.99 (*d*, $J = 6.7$, 3 H); 0.98 (*d*, $J = 6.7$, 3 H); 0.87 (*s*, 9 H); 0.75 (*s*, 3 H); 0.02 (*s*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.3; 170.0; 139.8; 138.0; 128.2; 128.0; 127.6; 126.2; 82.5; 75.6; 73.1; 57.5; 54.6; 44.7; 41.3; 38.1; 30.6; 26.3; 25.8; 25.7; 22.2; 21.9; 10.0; −4.2; −4.8. HR-MS: 514.3343 ($[M+1]^+$, $C_{30}H_{48}NO_4Si$; calc. 514.3353).

*(1*R*,4*S*)-2-(2-Methoxyacetyl)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**20**). A 37.4 ml portion of a 1.53M soln. of BuLi in hexanes (57 mmol) was added to a soln. of 8.0 g (52 mmol) of **21** [18] in 100 ml of THF at −20°. The mixture was stirred at 0° for 45 min and cooled to −78°. A 6.2 ml portion of 2-methoxyacetyl chloride (7.38 g, 68 mmol) was added neat, and the mixture was allowed to warm to −20°. After 13 h, the mixture was quenched with 15 ml of sat. aq. NH_4Cl soln. and diluted with 100 ml of AcOEt and 100 ml of H_2O. The layers were separated, and the aq. phase was extracted with 30 ml of AcOEt (2×). The combined org. phases were washed (2×) with 40 ml of H_2O and sat. brine, each dried over $MgSO_4$, and concentrated to afford a yellow solid, which was purified by FC (SiO_2; hexanes/AcOEt 5:1) to provide 8.8 g (76%) of **20**. M.p. 44–45°. $[\alpha]_D^{25} = -25.4$ ($c = 1.7$, CH_2Cl_2). IR (neat): 2968, 1745, 1702. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.49 (*d*, $J = 16$, 1 H); 4.35 (*d*, $J = 16$, 1 H); 3.45 (*s*, 3 H); 2.35 (*d*, $J = 4.4$, 1 H); 2.05–2.02 (*m*, 1 H); 1.96–1.93 (*m*, 1 H); 1.88–1.85 (*m*, 1 H); 1.61–1.57 (*m*, 1 H); 1.53 (*s*, 3 H); 1.04 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 178.3; 171.6; 74.0; 73.5; 59.3; 54.8; 32.3; 23.4; 18.6; 17.5; 13.4. HR-MS: 226.1436 ($[M+1]^+$, $C_{12}H_{19}NO_3$; calc. 225.1365).

*(Z)-2-Methoxy-1-[(1*S*,4*S*)-4,5,5-trimethyl-3-oxo-2-azabicyclo[2.2.1]hept-2-yl]ethen-1-yl 2-Methylpropionate* (**24**). A 1.3 ml portion of an 0.23M soln. of LDA in THF (0.29 mmol) was added to a soln. of 50 mg of **20** (0.22 mmol) in 1.5 ml of THF at −78°, and the mixture was stirred at that temp. for 45 min. A 50-µl portion of neat isobutyryl chloride (0.49 mmol) was added dropwise over 7 min, the mixture was stirred at −78° for 15 min, and quenched at that temp. by addition of 2 ml of sat. aq. NH_4Cl soln. The layers were separated, the aq. layer was extracted with 5 ml of Et_2O (2×), and the combined org. phases were washed successively with 5 ml of H_2O and 5 ml of sat. brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 62 mg (87%) of **24** as a clear oil. $[\alpha]_D^{25} = +20$ ($c = 0.24$, CH_2Cl_2). IR (neat): 2969, 1758, 1725. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.89 (*s*, 1 H); 3.69 (*s*, 3 H); 2.68 (*m*, $J = 7.0$, 1 H); 2.37 (*d*, $J = 4.4$, 1 H); 2.02–1.98 (*m*, 1 H); 1.85–1.79 (*m*, 1 H); 1.65–1.57 (*m*, 2 H); 1.27 (*d*, $J = 7.0$, 6 H); 1.22 (*s*, 3 H); 1.00 (*s*, 3 H); 0.91 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 178.5; 173.5; 138.6; 121.0; 77.3; 72.7; 60.5; 54.9; 49.4; 33.8; 33.6; 23.0; 18.9; 18.5; 18.1; 12.1. HR-MS: 296.1859 ($[M+1]^+$, $C_{16}H_{24}NO_4$; calc. 296.1862).

Attempted Reaction of **23** *with* S*-Phenyl Thioisobutyrate.* A 0.73 ml aliquot of an 0.22M soln. of LDA in THF (0.16 mmol) was added to a soln. of 30 mg of **20** (0.13 mmol) in 1.0 ml of THF at −78°, and the resulting mixture was stirred at −78° for 75 min. A 48 mg portion of *S*-phenyl thioisobutyrate (0.27 mmol) [19] in 0.3 ml

---

[4]) The soln. turns cloudy upon addition of TBSCl, but this does not affect the reaction.

of THF was added, and the mixture was warmed slowly and monitored by TLC to detect product formation or acyl cleavage. When the temp. had reached $-30°$, deacylation was observed. The mixture was stirred for an addition 9 h at $-30°$ and quenched with 2 ml of sat. aq. NH_4Cl soln. and warmed to r.t. The layers were separated, the aq. layer was extracted with 5 ml of Et_2O (2×), and the combined org. phases were washed successively with 5 ml of H_2O and 5 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Hexane (2 ml) was added, and the resulting white precipitate was collected by suction to afford 16 mg (80%) of the auxiliary **21**. The filtrate contained a complex mixture, including unreacted *S*-phenyl thioisobutyrate.

*(1*R*,4*S*)-2-(2-Methoxyacetyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**26**). A 29.4 ml portion of a 1.53M soln. of BuLi in hexanes (45 mmol) was added to a soln. of 6.3 g of **25** (41 mmol) in 80 ml of THF at $-20°$. The mixture was stirred at 0° for 1 h, and then cooled to $-78°$. A 4.8 ml portion of neat 2-methoxyacetyl chloride (5.75 g, 53 mmol) was added dropwise, and the mixture was allowed to warm to $-20°$. After 13 h, the mixture was quenched with 15 ml of sat. aq. NH_4Cl soln. and diluted with 25 ml of AcOEt and 20 ml of H_2O. The phases were separated, and the aq. phase was extracted with 30 ml of AcOEt (2×). The combined org. phases were washed with 35 ml of H_2O and 35 ml of brine (2× each), dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow solid, which was purified by FC (SiO_2; hexanes/AcOEt 4:1) to provide 7.4 g (80%) of **26**. $[\alpha]_D^{25} = +81°$ ($c = 0.55$, CH_2Cl_2). IR (neat): 2964, 1744, 1705. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.50 (*s*, 2 H); 4.33 (*d*, $J = 2.3$, 1 H); 3.49 (*s*, 3 H); 2.02–1.99 (*m*, 1 H); 1.86–1.83 (*m*, 1 H); 1.64–1.57 (*m*, 2 H); 1.06 (*s*, 3 H); 0.94 (*s*, 3 H); 0.93 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 178.7; 169.7; 73.1; 63.4; 59.4; 56.1; 48.1; 30.3; 26.7; 18.5; 17.7; 9.3. HR-MS: 226.1439 ($[M+1]^+$, $C_{12}H_{20}NO_3$; calc. 226.1443).

Isobutyric Pivalic Anhydride. A 10-ml round-bottomed flask was charged with 10 mg of 95% NaH (0.37 mmol) and 2.0 ml of anh. Et_2O, and the resulting mixture was cooled to 0°. A 38 µl portion of pivalic acid (0.33 mmol) was added dropwise, and the mixture was vigorously stirred at r.t. until H_2 evolution ceased. The white suspension was cooled to 0°, and 39 µl (40 mg, 0.37 mmol) of neat isobutryl chloride was added. The mixture was warmed to r.t. and stirred for 3 h. The resulting soln. of crude product was diluted with 2 ml of anh. toluene and used directly in the acylation reaction.

Trifluoroacetic Pivalic Anhydride. A 10-ml round-bottomed flask was charged with 10 mg of 95% NaH (0.37 mmol) and 2.0 ml of anh. Et_2O, and the resulting mixture was cooled to 0°. A 26-µl portion of CF_3COOH (39 mg, 0.33 mmol) was added dropwise, and the mixture was vigorously stirred at r.t. until H_2 evolution ceased. The resulting white suspension was cooled to 0°, and 39 µl (40 mg, 0.37 mmol) of neat isobutryl chloride was added. The mixture was warmed to r.t. and stirred for 2.5 h. The crude product was diluted with 2 ml of anh. toluene and used directly in the acylation reaction.

*(1*S*,4*S*)-2-[(2*S*)-2-Methoxy-4-methyl-3-oxopentanoyl]-4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**27**), *(1*S*,4*S*)-2-[(2*R*)-2-Methoxy-4-methyl-3-oxopentanoyl]-4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**28**), and *(*Z*)-2-Methoxy-1-((1*S*,4*S*)-4,5,5-trimethyl-3-oxo-2-azabicyclo[2.2.1]hept-2-yl)ethen-1-yl 2-Methylpropionate* (**24**). A 3.35-ml portion of an 0.23M soln. of LDA in THF (0.76 mmol) was added to a soln. of 0.14 g of **26** (0.63 mmol) in 2 ml of THF at $-78°$, and the resulting mixture was stirred at $-78°$ for 1 h. This soln. was added *via* cannula to a soln. of 74 µl of isobutryl chloride (81 mg, 0.76 mmol) in 1.0 ml of THF at $-78°$. The resulting mixture was stirred at $-78°$ for 30 min, quenched with 5 ml of sat. aq. NH_4Cl soln., and warmed to r.t. The phases were separated, and the aq. phase was extracted with 5 ml of Et_2O (2×). The combined org. phases were washed successively with 5 ml of H_2O and 5 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 167 mg (90%,) of a yellow oil, which consisted of **27** (30%), **28** (30%), and **24** (40%), as determined by NMR. Rapid FC (SiO_2; hexanes/AcOEt 4:1) afforded pure **27** and **28** as colorless oils.

Data of **27**. $[\alpha]_D^{25} = +55$ ($c = 1.5$, CH_2Cl_2). IR (neat): 2968, 1746, 1704. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.54 (*s*, 1 H); 4.36 (*d*, $J = 2.2$, 1 H); 3.51 (*s*, 3 H); 3.08 (*m*, $J = 6.9$, 1 H); 2.00–1.96 (*m*, 1 H); 1.84–1.76 (*m*, 2 H); 1.69–1.65 (*m*, 1 H); 1.19 (*d*, $J = 7.1$, 3 H); 1.08 (*d*, $J = 6.9$, 3 H); 1.02 (*s*, 3 H); 0.95 (*s*, 3 H); 0.94 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 208.1; 197.1; 167.9; 84.5; 63.8; 59.4; 56.1; 47.4; 37.6; 30.0; 26.5; 18.5; 18.4; 17.6; 17.4; 9.2. HR-MS: 296.1866 ($[M+1]^+$, $C_{16}H_{26}NO_4$; calc. 296.1862).

Data of **28**: $[\alpha]_D^{25} = +71$ ($c = 0.52$, CH_2Cl_2). IR (neat): 2968, 1744, 1700. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.40 (*s*, 1 H); 4.36 (*d*, $J = 2.3$, 1 H); 3.51 (*s*, 3 H); 3.12 (*m*, $J = 7.0$, 1 H); 2.03–2.00 (*m*, 1 H); 1.85–1.79 (*m*, 1 H); 1.65–1.55 (*m*, 2 H); 1.20 (*d*, $J = 7.0$, 3 H); 1.10 (*d*, $J = 7.0$, 3 H); 1.03 (*s*, 3 H); 1.02 (*s*, 3 H); 0.94 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 207.7; 178.6; 167.4; 85.7; 64.0; 59.4; 56.1; 48.1; 37.5; 30.4; 27.0; 18.5; 18.3; 17.8; 17.4; 9.4. HR-MS: 296.1862 ($[M+1]^+$, $C_{16}H_{26}NO_4$; calc. 296.1862).

Acylation of **26** *in the Presence of* Et_2Zn. A soln. of 1.6 ml of a 0.33M soln. of LDA (0.51 mmol) in THF was added to a soln. of 96 mg of **26** (0.43 mmol) in 2 ml of THF at $-78°$, and the resulting mixture was stirred at $-78°$ for 1 h. A 0.51 ml portion of a 1.0M soln. of Et_2Zn in hexane (0.51 mmol) was added dropwise at $-78°$, and the mixture was stirred for an additional 15 min at $-78°$. This soln. was added *via* cannula to a soln. of 50 µl

(54 mg, 0.51 mmol) of isobutyryl chloride in 1.5 ml of anh. THF at $-78°$. The resulting mixture was stirred at $-78°$ for 30 min, quenched with 3 ml of sat. aq. NH_4Cl soln. and warmed to r.t. The layers were separated, and the aq. phase was extracted with 5 ml of Et_2O (2×). The combined org. phases were washed with 5 ml of H_2O and 5 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 109 mg (88%) of a yellow oil, which consisted of **27** (33%), **28** (11%), and **24** (56%).

Acylation of **26** *in Toluene/THF.* A soln. of 1.4 ml of a 0.33M soln. of LDA in anh. THF (0.47 mmol) was added to a soln. of 89 mg of **26** (0.40 mmol) in 3 ml of anh. toluene at $-78°$, and the resulting mixture was stirred at that temp. for 1 h. This soln. was added *via* cannula to a soln. of 46 µl of isobutryl chloride (50 mg, 0.47 mmol) in 2.0 ml of anh. toluene at $-78°$. The resulting mixture was stirred at $-78°$ for 15 min, quenched with 5 ml of sat. aq. NH_4Cl soln., and warmed to r.t. The phases were separated, and the aq. phase was extracted with 5 ml of Et_2O (2×). The combined org. phases were washed with 15 ml of H_2O and 15 ml of brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 109 mg (94%) of a yellow oil, which consisted of **27** (77%), **28** (19%), and **24** (4%).

Acylation of **26** *in Hexane/Toluene with LHMDS.* A 0.76 ml portion of a 1.0M soln. of lithium hexamethyldisilazane in hexane (0.76 mmol) was added to a soln. of 0.14 g of **26** (0.63 mmol) in 2 ml of anh. toluene at $-78°$, and the resulting mixture was stirred at $-78°$ for 1 h. This soln. was added *via* cannula to a soln. of 74 µl of isobutryl chloride (81 mg, 0.76 mmol) in 1.0 ml of anh. toluene at $-78°$. The resulting mixture was stirred at $-78°$ for 10 min, then quenched with 5 ml of sat. aq. NH_4Cl soln., and warmed to r.t. The phases were separated, and the aq. phase was extracted with 5 ml of CH_2Cl_2 (2×). The combined org. phases were washed successively with 15 ml of H_2O and 15 ml of sat. brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 169 mg (91%) of a pale yellow oil, which consisted of **27** (75%) and **28** (25%).

Acylation of **26** *with Isobutyric Pivalic Anhydride in Toluene/Et_2O.* A 1.62 ml portion of a 0.23M soln. of LDA in anh. toluene (0.36 mmol) was added to a soln. of 75 mg of **26** (0.33 mmol) in 1.8 ml of toluene at $-78°$, and the resulting mixture was stirred at $-78°$ for 1 h. This soln. was then added *via* cannula to a $-78°$ cold soln. of 57 mg of isobutyric pivalic anhydride (0.32 mmol) in 4.0 ml of toluene/Et_2O 1:1. The resulting mixture was stirred at $-45°$ for 10 h, quenched with 5 ml of sat. aq. NH_4Cl soln., and warmed to r.t. The phases were separated, and the aq. phase was extracted with 5 ml of CH_2Cl_2 (2×). The combined org. phases were washed successively with 15 ml of H_2O and 15 ml of sat. brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 88 mg (94%) of a yellow oil, which consisted of **27** (71%) and **28** (29%).

Acylation of **26** *with Trifluoroacetic Isobutyric Anhydride in Toluene/Et_2O.* A 1.62-ml portion of a 0.23M soln. of LDA in anh. toluene (0.36 mmol) was added to a soln. of 75 mg of **26** (0.33 mmol) in 1.8 ml of toluene at $-78°$, and the resulting mixture was stirred at that temp. for 1 h. This soln. was added *via* cannula to a soln. of 59 mg of trifluoroacetic isobutyric anhydride (0.32 mmol) in 4.0 ml of anh. toluene/Et_2O 1:1 at $-78°$. The resulting mixture was stirred at $-45°$ for 8 h, quenched with 5 ml of sat. aq. NH_4Cl soln., and warmed to r.t. The phases were separated, and the aq. phase was extracted with 5 ml of CH_2Cl_2 (2×). The combined org. phases were washed successively with 15 ml of H_2O and 15 ml of sat. brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford 71 mg (75%) of a yellow oil, which consisted of **27** (77%) and **28** (23%).

S-*Ethyl (2*S*,3*R*,4*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-2-[(phenyl)methoxy]hept-4-enethioate* (**29**). A 250-ml round-bottom flask was charged with 0.44 g of ethanethiol (7.1 mmol) and 17 ml of anh. THF, and the contents were cooled to $-78°$. By syringe, 3.2 ml (5.0 mmol) of a 1.53M soln. of BuLi in hexanes was added over 15 min with magnetic stirring, and stirring was continued at $-78°$ for 20 min. A $-78°$ cold soln. of 1.8 g of **14** (3.6 mmol) in 70 ml of THF was added *via* cannula over 15 min, the mixture was warmed to $-40°$ and the reaction monitored by TLC (AcOEt/hexanes 1:5, visualized by dipping in *p*-anisaldehyde and UV). Consumption of **14** was complete within 5 h. After quenching at $-40°$ by addition of 13 ml of sat. aq. NH_4Cl soln., the mixture was diluted with 25 ml of H_2O and 8 ml of Et_2O. The phases were separated, and the aq. phase was extracted with 20 ml of Et_2O (3×). The combined org. phases were washed successively with 50 ml each of H_2O and sat. brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting viscous oil was triturated with hexanes, cooled to 0°, and 0.51 g of the precipitated auxiliary **8** (93%) was recovered by filtration. The filtrate was concentrated *in vacuo* to afford 1.4 g (95%) of **29** as a pale yellow oil. $[\alpha]_D^{25} = -10$ ($c = 0.70$, CH_2Cl_2). IR (neat): 2958, 1681. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.42–7.30 (*m*, 5 H); 5.55 (*dd*, $J_1 = 15.6$, $J_2 = 6.5$, 1 H); 5.39 (*dd*, $J_1 = 15.6$, $J_2 = 7.4$, 1 H); 4.81 (*d*, $J = 11.9$, 1 H); 4.47 (*d*, $J = 11.9$, 1 H); 4.35 (*dd*, $J_1 = 4.6$, $J_2 = 2.7$, 1 H); 3.80 (*d*, $J = 4.6$, 1 H); 2.85 (*q*, $J = 7.4$, 2 H); 2.22 (*m*, 1 H); 1.25 (*t*, $J = 7.4$, 3 H); 0.97 (*d*, $J = 6.8$, 3 H); 0.95 (*d*, $J = 6.8$, 3 H); 0.87 (*s*, 9 H); 0.03 (*s*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 201.7; 140.0; 137.2; 128.3; 127.8; 126.6; 125.9; 887; 75.4; 73.7; 30.6; 25.8; 22.4; 22.0; 21.9; 18.2; 14.5; −4.29; −4.86. HR-MS: 440.2638 ($[M + NH_4]^+$, $C_{23}H_{42}NO_3SSi$, calc. 440.2655).

*(2*S*,3*R*,4*E*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-6-methyl-2-[(phenyl)methoxy]hept-4-enal* (**31**). A 100-ml round-bottom flask was charged with a soln. of 1.3 g of **29** (3.0 mmol) in 35 ml of toluene[5]) and the contents were cooled to $-78°$. With vigorous stirring, 6.0 ml of a 1.0M soln. of DIBAL in hexanes (6.0 mmol) was added over 30 min (down the side of the flask to effect precooling). Within 10 min after completion of the addition, **29** was consumed, and the reaction was quenched by addition of 0.3 ml of H_2O. The mixture was warmed to r.t., stirred for 2 h, and anh. Na_2CO_3 was added until the salts became granular. After filtration of the solids and concentration *in vacuo* (bath temp. $>75°$ to complete the conversion of residual **30**), 0.99 g of the sensitive aldehyde **31** (91%) was obtained. The product was immediately used without further purification. IR (neat): 3642, 2957, 1735. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.67 (*d*, $J=5.1$, 1 H); 7.35–7.26 (*m*, 5 H); 5.64 (*ddd*, $J_1=15.5$, $J_2=6.6$, $J_3=0.8$, 1 H); 5.50 (*ddd*, $J_1=15.5$, $J_2=6.6$, $J_3=1.0$, 1 H); 4.75 (*d*, $J=12.2$, 1 H); 4.57 (*d*, $J=12.2$, 1 H); 4.41 (*t*, $J=5.7$, 1 H); 3.73 (*dd*, $J_1=5.0$, $J_2=1.7$, 1 H); 2.29 (*m*, $J=6.7$, 1 H); 1.00 (*d*, $J=6.7$, 3 H); 0.99 (*d*, $J=6.7$, 3 H); 0.88 (*s*, 9 H); 0.02 (*s*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 202.8; 140.4; 137.4; 128.4; 127.9; 125.3; 86.3; 74.0; 72.9; 30.7; 25.8; 22.1; 18.1; −4.3; −5.0.

*(*E/Z*)-[2-Methoxy-1-(phenylsulfanyl)ethenyl]trimethylsilane* (**32**). A 100-ml round-bottom flask was charged with a soln. of 4.0 g of *S*-phenyl 2-methoxyethanethioate (22 mmol) in 27 ml of CH_2Cl_2, and the contents were cooled to $-78°$ under Ar. At $-78°$, 4.0 ml of TMSOTf (4.91 g, 22 mmol) was added dropwise *via* syringe, followed by addition of 9.3 ml of Et_3N (6.75 g, 67 mmol) over 25 min. The resulting mixture was stirred at $-10°$ for 17 h, diluted with 40 ml of hexanes, and the biphasic mixture was cooled to $-78°$. The higher-density phase containing amine salts was removed by syringe, and the resulting pale yellow soln. was concentrated *in vacuo* and vented to Ar. A short-path-distillation head with cow receiver was attached, and the product was distilled at reduced pressure (b.p. 110°, 2 torr) to afford 4.3 g (76%) of **32** as a pale yellow, moisture-sensitive liquid that can be stored at r.t. under Ar. Inevitably, over time, some hydrolysis does occur, therefore, it is recommended to redistill **32** before use. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37(*d*, $J=8.1$, 2 H); 7.29 (*dd*, $J_1=8.1$, $J_2=7.4$, 2 H); 7.20 (*t*, $J=7.4$, 1 H); 6.16 (*s*, 1 H); 3.70 (*s*, 3 H); 0.15 (*s*, 9 H).

S-*Phenyl (2*R*,3*R*,4*R*,5*R*,6*E*)-5-[[(*tert*-Butyl)dimethylsilyl]oxy]-3-hydroxy-2-methoxy-8-methyl-4-[(phenyl)methoxy]non-6-enethioate* (**33**). A 100-ml round-bottom flask was charged with 1.6 g (6.1 mmol) of **32** and 40 ml of anh. CH_2Cl_2, and the contents were cooled to $-78°$ under Ar. Over 10 min, 5.6 ml of a 1.0M soln. of $SnCl_4$ in heptane (1.46 g, 5.6 mmol) was added dropwise, during which time the mixture turned bright yellow. The resulting mixture was stirred at $-78°$ for 30 min. A $-78°$ cold soln. of 1.7 g of **31** (4.7 mmol) in 30 ml of CH_2Cl_2 was added dropwise *via* cannula over 35 min, during which time the soln. turned pale yellow. The resulting mixture was stirred at $-78°$, and the reaction was monitored by TLC (AcOEt/hexanes 1:2, visualized with *p*-anisaldehyde and UV). Aldehyde **31** was consumed after 4 h, at which time the mixture was quenched at $-78°$ by addition of 5 ml of sat. aq. NH_4Cl soln. The mixture was diluted with 15 ml of H_2O and 15 ml of CH_2Cl_2, the phases were separated, and the aq. phase was extracted with 10 ml of CH_2Cl_2 (3×). The combined org. phases were washed with 20 ml of 1M aq. HCl soln., 20 ml of H_2O, 20 ml of sat. aq. $NaHCO_3$ soln., and 20 ml of sat. brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a mixture of the desired *anti*-adduct **33** and residual *S*-phenyl methoxyethanethioate. The volatile thioester was removed *in vacuo* (125°, 3.5 torr) by *Kugelrohr* distillation, and the residue was purified by FC (SiO_2; AcOEt/hexanes 1:20) to afford 1.8 g (73%) of **33** (d.r. 11.5:1). $[\alpha]_D^{25}=+49$ ($c=1.3$, CH_2Cl_2). IR (neat): 3582, 2956, 1705, 1253. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.30–7.41 (*m*, 10 H); 5.67 (*dd*, $J_1=15.6$, $J_2=6.7$, 1 H); 5.45 (*dd*, $J_1=15.6$, $J_2=7.5$, 1 H); 4.95 (*d*, $J=11.5$, 1 H); 4.69 (*d*, $J=11.6$, 1 H); 4.35 (*t*, $J=7.4$, 1 H); 3.95 (*t*, $J=7.9$, 1 H); 3.75 (*d*, $J=7.2$, 1 H); 3.61 (*d*, $J=7.1$, 1 H); 3.35 (*s*, 3 H); 2.68 (*d*, $J=9.0$, 1 H); 2.33 (*m*, $J=6.7$, 1 H); 1.01 (*d*, $J=6.7$, 6 H); 0.92 (*s*, 9 H); 0.06 (*d*, $J=4.5$, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 199.5; 140.9; 138.4; 134.7; 129.2; 128.4; 128.1; 127.8; 127.2; 126.7; 88.0; 79.6; 75.2; 74.4; 71.1; 59.0; 30.9; 25.9; 22.2; 22.0; 18.2; −4.1; −4.6. HR-MS: 567.2584 ($[M+Na]^+$, $C_{30}H_{44}O_3SSi$; calc. 567.2576).

*(2*R*,3*R*,4*R*,5*R*,6*E*)-5-[[(*tert*-Butyl)dimethylsilyl]oxy]-*N*-[(3*S*)-2,3,4,5,6,7-hexahydro-2-oxoazepin-3-yl]-3-hydroxy-2-methoxy-8-methyl-4-[(phenyl)methoxy]non-6-enamide* (**35**). To a soln. of 1.0 g (2.2 mmol) of **33** in 1.0 ml of 1,4-dioxane was added 0.3 g (2.2 mmol) of *3-amino-2,3,4,5,6,7-hexahydroazepin-2-one* (**34**). The resulting mixture was heated to reflux for 15 h. The mixture was cooled to r.t., diluted with 10 ml each of AcOEt and H_2O. The phases were separated, and the aq. layer was extracted with 5 ml of AcOEt (2×). The combined org. phases were washed with 10 ml each of H_2O and sat. brine, dried ($MgSO_4$), and concentrated to afford 1.21 g (98%) of **35** as a colorless, viscous oil. $[\alpha]_D^{25}=+8.7$ ($c=0.30$, MeOH). IR (film): 3346, 3061, 3030, 1660. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, $J=5.8$, 1 H); 7.45–7.25 (*m*, 5 H); 6.15–6.10 (*m*, 1 H); 5.66 (*dd*, $J_1=16$,

---

[5]) CH_2Cl_2 can also be used.

$J_2 = 6$, 1 H); 5.42 (*dd*, $J_1 = 15.4$, $J_2 = 7$, 1 H); 4.95 (*d*, $J = 11.3$, 1 H); 4.64 (*d*, $J = 11.4$, 1 H); 4.53–4.49 (*m*, 1 H); 4.38 (*t*, $J = 7$, 1 H); 3.85–3.79 (*m*, 1 H); 3.74 (*d*, $J = 7.2$, 1 H); 3.59 (*d*, $J = 6.9$, 1 H); 3.27 (*s*, 3 H); 3.30–3.22 (*m*, 1 H); 3.21–3.10 (*m*, 2 H); 2.35–2.25 (*m*, 1 H); 2.15–1.94 (*m*, 2 H); 1.85–1.25 (*m*, 3 H); 0.99 (*d*, $J_1 = 7.6$, $J_2 = 3.8$, 6 H); 0.90 (*s*, 9 H); 0.04 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.1; 170.5; 140.5; 138.7; 128.3; 127.9; 127.5; 126.8; 82.1; 80.7; 75.3; 74.5; 71.2; 58.4; 51.9; 42.0; 31.3; 30.7; 28.8; 27.9; 26.0; 22.2; 21.9; 18.2; −4.0; −4.5. MS: 563 ($[M+1]^+$). HR-MS: 585.3362 ($M+Na]^+$, $C_{30}H_{50}N_2NaO_6Si$; calc. 585.3336).

*(2*R*,3*R*,4*S*,5*R*,6*E*)-*N*-(2,3,4,5,6,7-Hexahydro-2-oxoazepin-3-yl)-3,4,5-trihydroxy-2-methoxy-8-methylnon-6-enamide* (= *Bengamide E*; **3**). A 50 ml round-bottom flask was charged with a soln. of 0.30 g of **35** (0.54 mmol) in 10 ml of THF, and 0.67 ml of anh. *t*-BuOH (7.1 mmol) was added. The flask was equipped with a dissolving 'metal addition' funnel containing freshly cut Na metal (0.6 g, 35 mmol) and a dry ice condenser, and the contents of the flask were cooled to −78° with stirring. Anh. NH_3 was condensed into the flask through the addition funnel, thereby adding the Na metal as a dark blue soln. As soon as the mixture had retained its blue color for 1 min, addition was stopped, and the resulting dark blue mixture was stirred at −78° for 20 min. The mixture was slowly quenched at −78° by portionwise addition of solid anh. NH_4Cl (*ca.* 1 g) until the blue color disappeared. The cooling bath was removed, and the ammonia was allowed to evaporate slowly. The residue was diluted with 10 ml each of AcOEt and H_2O, and the phases were separated. The aq. phase was extracted with 5 ml of AcOEt (2×). The combined org. phases were washed with 20 ml of sat. brine and dried ($MgSO_4$). Concentration afforded 0.18 g (70%) of (2*R*,3*R*,4*R*,5*R*,6*E*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-*N*-((3*S*)-2,3,4,5,6,7-hexahydro-2-oxoazepin-3-yl)-3,4-dihydroxy-2-methoxy-8-methylnon-6-enamide, which was utilized without further purification. For anal. purposes, a small sample was purified by FC (SiO_2). Colorless, viscous oil. $[\alpha]_D^{25} = +11.2$ (*c* = 0.25, MeOH). IR (film): 3313, 1657, 1575. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98–7.94 (*m*, 1 H); 6.28–6.24 (*m*, 1 H); 5.69 (*dd*, $J_1 = 15.5$, $J_2 = 7$, 1 H); 5.37 (*dd*, $J_1 = 16$, $J_2 = 8$, 1 H); 4.60–4.52 (*m*, 1 H); 4.24 (*t*, $J = 7.5$, 1 H); 3.82–3.74 (*m*, 3 H); 3.58 (*d*, $J = 7.2$, 1 H); 3.52 (*s*, 3 H); 3.31–3.24 (*m*, 2 H); 2.35–2.25 (*m*, 1 H); 2.15–2.05 (*m*, 2 H); 1.95–1.80 (*m*, 2 H); 1.60–1.20 (*m*, 3 H); 0.99 (*d*, $J_1 = 7.0$, $J_2 = 3.5$, 6 H); 0.90 (*s*, 9 H); 0.09 (*s*, 3 H); 0.06 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.1; 171.6; 141.5; 126.2; 81.6; 75.5; 73.0; 70.6; 59.7; 51.9; 42.1; 31.2; 30.7; 28.8; 27.9; 25.9; 22.2; 21.8; 18.1; −3.7; −4.7. MS: 473 ($[M+1]^+$). HR-MS: 495.2856 ($[M+Na]^+$, $C_{23}H_{44}N_2NaO_6Si$; calc. 495.2866).

Then, a soln. of 50 mg (0.10 mmol) of the above intermediate in 1.5 ml of anh. THF was cooled to 0°. A 0.30 ml portion of a 1.0M soln. of TBAF in THF (0.30 mmol) was added dropwise, and the resulting mixture was stirred at 0° for 2 h. The mixture was quenched by addition of 1 ml of sat. aq. NH_4Cl soln. and warmed to r.t. The phases were separated, and the aq. phase was extracted with 2 ml of AcOEt (2×). The combined org. phases were washed with 5 ml each of H_2O and sat. brine, and dried ($MgSO_4$). Concentration and purification by FC (SiO_2; AcOEt/hexanes 5:1) afforded 34 mg of **3** (95%) as a viscous, colorless oil that was indistinguishable from an authentic sample [12]. $[\alpha]_D^{25} = +27.3$ (*c* = 0.11, MeOH); lit. +36.9 (*c* = 0.043, MeOH) [12]. IR (film): 3332, 1650. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01(*d*, $J = 5.9$, 1 H); 5.99–5.95 (*m*, 1 H); 5.80 (*dd*, $J_1 = 15.5$, $J_2 = 6.4$, 1 H); 5.46 (*dd*, $J_1 = 16.0$, $J_2 = 7.0$, 1 H); 4.58–4.52 (*m*, 1 H); 4.40 (br. *s*, 1 H); 4.26–4.21 (*m*, 1 H); 3.84–3.77 (*m*, 2 H); 3.67–3.59 (*m*, 1 H); 3.56 (*s*, 3 H); 3.36–3.20 (*m*, 2 H); 3.19–3.00 (*m*, 2 H); 2.36–2.25 (*m*, 1 H); 2.13–1.98 (*m*, 2 H); 1.95–1.74 (*m*, 2 H); 1.73–1.30 (*m*, 4 H); 1.01 (*d*, $J = 6.8$, 3 H); 1.01 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.4; 172.0; 141.7; 125.2; 80.6; 74.0; 72.6; 72.1; 59.9; 51.8; 41.9; 30.9; 30.7; 28.7; 27.8; 22.1; 22.0. MS: 381 ($[M+Na]^+$).

2-(Oxiran-2-yl)ethyl 4-Methylphenylsulfonate (**37**). A 2.8-g portion NaH (60% in oil, 1.75 g, 73 mmol) was washed free of oil with three 5 ml portions of hexanes, the residual hexanes were evaporated, and the residue was diluted with 25 ml of anh. THF. The resulting suspension was cooled to −10°, and a soln. of 4.0 g (24 mmol) of *(*R*)-2-bromo-1,4 butanediol* (**36**) [27] in 25 ml of anh. THF was added dropwise over 15 min. The resulting mixture was stirred for 30 min at −10°, and 5.0 g of solid *p*-toluenesulfonyl chloride (26 mmol) was added. After 4 h at −10°, consumption of **36** was complete according to TLC. The mixture was diluted with 100 ml Et_2O and filtered through a pad of SiO_2. Concentration of the filtrate *in vacuo* and purification by FC (SiO_2; AcOEt/hexanes 1:5) afforded 4.52 g (89%) of **37** as a colorless oil. $[\alpha]_D^{25} = -17$ (*c* = 0.57, CH_2Cl_2). IR (neat): 2995, 1358, 1177. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 (*d*, $J = 8$, 2 H); 7.35 (*d*, $J = 8$, 2 H); 4.15 (*t*, $J = 9$, 2 H); 2.97 (*m*, $J = 2$, 1 H); 2.76 (*t*, $J = 5$, 1 H); 2.48 (*dd*, $J_1 = 4.9$, $J_2 = 2.7$, 1 H); 2.46 (*s*, 3 H); 2.05–1.97 (*m*, 1 H); 1.81–1.77 (*m*, 1 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 144.9; 132.7; 129.8; 127.8; 67.1; 48.6; 46.8; 32.0; 21.5. HR-MS: 243.0693 ($[M+1]^+$, $C_{11}H_{15}O_4S$; calc. 243.0691).

*(*S*)-2-(2-Iodoethyl)oxirane* (**10**). A soln. of 5.95 g (24.6 mmol) of **37** in 65 ml of acetone was combined with 3.68 g of solid NaI (24.6 mmol), and the mixture was heated at reflux for 2 h. After cooling to r.t., the mixture was diluted with 100 ml of Et_2O and filtered through a pad of *Celite*. The filtrate was concentrated *in vacuo* to afford 4.5 g (93%) of **10** as a colorless oil, which was used without further purification. $[\alpha]_D^{25} = -14$ (*c* = 3.4,

CH_2Cl_2). IR (neat): 2988, 1423. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.30–3.26 (*m*, 2 H); 3.05–3.03 (*m*, 1 H); 2.84 (*t*, $J = 5$, 1 H); 2.60 (*dd*, $J_1 = 5.0$, $J_2 = 3.0$, 1 H); 2.19–2.15 (*m*, 1 H); 2.09–2.05 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 52.3; 46.9; 36.3; 0.13. HR-MS: 197.9541 (M^+, C_4H_7IO; calc. 197.9542).

tert-*Butyl (2*S*)-2-[(1,1-Diphenylmethylidene)amino]-4-[(2*S*)-oxiran-2-yl]butanoate* (**40**). A 100 ml round-bottom flask was charged with 7.56 g of $CsOH \cdot H_2O$ (50 mmol), which had been finely pulverized under Ar, and with 15 ml of anh. CH_2Cl_2, and the contents were cooled to $-78°$. To the resulting suspension, 2.97 g (10 mmol) of commercial neat tert-*butyl diphenyliminoacetate* (**9**) was added followed by 0.59 g of the phase-transfer catalyst **38** (1.0 mmol) [25]. The mixture was gently swirled, and 2.6 g of neat *2-(2-iodoethyl)oxirane* (**10**) (13 mmol) was added. A mechanical stirrer was attached, and the slurry was vigorously stirred at $-60°$ for 18 h under Ar. The reaction mixture was diluted with 65 ml of Et_2O, quenched with 40 ml of H_2O, and warmed to r.t. After separation of the layers, the aq. phase was extracted three times with 20 ml of Et_2O. The combined org. phases were washed successively with 30 ml each of H_2O and sat. brine, dried (Na_2CO_3), filtered, and concentrated *in vacuo* to afford a mixture of the desired alkylation product **40** and excess iodide **10**. Volatiles (including **10**) were removed under high vacuum (100°, 0.5 torr) *via* a *Kugelrohr* apparatus to afford 3.04 g (83%) of **40** as an orange solid. The product was established to be a single detectable diastereoisomer (400-MHz ^{1}H-NMR) and was used without further purification, since it is unstable on SiO_2 or basic alumina. Extraction of the aq. phase with CH_2Cl_2 allowed recovery of 85% of the catalyst **38** as the chloride salt, which was successfully used again with similar results.

Data for **40**: IR (neat): 2976, 1732, 1149. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.80–7.16 (*m*, 10 H); 3.95 (*dd*, $J_1 = 7.8$, $J_2 = 5.0$, 1 H); 2.88–2.86 (*m*, 1 H); 2.70 (*t*, $J = 4.5$, 1 H); 2.43 (*dd*, $J_1 = 4.8$, $J_2 = 2.7$, 1 H); 2.07–1.99 (*m*, 2 H); 1.62–1.40 (*m*, 2 H); 1.44 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.1; 170.3; 139.5; 136.6; 130.3; 128.8; 128.6; 128.3; 128.0; 127.8; 81.1; 65.5; 51.9; 47.0; 29.7; 29.0; 28.0. HR-MS: 366.2083 ($[M+1]^+$, $C_{23}H_{28}NO_3$; calc. 366.2069).

tert-*Butyl (2*S*,5*S*)-2-[(1,1-Diphenylmethylidene)amino]-5-hydroxy-6-[methyl(phenylmethyl)amino]hexanoate* (**43**). To a soln. of 2.5 g of **40** (6.8 mmol) in 5.0 ml of anh. MeOH at r.t. was added 7.0 ml of *N*-benzyl-*N*-methylamine (6.67 g, 55 mmol). The soln. was stirred at r.t. for 13 h, at which time consumption of **40** was complete (as analyzed by ESI-MS). The MeOH was removed at aspirator pressure, and the remainder (excess benzyl(methyl)amine) was removed under high vacuum (75° at 7 torr) with a *Kugelrohr* apparatus to afford crude **43** in quant. yield. After purification by FC (SiO_2; AcOEt/hexanes 1:15), 3.2 g (98%) of pure **43** was obtained as a colorless oil. $[\alpha]_D^{25} = -35$ ($c = 0.66$, CH_2Cl_2). IR (neat): 3579, 2930, 1732, 1500. ^{1}H-NMR (400 MHz, CD_3OD): 7.57–7.15 (*m*, 15 H); 3.93 (*dd*, $J_1 = 8.0$, $J_2 = 5.2$, 1 H); 3.66–3.59 (*m*, 1 H); 3.51 (*dd*, $J_1 = 17.7$, $J_2 = 13.0$, 2 H); 2.40–2.30 (*m*, 2 H); 2.19 (*s*, 3 H); 2.00–1.93 (*m*, 2 H); 1.45 (*s*, 9 H); 1.23–1.37 (*m*, 2 H). ^{13}C-NMR (100 MHz, CD_3OD): 173.2; 173.1; 140.8; 139.8; 137.8; 131.7; 130.4; 130.1; 129.9; 129.8; 129.3; 129.2; 128.9; 128.2; 82.5; 69.0; 67.1; 64.5; 63.8; 43.1; 32.8; 30.7; 28.3. HR-MS: 487.2974 ($[M+1]^+$, $C_{31}H_{39}N_2O_3$; calc. 487.2961).

tert-*Butyl 2-Amino-5-hydroxy-6-(methylamino)hexanoate* (**44**). To a soln. of 0.59 g of **43** (1.2 mmol) in 4.4 ml of THF at r.t. was added 4.0 ml of 10% aq. citric acid. The soln. was stirred at r.t. for 30 min at which time ESI-MS analysis indicated that consumption of **43** was complete. The mixture was diluted with 20 ml each of H_2O and hexanes, and the phases were separated. The aq. phase was extracted with 10 ml of hexanes (2×), rendered basic with pH 8.5 phosphate buffer, and extracted with 15 ml of AcOEt (3×). The combined AcOEt extracts were dried (Na_2CO_3), filtered, and concentrated *in vacuo* to afford 0.33 g (86%) of tert-*Butyl (2*S*,5*S*)-2-Amino-5-hydroxy-6-[methyl(phenylmethyl)amino]hexanoate* as a colorless oil, which was utilized without further purification: ^{1}H-NMR (400 MHz, CD_3OD): 7.33–7.23 (*m*, 5 H); 3.79–3.59 (*m*, 1 H); 3.55 (*dd*, $J = 17.3$, 13.0, 2 H); 3.30–3.26 (*m*, 1 H); 2.40–2.32 (*m*, 2 H); 2.24 (*s*, 3 H); 1.74–1.67 (*m*, 2 H); 1.67–1.58 (*m*, 1 H); 1.47 (*s*, 9 H); 1.38–1.32 (*m*, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 176.0; 139.7; 130.4; 129.3; 128.2; 82.3; 64.9; 64.4; 63.8; 55.8; 43.1; 32.5; 32.1; 28.3. HR-MS: 323.2340 ($[M+1]^+$, $C_{18}H_{31}N_2O_3$; calc. 323.2335).

A 100-ml round-bottom flask was charged with a soln. of 0.55 g (1.7 mmol) of the above intermediate in 40 ml of EtOH and 0.24 g of wet *Pearlman*'s catalyst (0.17 mmol). The flask was purged with H_2 gas, and the mixture was vigorously stirred under H_2 (balloon pressure) for 11 h, at which time ESI-MS analysis indicated completion of the reaction. The mixture was filtered through *Celite*, the *Celite* was rinsed with MeOH, and the filtrate was concentrated *in vacuo* to afford 0.39 g of **44** (86% overall yield from **40**) as a colorless oil. $[\alpha]_D^{25} = +8.7$ ($c = 0.23$, MeCN). IR (neat): 3382, 2921, 1727, 1367, 1155. ^{1}H-NMR (400 MHz, CD_3OD): 3.71–3.65 (*m*, 1 H); 3.53–3.48 (*m*, 1 H); 2.60–2.54 (*m*, 2 H); 2.43 (*s*, 3 H); 1.75–1.71 (*m*, 2 H); 1.57–1.52 (*m*, 2 H); 1.50 (*s*, 9 H); 1.49–1.41 (*m*, 2 H). ^{13}C-NMR (100 MHz, CD_3OD): 176.0; 82.2; 70.5; 58.4; 5.7; 36.1; 32.7; 32.1; 28.3. HR-MS: 233.1876 ($[M+1]^+$, $C_{11}H_{25}N_2O_3$; calc. 233.1865).

*(3*S*,6*S*)-3-Amino-2,3,4,5,6,7-hexahydro-6-hydroxy-1-methylazepin-2-one* (**45**). A 30 ml screw-cap vial was charged with a soln. of 0.20 g of **44** (0.86 mmol) in 15 ml of MeOH, and 0.39 ml of a 3.3M soln. of MeONa

(70.24 mg, 1.3 mmol) in MeOH was added. The vial was sealed and heated to 85° (bath temp.) for 1.5 h. The mixture was cooled to r.t., quenched with 0.11 g of solid $NaHCO_3$ (1.3 mmol), and the MeOH was removed *in vacuo*. The remainder was dissolved in 10 ml of AcOEt/MeOH 15:1, filtered through basic alumina to remove inorg. salts, and the filtrate was concentrated *in vacuo* to afford 0.12 g (88%) of **45** as a white solid. M.p. 119–122°. $[\alpha]_D^{25} = +14.1$ ($c = 0.22$, MeOH). IR (neat): 3360, 2924, 1646. ^{1}H-NMR (400 MHz, CD_3OD): 3.73 (*dd*, $J_1 = 11.0$, $J_2 = 1.8$, 1 H); 3.61 (*dd*, $J_1 = 14.5$, $J_2 = 10.1$, 1 H); 3.54 (*m*, 1 H); 3.17 (br. *d*, $J = 14.5$, 1 H); 3.02 (*s*, 3 H); 2.11 (br. *d*, 1 H); 1.82 (br. *d*, 1 H); 1.70–1.46 (*m*, 2 H). ^{13}C-NMR (100 MHz, CD_3OD): 177.6; 68.5; 57.3; 53.9; 37.5; 36.8; 32.6. HR-MS: 159.1126 ($[M+1]^+$, $C_7H_{15}N_2O_2$; calc. 159.1134).

*(3*S*,6*S*)-6-Amino-2,3,4,5,6,7-hexahydro-1-methyl-7-oxoazepin-3-yl Acetate* (**46**). A soln. of 17 mg of **45** (0.11 mmol) in 0.3 ml of anh. TFA was stirred at r.t. for 10 min. Over 5 min, 15 µl of AcCl (17.3 mg, 0.22 mmol) was added dropwise to the mixture at r.t., and stirring was continued for 30 min, at which time ESI-MS analysis showed that the reaction was complete. The mixture was concentrated *in vacuo* to a viscous oil, which was dissolved in MeOH and treated with *Amberlyst IR-400* resin for 10 min at r.t.. After filtration of the resin, concentration *in vacuo* afforded a yellow oil, which was filtered through basic alumina (AcOEt/MeOH 5:1) to provide 18 mg (82%) of **46** as a pale yellow oil used without further purification: ^{1}H-NMR (400 MHz, CD_3OD): 4.61–4.56 (*m*, 1 H); 3.79 (*d*, $J = 10.2$, 1 H); 3.71 (*dd*, $J_1 = 14.9$, $J_2 = 10.0$, 1 H); 3.30–3.26 (*d*, $J = 14.6$, 2 H); 3.04 (*s*, 3 H); 2.11–2.05 (*m*, 1 H); 2.03 (*s*, 3 H); 1.90–1.84 (*m*, 2 H); 1.61–1.55 (*m*, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 177.5; 171.8; 71.0; 53.9; 53.6; 36.6; 33.7; 32.2; 21.0.

*(3*S*,6*S*)-6-Amino-2,3,4,5,6,7-hexahydro-1-methyl-7-oxoazepin-3-yl Tetradecanoate* (**47**). A soln. of 61 mg of **45** (0.38 mmol) in 0.8 ml of TFA was stirred at r.t. for 10 min. Dropwise over 5 min, 0.208 ml of myristoyl chloride (189 mg, 0.77 mmol) was added to the mixture at r.t., and stirring was continued at r.t. for 30 min at which time ESI-MS analysis indicated completion of the reaction. The mixture was quenched by careful addition of 2 ml of H_2O, diluted with 10 ml of CH_2Cl_2, and rendered basic with pH 8.5 phosphate buffer. The phases were separated, and the aq. phase was extracted with 10 ml of CH_2Cl_2 (3×). The combined org. phases were washed with 15 ml of a 1:1 mixture of phosphate buffer pH 8.5 and H_2O, dried (Na_2CO_3), and filtered through a pad of *Celite* to afford 0.12 g (90%) of **47** as a white solid. M.p. 90–92°. $[\alpha]_D^{25} = +69$ ($c = 0.85$, CH_2Cl_2). IR (neat): 3487, 2914, 2849, 1732. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.62 (*tt*, $J_1 = 2.7$, $J_2 = 0.9$, 1 H); 3.8 (br. *d*, 1 H); 3.61 (*dd*, $J_1 = 14.7$, $J_2 = 10.0$, 1 H); 3.22 (*dt*, $J_1 = 14.9$, $J_2 = 2.2$, 1 H); 3.10 (*s*, 3 H); 2.31 (*t*, $J = 7.4$, 2 H); 2.21–2.07 (*m*, 1 H); 2.00–1.88 (*m*, 1 H); 1.87–1.67 (*m*, 3 H); 1.65–1.53 (*m*, 3 H); 1.35–1.16 (*m*, 20 H); 0.89 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 176.2; 173.0; 69.6; 453.3; 53.1; 36.5; 34.4; 33.0; 31.9; 31.5; 29.7; 29.6; 29.6; 29.4; 29.3; 29.2; 29.1; 24.9; 22.7; 14.1. HR-MS: 369.3106 ($[M+1]^+$, $C_{21}H_{41}N_2O_3$; calc. 369.3117).

*(3*S*,6*S*)-6-[((2*R*,3*R*,4*R*,5*R*,6*E*)-5-[[(*tert*-Butyl)dimethylsilyl]oxy]-3-hydroxy-2-methoxy-8-methyl-4-(phenylmethoxy)non-6-enoyl)amino]-2,3,4,5,6,7-hexahydro-1-methyl-7-oxoazepin-3-yl Acetate* (**48**). A 5-ml round-bottom flask equipped with a cold finger was charged with 35 mg of **33** (0.065 mmol), 14 mg of **46** (0.068 mmol), and 0.14 ml of anh. dioxane. The resulting soln. was heated to reflux and was monitored by TLC (hexane/AcOEt 2:1, visualization with *p*-anisaldehyde and UV). Within 18 h, consumption of **33** was complete. The mixture was cooled to r.t., diluted with 5 ml of AcOEt and 3 ml of H_2O. The phases were separated, and the aq. phase was extracted with 2 ml of AcOEt (3×). The combined org. phases were washed successively with 3 ml of H_2O (2×) and 5 ml of sat. brine (2×), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in hexanes/AcOEt 5:1 and filtered through a plug of SiO_2 to remove the phenylthiol. Then, the column was flushed with AcOEt/hexanes 3:1, and the filtrate was concentrated to afford 38 mg (94%) of **48** as a glassy white solid. $[\alpha]_D^{25} = +40$ ($c = 0.9$, CH_2Cl_2). IR (neat): 3483, 2956, 1736, 1655. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.78 (*d*, $J = 6.2$, 1 H); 7.40–7.26 (*m*, 5 H); 5.66 (*dd*, $J_1 = 15.4$, $J_2 = 6.4$, 1 H); 5.44 (*ddd*, $J_1 = 15.4$, $J_2 = 7.4$, $J_3 = 1.0$, 1 H); 4.96 (*d*, $J = 11.6$, 1 H); 4.64 (*d*, $J = 11.6$, 1 H); 4.64–4.60 (*m*, 2 H); 4.37 (*t*, $J = 7.2$, 1 H); 3.85 (*dt*, $J_1 = 7.0$, $J_2 = 1.8$, 1 H); 3.65 (*d*, $J = 6.9$, 1 H); 3.63–3.56 (*m*, 1 H); 3.54 (*dd*, $J_1 = 7.1$, $J_2 = 1.8$, 1 H); 3.25 (*s*, 3 H); 3.26–3.22 (*m*, 1 H); 3.10 (*s*, 1 H); 3.04 (*d*, $J = 7.1$, 1 H); 2.30 (*sept.*, $J = 6.8$, 1 H); 2.18–2.08 (*m*, 1 H); 2.06 (*s*, 3 H); 2.04–1.89 (*m*, 1 H); 1.72–1.58 (*m*, 2 H); 1.00 (*dd*, $J_1 = 6.7$, $J_2 = 3.4$, 6 H); 0.90 (*s*, 9 H); 0.10 (*s*, 3 H); 0.06 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 172.0; 170.5; 170.1; 140.5; 138.8; 128.3; 127.8; 127.4; 126.7; 82.5; 80.4; 75.2; 74.3; 71.1; 69.5; 60.4; 58.5; 53.3; 51.2; 36.2; 32.6; 30.7; 29.2; 25.9; 22.2; 22.0; 21.1; 18.1; 14.2; −4.04; −4.58. HR-MS: 635.3700 ($[M+1]^+$, $C_{33}H_{55}N_2O_8Si$; calc. 635.3728).

*(2*R*,3*R*,4*S*,5*R*,6*E*)-*N*-((3*S*,6*S*)-2,3,4,5,6,7-Hexahydro-6-hydroxy-1-methyl-2-oxoazepin-3-yl)-3,4,5-trihydroxy-2-methoxy-8-methylnon-6-enamide* (= *Bengamide Z*; **2**). A 25-ml two-necked round-bottom flask equipped with a dry-ice condenser was charged with a soln. of 15 mg of **48** (0.024 mmol) in 0.5 ml of anh. THF and 23 µl of anh. *t*-BuOH (0.24 mmol), and the contents were cooled to −78°. Approximately 15 ml of anh. NH_3 was condensed into the flask, and three 5 mg pieces (0.7 mmol) of Na metal (freshly cut and rinsed with anh. EtOH) were added until a blue color persisted. After stirring for 15 min at −78°, the reaction was

quenched by addition of solid anh. NH_4Cl, and the mixture was diluted slowly with 5 ml of AcOEt, resulting in a cloudy white soln. The NH_3 was allowed to evaporate upon warming to r.t., and the resulting mixture was filtered through *Celite* and concentrated to afford 9 mg (73%) of 5-{[(*tert*-butyl)dimethylsilyl]oxy}-*N*-(2,3,4,5,6,7-hexahydro-6-hydroxy-1-methyl-2-ox oazepin-3-yl)-3,4-dihydroxy-2-methoxy-8-methylnon-6-enamide, which was used without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.02 (br. *d*, *J* = 7, 1 H); 5.68 (*dd*, J_1 = 15.6, J_2 = 6.5, 1 H); 5.36 (*dd*, J_1 = 15.6, J_2 = 6.7, 1 H); 4.68–4.52 (*m*, 2 H); 4.22 (*t*, *J* = 7.4, 1 H); 3.77 (*dd*, J_1 = 7.4, J_2 = 5.5, 1 H); 3.70–3.34 (*m*, 3 H); 3.51 (*s*, 3 H); 3.23 (*d*, *J* = 14.9, 1 H); 3.10 (*s*, 3 H); 2.28 (*sept.*, *J* = 6.7, 1 H); 2.25–2.16 (*m*, 2 H); 2.12 (*s*, 3 H); 2.11–2.04 (*m*, 1 H); 1.64–1.54 (*m*, 2 H); 1.31–1.25 (*m*, 1 H); 0.99 (*d*, *J* = 6.7, 3 H); 0.98 (*d*, *J* = 6.7, 3 H); 0.89 (*s*, 9 H); 0.09 (*s*, 3 H); 0.05 (*s*, 3 H).

To a soln. of 7.3 mg (0.015 mmol) of the above intermediate in 0.8 ml of anh. THF at r.t. was added dropwise 30 µl of a 1.0M soln. of TBAF in THF (0.03 mmol). The soln. was stirred at r.t. for 15 min and quenched with 3 ml of H_2O. The phases were separated, and the aq. phase was washed with 1 ml of CH_2Cl_2, treated with 5 mg of solid $NaHCO_3$, and lyophilized. The residue was purified by FC (C_{18} reversed-phase SiO_2; MeOH/H_2O 1:10 → 2:1) to afford 4.3 mg (74%) of *bengamide Z* (**1**) as a colorless, viscous oil, which was spectroscopically indistinguishable from an authentic sample [3]. $[\alpha]_D^{25} = +44$ (*c* = 0.9, MeOH); lit.: +45 (*c* = 0.11, MeOH) [3][4]. IR (neat): 3380, 2928, 1644. ^{1}H-NMR (400 MHz, CD_3OD): 5.72 (*dd*, J_1 = 15.5, J_2 = 6.6, 1 H); 5.43 (*dd*, J_1 = 15.5, J_2 = 7.5, 1 H); 4.71 (*d*, *J* = 10.9, 1 H); 4.69 (*t*, *J* = 7.2, 1 H); 3.82–3.65 (*m*, 3 H); 3.55 (*dd*, J_1 = 7.0, J_2 = 2.0, 2 H); 3.39 (*s*, 3 H); 3.21 (br. *d*, *J* = 14.8, 1 H); 3.04 (*s*, 3 H); 2.28 (*sept.*, *J* = 6.7, 1 H); 2.21–2.09 (*m*, 1 H); 1.99 (br. *d*, *J* = 14.1, 1 H); 1.79–1.52 (*m*, 2 H); 1.00 (*d*, *J* = 6.7, 6 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 174.2; 173.0; 142.1; 127.6; 83.5; 75.0; 74.3; 68.4; 58.7; 57.5; 52.9; 37.2; 36.7; 32.2; 30.1; 22.7; 22.6.

*(3*S*,6*S*)-6-[((2*R*,3*R*,4*R*,5*R*,6*E*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-3-hydroxy-2-methoxy-8-methyl-4-[(phenyl)methoxy]non-6-enoyl)amino]-2,3,4,5,6,7-hexahydro-1-methyl-7-oxoazepin-3-yl Tetradecanoate* (**49**). A 25-ml round-bottom flask, equipped with a cold finger, was charged with 0.322 g of **33** (0.61 mmol), 0.209 g of **47** (0.61 mmol), and 1.5 ml of anh. dioxane. The soln. was heated to reflux under Ar, and the reaction was monitored by TLC (hexanes/AcOEt 2:1, visualization by *p*-anisaldehyde and UV). After 23 h, the reaction was complete according to TLC. The mixture was cooled to r.t. and diluted with 30 ml of AcOEt and 20 ml of H_2O. The phases were separated, and the aq. phase was extracted with 10 ml of AcOEt (3×). The combined org. phases were washed with 20 ml of H_2O (2×) and 30 ml of sat. brine (2×), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in hexanes/AcOEt 5:1 and filtered through a plug of SiO_2 to remove the phenylthiol. The column was then flushed with AcOEt/hexanes 3:1, and the eluate was concentrated *in vacuo* to afford 0.48 g (98%) of **49** as a clear, glassy solid. $[\alpha]_D^{25} = +28$ (*c* = 0.76, CH_2Cl_2). IR (neat): 3405, 2925, 1737, 1659. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 6.2, 1 H); 7.38–7.24 (*m*, 5 H); 5.64 (*dd*, J_1 = 15.6, J_2 = 6.5, 1 H); 5.42 (*dd*, J_1 = 15.6, J_2 = 7.4, 1 H); 4.93 (*d*, *J* = 11.6, 1 H); 4.65–4.56 (*m*, 2 H); 4.62 (*d*, *J* = 11.6, 1 H); 4.35 (*t*, *J* = 7.2, 1 H); 3.83 (br. *d*, *J* = 5.8, 1 H); 3.64–3.50 (*m*, 3 H); 3.23 (*s*, 3 H); 3.22–3.15 (*m*, 1 H); 3.07 (*s*, 3 H); 3.08–3.00 (*m*, 1 H); 2.3 (*t*, *J* = 7.5, 2 H); 2.32–2.26 (*m*, 1 H); 2.18–2.10 (*m*, 1 H); 2.05–1.84 (*m*, 1 H); 1.63–1.55 (*m*, 4 H); 1.25–1.29 (*m*, 18 H); 0.97 (*d*, *J* = 6.7, 6 H); 0.88 (*t*, *J* = 5.6, 3 H); 0.86 (*s*, 9 H); 0.03 (*s*, 3 H); 0.01 (*s*, 3 H). ^{13}C-NMR (400 MHz, $CDCl_3$): 173.0; 172.0; 170.5; 140.5; 138.8; 128.3; 127.8; 127.4; 126.8; 82.5; 80.4; 75.2; 74.3; 71.1; 69.3; 58.5; 53.3; 51.2; 36.2; 34.3; 32.7; 31.9; 30.7; 29.6; 29.6; 29.4; 29.3; 29.2; 29.1; 25.9; 24.8; 22.7; 22.2; 22.0; 18.1; 14.1; −4.0; −4.6. HR-MS: 803.5622 ($[M+1]^+$, $C_{45}H_{79}N_2O_8Si$; calc. 803.5606).

Sodium 2-[(2-Naphthyl)methoxy]acetate (**55**). To a slurry of 4.06 g of NaH (169 mmol) in 150 ml of anh. THF at 0° was slowly added 14.8 ml (16.03 g, 154 mmol) of neat *ethyl 2-hydroxyacetate* (**54**) over 15 min, and the cooling bath was removed. After 30 min, a soln. of 34.0 g of 2-(bromomethyl)naphthalene (154 mmol) in 100 ml of THF was added *via* cannula at r.t. followed by the addition of a catalytic amount (*ca.* 300 mg) of Bu_4NI. After 18 h at r.t., 100 ml of sat. aq. NH_4Cl soln. was added, and the layers were separated. The aq. phase was extracted with 100 ml of AcOEt (3×), and the combined org. extracts were washed successively with 150 ml each of H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (SiO_2; hexanes/AcOEt 9:1) to afford 35.0 g (80%) of ethyl 2-[(2-naphthyl)methoxy]acetate as a yellow oil. IR (film): 3055, 1748, 1602. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.90–7.77 (*m*, 4 H); 7.57–7.45 (*m*, 3 H); 4.82 (*s*, 2 H); 4.26 (*q*, *J* = 7.1, 2 H); 4.16 (*s*, 2 H); 1.31 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.2; 134.5; 133.1; 133.0; 128.2; 127.8; 127.6; 126.8; 126.1; 126.0; 125.8; 73.3; 67.1; 30.8; 14.1. MS: 243 ($[M-1]^+$). HR-MS: 244.1107 (M^+, $C_{15}H_{16}O_3$; calc. 244.1099).

A 7.28-g sample of solid NaOH pellets (182 mmol) was added to a magnetically stirred soln. of 12.21 g (50 mmol) of the above intermediate in 90 ml of MeOH. After 10 h at r.t., the resulting precipitate was collected by suction and dried *in vacuo* overnight to afford 11.55 g (97%) of **55** as a white solid used without further purification.

(1S,4S)-2-[2-[(2-Naphthyl)methoxy]acetyl]-4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**56**). To a suspension of 11.55 g (48.5 mmol) of **55** in 100 ml of THF was added dropwise 5.848 g of neat pivaloyl chloride (48.5 mmol) at r.t. After 30 min stirring at r.t., the resulting mixture was cooled to $-78°$, and 200 ml of a $-78°$ cold 0.27M soln. of the lithiated chiral auxiliary (obtained by treatment of a soln. of 8.38 g of **8** (54.7 mmol) in *ca.* 175 ml of anh. THF with 36.5 ml of a 1.5M soln. of BuLi in hexanes) was added *via* cannula. The soln. was allowed to warm slowly to r.t. in the cold bath for *ca.* 4–5 h. After an additional 12 h at r.t., the mixture was diluted with 100 ml of sat. aq. NH_4Cl soln. and mixed well. After separation of the phases, the aq. phase was extracted with 50 ml of AcOEt (3×), the org. phases were combined, washed successively with 100 ml each of H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (SiO_2; hexanes/AcOEt 3:2) to afford 11.9 g (71%, two steps) of **56** as a white solid. M.p. 80–82°. $[\alpha]_D^{25} = +2.3$ ($c = 2.9$, AcOEt). IR (film): 3054, 3013, 1746, 1704, 1602. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.85–7.80 (*m*, 4 H); 7.58–7.43 (*m*, 3 H); 4.84 (*s*, 2 H); 4.69 (*s*, 1 H); 4.61 (*s*, 2 H); 1.86 (*d*, $J = 10.3$, 1 H); 1.78–1.60 (*m*, 3 H); 1.10 (*s*, 3 H); 1.05 (*s*, 3 H); 0.86 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.9; 169.2; 134.7; 133.1; 133.0; 128.1; 127.8; 127.5; 126.8; 125.9; 125.8; 125.8; 109.3; 73.4; 70.4; 57.2; 53.9; 44.6; 42.0; 38.0; 26.2; 25.6; 9.6. MS: 352 ($[M+1]^+$). HR-MS: 352.1914 ($[M+1]^+$, $C_{22}H_{26}NO_3$; calc. 352.1913).

*(1S,4S)-2-((2S,3R,4E)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-6-methyl-2-[(2-naphthyl)methoxy]hept-4-enoyl)-4,5,5-trimethyl-2-azabicyclo[2.2.1]heptan-3-one* (**57**). A soln. of 50 mg of **56** (0.14 mmol) in 0.75 ml of anh. CH_2Cl_2 was cooled to $-78°$, and 49 µl of neat (i-Pr)NEt (0.28 mmol) was added. The resulting mixture was treated dropwise with 29 µl of neat Et_2BOTf (0.15 mmol)[3]) and the $-78°$ cooling bath was replaced with a 0° cold bath. After 1 h, the mixture was cooled again to $-78°$, 18 mg of neat aldehyde **6** (0.18 mmol) was added slowly over several min and rinsed in with a small amount of THF, and the resulting mixture was warmed to $-40°$. After 23 h at that temp., 0.5 ml of a mixture of pH 7.5 buffer/MeOH 3:1 was added, followed by the cautious addition of 0.5 ml of a mixture of MeOH/30% aq. H_2O_2 3:1 with vigorous stirring at 0°. After 1 h, the layers were separated, and the aq. phase was extracted thoroughly with 2 ml portions of CH_2Cl_2 (3×). The combined org. phases were washed with 5 ml each of H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 60–66 mg of the expected aldol adduct as a light yellow solid used without further purification.

A soln. of the above intermediate (*ca.* 0.14 mmol) in 1.0 ml of CH_2Cl_2 was treated with 38 mg of solid imidazole (0.57 mmol) and 42 mg (0.28 mmol) of solid TBSCl[3]). After stirring for 11 h at r.t., 2 ml of sat. aq. $NaHCO_3$ soln. was added, and the phases were separated. The aq. phase was extracted thoroughly with 2 ml of CH_2Cl_2 (3×), and the org. extracts were combined, washed with 5 ml H_2O and sat. brine, dried ($MgSO_4$), concentrated, and purified by FC (SiO_2; hexanes/AcOEt 9:1) to afford 56 mg (70%, two steps) of **57** (d.r. 55:1)[6]) as a clear oil. $[\alpha]_D^{25} = +1.3$ ($c = 2.9$, AcOEt). IR (film): 3051, 3012, 1746, 1698. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.82–7.71 (*m*, 4 H); 7.50–7.40 (*m*, 3 H); 5.65 (*dd*, $J_1 = 15.7$, $J_2 = 6$, 1 H); 5.54 (*dd*, $J_1 = 16.0$, $J_2 = 7.0$, 1 H); 5.04 (*d*, $J = 4.9$, 1 H); 4.78 (*s*, 2 H); 4.55 (br. *s*, 1 H); 4.48 (*dd*, $J_1 = 7.2$, $J_2 = 5.1$, 1 H); 2.35–2.20 (*sept.*, $J = 7.0$, 1 H); 1.80 (*d*, $J = 10.4$, 1 H); 1.67–1.62 (*m*, 1 H); 1.57–1.53 (*m*, 1 H); 1.47–1.42 (*m*, 1 H); 1.27 (*t*, $J = 7.1$, 1 H); 1.05 (*s*, 3 H); 1.00–0.76 (*m*, 23 H); 0.43 (*s*, 2 H); 0.02 (*s*, 3 H); 0.01 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.1; 169.8; 139.8; 135.4; 133.0; 132.9; 127.8; 127.4; 126.6; 126.0; 125.7; 125.6; 109.3; 82.4; 75.5; 73.2; 57.3; 54.4; 44.4; 41.1; 37.8; 30.5; 26.1; 25.9; 25.7; 25.0; 22.1; 21.8; 18.1; 9.8; −4.3; −4.9. MS: 587 ($[M+Na]^+$. HR-MS: 586.3310 ($C_{34}H_{49}NNaO_4Si^+$; calc. 586.3329).

Preparation of **57** *on Larger Scale.* A soln. of 1.16 g of **56** (3.31 mmol) in 20 ml of anh. CH_2Cl_2 was cooled to $-78°$, and 1.15 ml of neat (i-Pr)NEt (6.61 mmol) was added. The resulting mixture was treated dropwise with 0.68 ml of neat Et_2BOTf (3.47 mmol)[3]), and the $-78°$ cooling bath was replaced with a 0° cold bath. After 1 h, the resulting mixture was cooled again to $-78°$, 421 mg of neat aldehyde **6** (4.30 mmol) was added slowly over several min and rinsed in with a small amount of THF, and the reaction mixture was warmed to $-40°$. After 20 h at that temp., 8 ml of a mixture of pH 7.5 buffer/MeOH 3:1 was added, followed by the cautious addition of 8 ml of a mixture of MeOH/30% aq. H_2O_2 3:1 with vigorous stirring at 0°. After 1 h, the layers were separated, and the aq. phase was extracted thoroughly with 20 ml of CH_2Cl_2 (3×). The combined org. phases were washed successively with H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 1.45–1.57 g of the expected aldol adduct as a light yellow solid used without further purification.

A soln. of the above intermediate (*ca.* 3.31 mmol) in 12 ml of CH_2Cl_2 was treated with 788 mg of solid imidazole (11.58 mmol) followed by the addition of 871 mg (5.78 mmol) of solid TBSCl[4]). After stirring for 15 h at r.t., 12 ml of a sat. aq. $NaHCO_3$ soln. was added, and the phases were separated. The aq. phase was extracted thoroughly with 12 ml of CH_2Cl_2 (3×), and the org. extracts were combined, washed successively with 10 ml of

---

6) Determined by HPLC.

H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (SiO_2; hexanes/AcOEt 9:1) to afford 1.32 g (71%, two steps) of **57** (dr >24:1)[7]) as a clear oil. $[\alpha]_D^{25} = +1.3$ ($c = 2.9$, AcOEt). For anal. data, see above.

S-*Ethyl (2*S*,3*R*,4*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-2-[(2-naphthyl)methoxy]hept-4-enethioate* (**58**). A soln. of 0.82 ml of ethane-1,2-thiol (11.03 mmol) in 50 ml of THF was cooled to −78°, and 6.13 ml of a 1.35M soln. of BuLi in hexanes (8.28 mmol) was added. After 30 min at −78°, a soln. of 3.24 g of **57** (5.52 mmol) in 25 ml of THF (precooled to −78°) was added *via* cannula, and the resulting mixture was warmed to −40°. After 10 h at that temp., the mixture was warmed to r.t., quenched with 25 ml of sat. aq. NH_4Cl soln., and the resulting mixture was diluted with 150 ml Et_2O. The phases were separated, and the aq. phase was extracted with 50 ml of Et_2O (3×). The org. phases were combined, washed successively with 50 ml each of H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (SiO_2; hexanes/AcOEt 9:1) to afford 2.38 g (91%) of **58** as a clear oil. $[\alpha]_D^{25} = -59.7$ ($c = 2.3$, AcOEt). IR (film): 3055, 3030, 1682, 1605. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.84 (*d*, *J* = 8, 4 H); 7.55–7.45 (*m*, 3 H); 5.56 (*dd*, $J_1 = 15.5$, $J_2 =$ 7.4, 1 H); 4.99 (*d*, *J* = 12.0, 1 H); 4.65 (*d*, *J* = 12.0, 1 H); 4.41–4.36 (*m*, 1 H); 3.89 (*d*, *J* = 4.4, 1 H); 2.89 (*dd*, $J_1 =$ 14.8, $J_2 = 7.4$, 2 H); 2.27–2.14 (*m*, 1 H); 1.28 (*t*, *J* = 7, 4 H); 0.94 (*d*, *J* = 6.8, 6 H); 0.88 (*s*, 9 H); 0.03 (*s*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 201.6; 140.0; 134.6; 133.0; 133.0; 127.9; 127.8; 127.5; 127.0; 126.2; 125.9; 125.8; 88.6; 75.4; 73.7; 30.6; 25.7; 22.4; 21.9; 18.1; 14.4; −4.4; −4.9. MS: 473 ($[M+1]^+$). HR-MS: 473.2529 ($[M+1]^+$, $C_{27}H_{41}O_3SSi$; calc. 473.2545).

S-*Phenyl (2*R*,3*R*,4*R*,5*R*,6*E*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-3-hydroxy-2-methoxy-8-methyl-4-[(2-naphthyl)methoxy]non-6-enethioate* (**53**). A soln. of 2.02 g of **58** (4.28 mmol) in 40 ml of anh. toluene was cooled to −78°, and 5.3 ml (7.95 mmol) of a 1.0M soln. of DIBAL in hexanes was added dropwise by slow addition down the side of the flask to effect precooling[8]). After 45 min at −78°, the mixture was quenched with 8 ml of a 1.0M soln. of aq. HCl, and the cooling bath was removed. After 35 min, excess solid Na_2CO_3 was added, and the mixture was filtered and concentrated *in vacuo*. The contents were permitted to remain on the rotary evaporator for 20 min at 90° after the bulk of the solvent had been removed (to assure complete decomposition of the hemithioacetal to the aldehyde) to afford 1.75 g (99%) of *(2*S*,3*R*,4*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-2-[(2-naphthyl)methoxy]hept-4-enal* (**59**) as a clear oil used without further purification. $[\alpha]_D^{25} = -22.8$ ($c = 0.9$, AcOEt). IR (film): 3051, 2711, 1734, 1581. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.71 (*d*, *J* = 1.4, 1 H); 7.87–7.76 (*m*, 4 H); 7.53–7.46 (*m*, 3 H); 5.66 (*dd*, $J_1 = 15.5$, $J_2 = 6.5$, 1 H); 5.54 (*dd*, $J_1 = 15.6$, $J_2 = 6.6$, 1 H); 4.94 (*d*, *J* = 12.3, 1 H); 4.74 (*d*, *J* = 12.3, 1 H); 4.47–4.42 (*m*, 1 H); 3.83–3.79 (*m*, 1 H); 2.31–2.26 (*m*, 1 H); 0.99 (*t*, *J* = 6.0, 6 H); 0.88 (*s*, 9 H); 0.03 (*s*, 3 H); 0.02 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 202.8; 140.5; 134.9; 133.1; 133.1; 128.3; 127.9; 127.7; 126.8; 126.2; 126.0; 125.8; 125.4; 86.3; 74.1; 73.0; 30.7; 25.8; 22.1; 22.1; 18.1; −4.3; −5.0. MS: 430 ($[M+H_2O]^+$).

A soln. of 1.94 g of **32** ((*E*)/(*Z*) *ca.* 10:1) (7.63 mmol) in 15 ml of anh. CH_2Cl_2 was cooled to −78° under Ar, and 3.8 ml of a 1.0M soln. of $SnCl_4$ in heptane (990 mg, 3.8 mmol) was added dropwise. After 45 min at −78°, a soln. of 1.57 g of **59** (3.82 mmol) in 22 ml of CH_2Cl_2 (precooled to −78°) was added dropwise *via* cannula. After 1.5 h at that temp., 20 ml of sat. aq. $NaHCO_3$ soln. was added. After warming to r.t., the biphasic mixture was diluted with 20 ml of H_2O and shaken vigorously. The phases were separated, and the aq. phase was extracted with 20 ml of CH_2Cl_2 (3×). The org. phases were combined, washed successively with 25 ml each of sat. aq. $NaHCO_3$ soln. and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (SiO_2; hexanes/AcOEt 9:1) to afford 1.41 g (62%) of **53** (dr >8:1)[7]) as a clear oil. $[\alpha]_D^{25} = +55.9$ ($c = 3.7$, AcOEt). IR (film): 3478, 3059, 3025, 1704. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.92–7.85 (*m*, 4 H); 7.58–7.48 (*m*, 3 H); 7.42 (*s*, 5 H); 5.73 (*dd*, $J_1 = 15.6$, $J_2 = 6.7$, 1 H); 5.52 (*dd*, $J_1 = 15.6$, $J_2 = 7.5$, 1 H); 5.15 (*d*, *J* = 11.8, 1 H); 4.89 (*d*, *J* = 11.8, 1 H); 4.22 (*t*, *J* = 7.4, 1 H); 4.02 (*t*, *J* = 8.0, 1 H); 3.80 (*d*, *J* = 7.1, 1 H); 3.72 (*d*, *J* = 7.2, 1 H); 3.28 (*s*, 3 H); 2.80 (*d*, *J* = 8.9, 1 H); 2.40–2.32 (*m*, 1 H); 1.05 (*d*, *J* = 6.7, 6 H); 0.95 (*s*, 9 H); 0.10 (*s*, 3 H); 0.09 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 199.4; 140.9; 135.8; 134.6; 133.1; 132.9; 129.1; 129.0; 128.1; 127.8; 127.6; 127.1; 126.6; 126.1; 126.0; 125.9; 88.0; 79.6; 75.1; 74.4; 71.1; 58.9; 30.8; 25.9; 22.1; 22.0; 18.1; −4.2; −4.7. MS: 617 ($[M+Na]^+$). HR-MS: 617.2762 ($[M+Na]^+$, $C_{34}H_{46}NaO_5SSi$; calc. 617.2733).

*(3*S*,6*S*)-6-[((2*R*,3*R*,4*R*,5*R*,6*E*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-3-hydroxy-2-methoxy-8-methyl-4-[(2-naphthyl)methoxy]non-6-enoyl)amino]-2,3,4,5,6,7-hexahydro-7-oxo-1-methylazepin-3-yl Tetradecanoate* (**60**). To a soln. of 304 mg of **53** (0.51 mmol) in 7.0 ml of anh. dioxane was added 189 mg of **47** (0.51 mmol), and the resulting soln. was heated at reflux for 30 h under Ar. The mixture was cooled to r.t., 25 ml each of AcOEt and

---

7) Determined by ^{1}H-NMR.

8) Less than 1.8 equiv. of DIBAL are insufficient to complete the reaction.

H_2O were added and, after thorough mixing, the phases were separated. The aq. phase was extracted with 5 ml of AcOEt (3×), and the combined org. phases were washed successively with 20 ml each of H_2O and sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by radial chromatography on a 1 mm silica-gel plate (hexanes/AcOEt 3:2) to afford 296 mg (69%) of **60** as a clear oil. $[\alpha]_D^{25} = +37.3$ ($c = 0.9$, AcOEt): ^{1}H-NMR (400 MHz, $CDCl_3$): 7.82–7.77 (*m*, 5 H); 7.52–7.41 (*m*, 3 H); 5.67 (*dd*, $J_1 = 15.6$, $J_2 = 6.5$, 1 H); 5.46 (*dd*, $J_1 = 15.6$, $J_2 = 7.4$, 1 H); 5.11 (*d*, $J = 11.8$, 1 H); 4.79 (*d*, $J = 11.8$, 1 H); 4.61–4.52 (*m*, 2 H); 4.40 (*t*, $J = 7.2$, 1 H); 3.91–3.85 (*m*, 1 H); 3.68 (*d*, $J = 6.6$, 1 H); 3.59 (*d*, $J = 7.0$, 1 H); 3.43 (*dd*, $J_1 = 14.7$, $J_2 = 10.0$, 1 H); 3.2 (*s*, 3 H); 3.07 (br. *s*, 1 H); 3.03 (*s*, 3 H); 2.35–2.27 (*m*, 3 H); 2.20–2.04 (*m*, 2 H); 1.99–1.82 (*m*, 1 H); 1.65–1.50 (*m*, 3 H); 1.30–1.15 (*m*, 21 H); 0.99 (*dd*, $J_1 = 6.6$, $J_2 = 4.0$, 1 H); 0.88 (*s*, 9 H); 0.03 (*s*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.9; 171.9; 170.4; 140.4; 136.2; 133.1; 132.7; 132.1; 127.8; 127.5; 126.7; 126.0; 125.8; 125.8; 125.6; 113.5; 82.6; 80.3; 75.1; 74.2; 71.0; 69.1; 58.3; 55.3; 53.0; 51.0; 36.0; 34.2; 32.5; 31.8; 30.6; 29.5; 29.5; 29.3; 29.2; 29.1; 29.0; 25.8; 24.7; 22.5; 22.1; 21.9; 18.0; 14.0; 2.9; −4.2; −4.7. MS: 888 ($[M + Cl]^+$. HR-MS: 875.5557 ($[M + Na]^+$, $C_{49}H_{80}N_2NaO_8Si$; calc. 875.5581).

(3S,6S)-6-{[(2R,3R,4S,5R,6E)-3,4,5-Trihydroxy-2-methoxy-8-methylnon-6-enoyl]amino}-2,3,4,5,6,7-hexahydro-7-oxo-1-methylazepin-3-yl Tetradecanoate (=(+)-Bengamide B; **1**). *Procedure A:* To a soln. of 111 mg of **60** (0.13 mmol) in 3.0 ml of a mixture of CH_2Cl_2/MeOH 4:1 at r.t. was added 44 mg of solid DDQ (0.20 mmol). After 2 h, 1.8 ml of MeOH (resulting in a 1:1 mixture of CH_2Cl_2/MeOH) and 163 mg of solid PPTS (0.65 mmol) were added, and the resulting mixture was warmed to 45°. After 6 h at that temp., the mixture was cooled to r.t., and the solvent was removed *in vacuo*. The residual oil was taken up in 10 ml of CH_2Cl_2, and the soln. was washed with 5 ml of sat. aq. $NaHCO_3$ soln. (2×), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by radial chromatography (1 mm SiO_2 plate; CH_2Cl_2/MeOH 19:1) to afford 69 mg (89%) of **1**[9]) as a waxy, white solid. M.p. 27–29°. $[\alpha]_D^{25} = +42.3$ ($c = 0.3$, MeOH); lit.: +34.6 ($c = 0.11$, MeOH) [12]. IR (film): 3368, 1734, 1660, 1639, 1587. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.13 (*d*, $J = 6.1$, 1 H); 5.79 (*dd*, $J_1 = 15.5$, $J_2 = 6.5$, 1 H); 5.46 (*dd*, $J_1 = 15.5$, $J_2 = 7.2$, 1 H); 4.70–4.55 (*m*, 2 H); 4.40–4.25 (*m*, 1 H); 4.24–4.20 (*m*, 1 H); 3.85–3.77 (*m*, 2 H); 3.70–3.58 (*m*, 3 H); 3.55 (*s*, 3 H); 3.24 (*d*, $J = 14.8$, 2 H); 3.11 (*s*, 3 H); 2.35–2.28 (*m*, 3 H); 2.20–2.13 (*m*, 2 H); 2.05–1.90 (*m*, 2 H); 1.72–1.60 (*m*, 4 H); 1.40 (*t*, $J = 7.3$, 2 H); 1.35–1.20 (*m*, 24 H); 1.00 (*dd*, $J_1 = 7.0$, $J_2 = 2.0$, 6 H); 0.88 (*t*, $J = 7$, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.9; 172.0; 171.6; 141.7; 125.2; 80.6; 74.2; 72.7; 72.2; 69.0; 59.9; 53.2; 51.2; 45.8; 36.2; 34.2; 32.5; 31.8; 30.6; 29.5; 29.5; 29.5; 29.3; 29.2; 29.1; 28.9; 28.8; 24.7; 22.5; 22.1; 22.0; 14.0; 8.5. MS: 634 ($[M + Cl]^+$).

Procedure B: To a soln. of 8.0 mg of **60** (9.37 μmol) and H_2O (0.5 μl, 28.11 μmol) in 0.5 ml of CH_2Cl_2/MeOH 4:1 was added 3.2 mg of DDQ (14.06 μmol). After 2 h at r.t., 0.5 ml of sat. aq. $NaHCO_3$ soln. was added, and the resulting soln. was concentrated to dryness at r.t. *in vacuo*. The solid residue was diluted with 1.0 ml each of H_2O and CH_2Cl_2, mixed well, and the phases were separated. The aq. phase was extracted with 1 ml of CH_2Cl_2 (3×), and the combined org. phases were washed with 1 ml of sat. aq. $NaHCO_3$ soln. (3×). The combined aq. layers were re-extracted with 5 ml of CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), and concentrated *in vacuo* to afford 6.6 mg of a mixture of **61** and **62** (see *Scheme 13*), which, for anal. purposes, was purified by radial chromatography (1 mm SiO_2 plate; hexanes/AcOEt 19:1) to afford 3.1 mg (46%) of **61** and 3.5 mg (44%) of **62** as colorless oils.

Data of **61**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.05 (*d*, $J = 7.2$, 1 H); 5.68 (*dd*, $J_1 = 15.7$, $J_2 = 6.5$, 1 H); 5.36 (*dd*, $J_1 = 16.0$, $J_2 = 8.0$, 1 H); 4.75–4.55 (*m*, 2 H); 4.23 (*t*, $J = 7.4$, 1 H); 3.78 (*t*, $J = 7$, 1 H); 3.73–3.53 (*m*, 3 H); 3.52 (*s*, 3 H); 3.22 (*d*, $J = 14.9$, 1 H); 3.11 (*s*, 3 H); 2.36–2.22 (*m*, 3 H); 2.20–2.10 (*m*, 2 H); 2.05–1.94 (*m*, 1 H); 1.68–1.58 (*m*, 4 H); 1.37–1.20 (*m*, 25 H); 0.99 (*d*, $J = 6.7$, 3 H); 0.98 (*d*, $J = 6.7$, 3 H); 0.90 (*s*, 9 H); 0.09 (*s*, 3 H); 0.05 (*s*, 3 H).

Data of **62**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.02 (*d*, $J = 6.0$, 1 H); 7.94 (*s*, 1 H); 7.85–7.79 (*m*, 3 H); 7.65 (*d*, $J = 8.5$, 1 H); 7.50–7.44 (*m*, 2 H); 6.08 (*s*, 1 H); 5.66 (*dd*, $J_1 = 15.0$, $J_2 = 6.0$, 1 H); 5.52 (*dd*, $J_1 = 16.2$, $J_2 = 6.8$, 1 H); 4.75–4.67 (*m*, 1 H); 4.65–4.57 (*m*, 1 H); 4.55–4.49 (*m*, 1 H); 4.47–4.42 (*m*, 1 H); 3.98 (*d*, $J = 2.8$, 1 H); 3.73–3.63 (*m*, 1 H); 3.53 (*s*, 3 H); 3.24 (*d*, $J = 14.6$, 1 H); 3.12 (*s*, 3 H); 2.36–2.29 (*m*, 3 H); 2.28–2.14 (*m*, 2 H); 2.08–1.98 (*m*, 1 H); 1.65–1.56 (*m*, 4 H); 1.39–1.20 (*m*, 25 H); 1.00 (*d*, $J = 6.7$, 3 H); 0.98 (*d*, $J = 6.7$, 3 H); 0.91 (*s*, 9 H); 0.07 (*s*, 3 H); 0.04 (*s*, 3 H).

To a soln. of 5.0 mg of the above mixture of **61** (*ca.* 3.51 μmol) and **62** (*ca.* 2.94 μmol) in 0.3 ml of MeOH, containing 10 equiv. of H_2O, was added 14.8 mg of solid PPTS (58.8 μmol), the resulting soln. was warmed to 50°. After 12 h[10]), the mixture was cooled to r.t., 0.2 ml of sat. aq. $NaHCO_3$ soln. was added, and the resulting

---

[9]) Purification also afforded the dimethyl acetal of 2-naphthaldehyde.

[10]) The acetal is cleaved first, but the extended reaction time gives rise to partial cleavage of the silyl protecting group.

mixture was concentrated to dryness at r.t. *in vacuo*. The solid remainder was diluted with 2 ml each of H_2O and CH_2Cl_2, the resulting biphasic mixture was agitated well, and the phases were separated. The aq. phase was extracted with 2 ml of CH_2Cl_2 (2 ×), and the combined org. phases were washed with 5 ml of sat. brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by radial chromatography (1 mm SiO_2 plate; CH_2Cl_2/MeOH 49:1) to afford 2.9 mg (74%) of *Bengamide B* (**1**) as a white solid identical in all respects to natural *Bengamide B* and the sample obtained by *Procedure A*[9]).

REFERENCES

[1] D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1; R. J. Capon, *Eur. J. Org. Chem.* **2001**, 633; D. J. Faulkner, *Nat. Prod. Rep.* **2000**, *17*, 1; J. I. Kobayashi, M. Ishibashi, *Comp. Nat. Prod. Chem.* **1999**, *8*, 415.

[2] P. E. Phillips, K. W. Bair, J. Bontempo, P. Crews, A. M. Czuchta, F. R. Kinder, A. Vattay, R. W. Versace, B. Wang, J. Wang, A. Wood, S. Zabludoff, *Proc. Am. Assoc. Cancer Res.* **2000**, *41*, 59.

[3] Z. Thale, F. R. Kinder, K. W. Bair, J. Bontempo, A. M. Czuchta, R. W. Versace, P. E. Phillips, M. L. Sanders, S. Wattanasin, P. Crews, *J. Org. Chem.* **2001**, *66*, 1733.

[4] R. M. Valadao, P. Crews, Z. Thale, *Abstr. Pap. – Am. Chem. Soc.* **2001**, *221*, CHED-742; A. Groweiss, J. J. Newcomer, B. R. O'Keefe, A. Blackman, M. R. Boyd, *J. Nat. Prod.* **1999**, *62*, 1691; R. Fernandez, M. Dherbomez, Y. Letourneux, M. Nabil, J. F. Verbist, J. F. Biard, *J. Nat. Prod.* **1999**, *62*, 678; M. V. D'Auria, C. Giannini, L. Minale, A. Zampella, C. Debitus, M. Frostin, *J. Nat. Prod.* **1997**, *60*, 814; M. Adamczeski, E. Quinoa, P. Crews, *J. Org. Chem.* **1990**, *55*, 240; M. Adamczeski, E. Quinoa, P. Crews, *J. Am. Chem. Soc.* **1989**, *111*, 647; E. Quinoa, M. Adamczeski, P. Crews, G. J. Bakus, *J. Org. Chem.* **1986**, *51*, 4494.

[5] F. R. Kinder Jr., R. W. Versace, K. W. Bair, J. M. Bontempo, D. Cesarz, S. Chen, P. Crews, A. M. Czuchta, C. T. Jagoe, Y. Mou, R. Nemzek, P. E. Phillips, L. D. Tran, R. Wang, S. Weltchek, S. Zabludoff, *J. Med. Chem.* **2001**, *44*, 3692.

[6] P. E. Phillips, P. Allegrini, K. W. Bair, J. Bontempo, A. M. Czuchta, F. R. Kinder, D. Müller, P. Schindler, B. Stolz, H. Towbin, J. van Oostrum, A. Vattay, R. W. Versace, H. Voshol, A. W. Wood, S. Zabludoff, *Proc. Am. Assoc. Cancer Res.* **2001**, *42*, 182.

[7] H. Dumez, G. Giaccone, A. Yap, N. Barbier, C. Pfister, P. Cohen, S. F. Reese, A. T. Van Oosterom, H. M. Pinedo, *Proc. Am. Assoc. Cancer Res.* **2001**, *42*, 227.

[8] W. Liu, J. M. Szewczyk, L. Waykole, O. Repic, T. J. Blacklock, *Tetrahedron Lett.* **2002**, *43*, 1373; M. G. Banwell, K. J. McRae, *J. Org. Chem.* **2001**, *66*, 6768; N. Chida, T. Tobe, S. Okada, S. Ogawa, *J. Chem. Soc., Chem. Commun.* **1992**, 1064; H. Kishimoto, H. Ohrui, H. Meguro, *J. Org. Chem.* **1992**, *57*, 5042; N. Chida, T. Tobe, S. Ogawa, *Tetrahedron Lett.* **1991**, *32*, 1063.

[9] C. Mukai, S. M. Moharram, O. Kataoka, M. Hanaoka, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2849; C. Mukai, O. Kataoka, M. Hanaoka, *J. Org. Chem.* **1995**, *60*, 5910.

[10] J. A. Marshall, G. P. Luke, *J. Org. Chem.* **1993**, *58*, 6229.

[11] C. A. Broka, J. Ehrler, *Tetrahedron Lett.* **1991**, *32*, 5907; N. Chida, T. Tobe, K. Murai, K. Yamazaki, S. Ogawa, *Heterocycles* **1994**, *38*, 2383.

[12] F. R. Kinder Jr., S. Wattanasin, R. W. Versace, K. W. Bair, J. Bontempo, M. A. Green, Y. J. Lu, H. R. Marepalli, P. E. Phillips, D. Roche, L. D. Tran, R. Wang, L. Waykole, D. D. Xu, S. Zabludoff, *J. Org. Chem.* **2001**, *66*, 2118.

[13] R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, *4*, 2109.

[14] R. K. Boeckman Jr., B. T. Connell, *J. Am. Chem. Soc.* **1995**, *117*, 12368.

[15] W. Chodkiewicz, *Ann. Chim. (Fr.)* **1957**, *2*, 819.

[16] P. Chabardes, *Tetrahedron Lett.* **1988**, *29*, 6253.

[17] R. K. Boeckman Jr., A. T. Johnson, R. A. Musselman, *Tetrahedron Lett.* **1994**, *35*, 8521.

[18] R. K. Boeckman Jr., D. J. Boehmler, R. A. Musselman, *Org. Lett.* **2001**, *3*, 3777.

[19] R. L. Danheiser, J. S. Nowick, J. H. Lee, R. F. Miller, A. H. Huboux, *Org. Synth.* **1996**, *73*, 61.

[20] M. B. Andrus, B. B. V. Soma Sekhar, T. M. Turner, E. L. Meredith, *Tetrahedron Lett.* **2001**, *42*, 7197.

[21] X. Sun, D. B. Collum, *J. Am. Chem. Soc.* **2000**, *122*, 2459; A. Streitwieser, E. Juaristi, Y.-J. Kim, J. K. Pugh, *Org. Lett.* **2000**, *2*, 3739; A. Streitwieser, S. S. W. Leung, Y.-J. Kim, *Org. Lett.* **1999**, *1*, 145; A. Facchetti, A. Streitwieser, *J. Org. Chem.* **1999**, *64*, 2281; D. Seebach, R. Amstutz, J. D. Dunitz, *Helv. Chim. Acta* **1981**, *64*, 2622.

[22] C. Gennari, M. Grazia Beretta, A. Bernardi, G. Moro, C. Scolastico, R. Todeschini, *Tetrahedron* **1986**, *42*, 893.

[23] M. Demarcus, M. L. Ganadu, G. M. Mura, A. Porcheddu, L. Quaranta, G. Reginato, M. Taddei, *J. Org. Chem.* **2001**, *66*, 697; S. Kobayashi, M. Horibe, Y. Saito, *Tetrahedron* **1994**, *50*, 9629; A. Martel, J. P. Daris, C. Bachand, J. Corbeil, M. Menard, *Can. J. Chem.* **1988**, *66*, 1537.
[24] R. L. Danheiser; J. S. Nowick, *J. Org. Chem.* **1991**, *56*, 1176.
[25] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414.
[26] E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347.
[27] J. A. Frick, J. B. Klassen, A. Bathe, J. M. Abramson, H. Rapoport, *Synthesis* **1992**, 621.
[28] S. Kroger, G. Haufe, *Amino Acids* **1997**, *12*, 363.
[29] R. C. Bernotas, R. V. Cube, *Synth. Commun.* **1990**, *20*, 1209; W. M. Pearlman, *Tetrahedron Lett.* **1967**, 1663.
[30] P. Ducrot, C. Rabhi, C. Thal, *Tetrahedron* **2000**, *56*, 2683; K. Kefurt, Z. Kefurtova, J. Jary, *Collect. Czech. Chem. Commun.* **1988**, *53*, 1795; K. Kefurt, K. Capek, Z. Kefurtova, J. Jary, *Collect. Czech. Chem. Commun.* **1986**, *51*, 391.
[31] C. Dostal, S. Lauritz, E. Urban, *Heterocycles* **1992**, *34*, 135.
[32] R. J. Borgman, J. J. McPhillips, R. E. Stitzel, I. J. Goodman, *J. Med. Chem.* **1973**, *16*, 630.
[33] T. W. Greene, P. G. M. Wuts, 'Protective Groups in Organic Synthesis', 3rd edn., John Wiley & Sons, New York, 1999.
[34] J. Xia, S. A. Abbas, R. D. Locke, C. F. Piskorz, J. L. Alderfer, K. L. Matta, *Tetrahedron Lett.* **1999**, *41*, 169.
[35] E. Piers, G. L. Jung, E. H. Ruediger, *Can. J. Chem.* **1987**, *65*, 670.
[36] D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099.

Received June 24, 2002