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# Design, synthesis, and evaluation of azepine-based cryptophycin mimetics

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Dedicated to Professor K. C. Nicolaou, on the occasion of the 2002 Tetrahedron Prize, with admiration and respect, for his many seminal contributions to chemistry including, in particular, his early involvement in the Nonpeptidal Peptidomimetic Program at the University of Pennsylvania

**Abstract**—Cryptophycins, depsipeptides isolated from terrestrial blue–green algae, show potent activity against a variety of tumor cell lines. Given the potential of the cryptophycins for cancer therapy, we developed a new class of non-peptide peptidomimetic, designed to replace the 16-membered macrolide ring with a 7-membered azepine ring for attachment of the cryptophycin side chains with the required spatial orientation to mimic the conformation of the relevant region of the natural product. Monte Carlo conformational analysis revealed excellent overlay of the local minimum structural model **6** and X-ray structure of (+)-cryptophycin-3 (**5**). Starting from this structural model, we designed and synthesized compounds (+)-**25**, (+)-**30**, and (+)-**34** as potential mimics of cryptophycins. Compounds (+)-**25**, (+)-**30**, and (+)-**34** were tested for in vitro cytotoxicity against six human cancer cell lines. Although only modest activities were observed, these results suggested that a new series of bioactive cryptophycin analogues might be available by structural modification of the central ring system of the cryptophycins.


## 1. Introduction

In 1990, Schwartz and co-workers reported a novel, cyclic depsipeptide isolated from the terrestrial blue–green algae *Nostoc* sp. ATCC 53789.[1] Initially observed to have potent antifungal activity against strains of *Cryptococcus*, which frequently infect immunodeficient Acquired Immuno Deficiency Syndrome (AIDS) and cancer patients, this compound was named (+)-cryptophycin-1 (**1**, Fig. 1; also known as cryptophycin A). Concurrently, a related cytotoxin, (+)-arenastatin A (**2**, cryptophycin-24), was isolated from the Okinawa marine sponge *Dysidea arenaria* by Kitagawa and Kobayashi.[2] The structures and stereochemistries of the cryptophycins, initially proposed on the basis of chemical and spectroscopic studies,[3] were later revised by total synthesis.[4]

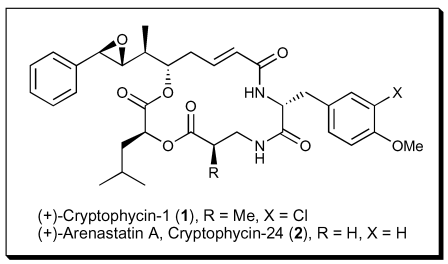


**Figure 1.** The structure of cryptophycin-1 and cryptophycin-24.

Cryptophycin-1 (**1**), the most abundant member of the family, is a potent tumor-selective cytotoxin displaying significant in vitro activity against tumor cell lines ($IC_{50}$=9–20 pM).[5] The broad spectrum of antitumor activity of **1** against a variety of human tumor xenographs and murine solid tumor models is particularly noteworthy.[4,5a,6] Importantly, cryptophycin-1 demonstrates low susceptibility to P-glycoprotein-mediated multiple drug resistance when compared to currently utilized natural product anticancer drugs.[6b,c] The KB human nasopharyngeal carcinoma cell line which demonstrates resistance to vinblastine, colchicines, and Taxol®, displays no resistance to cryptophycin-1. Thus, overexpression of P-glycoprotein does not lead to resistance to **1**.[6b]

At the molecular level (+)-cryptophycin-1 (**1**) inhibits tubulin polymerization by binding to the ends of microtubules, resulting in potent suppression of microtubule

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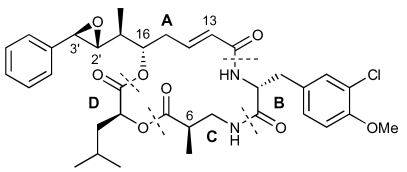
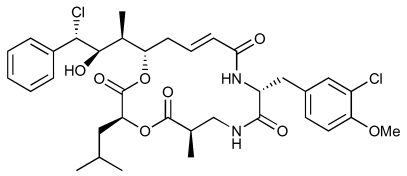
dynamics, which in turn induces apoptosis, and thereby the observed antiproliferative activity.[6,7]

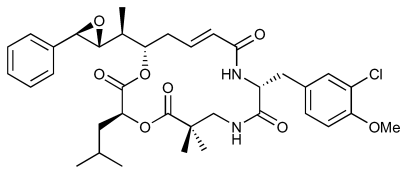
Further studies by Moore and co-workers led to the isolation of 26 closely related cryptophycins providing important structure–activity relationship (SAR) information,[3,6a] suggesting the presence of several important pharmacophores[3] (Fig. 2) including: (i) the intact macrolide ring, (ii) the β-epoxide (C2′, C3′) in unit A, (iii) the chloro and the methoxy substituents in unit B, and (iv) the C(6) methyl group in unit C.




(+)-Cryptophycin-1 (**1**)




(+)-Cryptophycin-8 (**3**)




Cryptophycin-52 (**4**)

**Figure 2.** Analogues of (+)-cryptophycin-1 with improved therapeutic index.

Efforts to develop cryptophycin analogues possessing enhanced pharmacokinetic properties have produced (+)-cryptophycin-8[3,8] and cryptophycin-52[9] (**3** and **4**, respectively; Fig. 2). The semisynthetic chlorohydrin (+)-**3** showed similar in vitro cytotoxic activity relative to (+)-**1**, but was found to have an improved therapeutic index in several animal models implying potential clinical activity.[10] These results suggested that (+)-cryptophycin-8 might be a prodrug, which can accumulate at the tumor site where it is transformed into (+)-cryptophycin-1.[3] Indeed, the much lower activity of (+)-**3** in an in vitro microtubule assembly assay, compared to that of (+)-1, indicated that the chlorohydrin derivative has reduced or no biological activity and that the observed activity results from the generation of (+)-**1**.[10d] Also noteworthy, (+)-cryptophycin-8 was curative for four of the tumor models evaluated (mouse colon-38, human prostate TSU, human prostate LNCaP, and human breast MX-1).[10b,c]

Cryptophycin-52 (**4**), designed to enhance hydrolytic stability relative to (+)-**1** while maintaining a favorable profile of antitumor activity,[9] is currently in phase II clinical trials.[9c] As noted by Moore et al., the ester functionality connecting units C and D of cryptophycin-1 is very susceptible to base hydrolysis.[3] Dimethyl substitution in **4** was therefore introduced to reduce this susceptibility. Cryptophycin-52 (**4**), the most potent suppressor of microtubule dynamics studied thus far, is very effective against numerous human tumor cell lines.[11] Compared to other antimitotic agents, such as Taxol®, vinblastine, and vincristine, the potency of **4** was shown to be maintained against multidrug-resistant cells.

In view of the significant potential of the cryptophycins as leads for new anticancer agents, there has been considerable interest in recent years in addressing the synthetic challenges associated with this structurally intriguing class of molecules. The first reports on the total synthesis of cryptophycins appeared in 1994 and 1995, respectively, from the research groups of Kobayashi and Kitagawa,[12] and Moore and Tius.[4] Numerous approaches followed thereafter comprising both formal and total syntheses. A strategy common to the reported syntheses has been utilization of amide and ester linkages to provide highly convergent approaches. A recent review by Eggen and Georg[13] summarized the synthetic efforts targeting the cryptophycins over the last decade.

## 2. Results and discussion

### 2.1. First generation analogues based on the azepine scaffold: strategy and design

Cognizant of the significant potential of the cryptophycins for therapeutic use, we initiated a program to develop a new class of analogues, exploiting the concept of non-peptide peptidomimetics.[14] We anticipated that the analogues would have both better stability and bioavailability since the designed scaffolds would lack the peptide bonds present in the 16-membered depsipeptide of the cryptophycins; peptides, in general, possess poor pharmacokinetic properties (e.g., poor transport properties and/or biliary secretion). Furthermore, peptides recognized by proteolytic enzymes are hydrolytically unstable.

The broad concept of placing pharmacophoric groups on non-peptide scaffolds was first proposed by Farmer in 1980.[15a] He did not, however, explore the potential of this idea, nor propose any specific scaffolds. In 1986 Bélanger and DuFresne were the first to implement this concept using a bicyclooctane scaffold,[15b] but they did not develop this important achievement further. It remained for the researchers at the University of Pennsylvania to finally put the full potential of this idea on a firm basis. In particular Hirschmann, Nicolaou, and Smith recognized the distinction in design required for peptidomimetics that are receptor ligands and those that are enzyme inhibitors.[16] This insight led them to design non-peptide peptidomimetics based on glycoside[17a,b] and polypyrrolinone[17c] scaffolds respectively. Continuing efforts by Hirschmann and Smith on the design and synthesis of non-peptide peptidomimetics has produced: (a) potent β-D-glucose-based agonists and antagonists for somatostatin (SRIF)[18a,b] and substance P (NK-1)[18c] receptors, respectively; (b) pyrrolinone-based renin[18d] and HIV-1 protease inhibitors,[18e–g] the latter having oral bioavailability in dogs, improved transport properties, and potency comparable to Crixivan® against several mutant HIV-1 viral strains;[18e] (c) pyrrolinone-based matrix metalloprotease inhibitors;[18h] and (d) competent

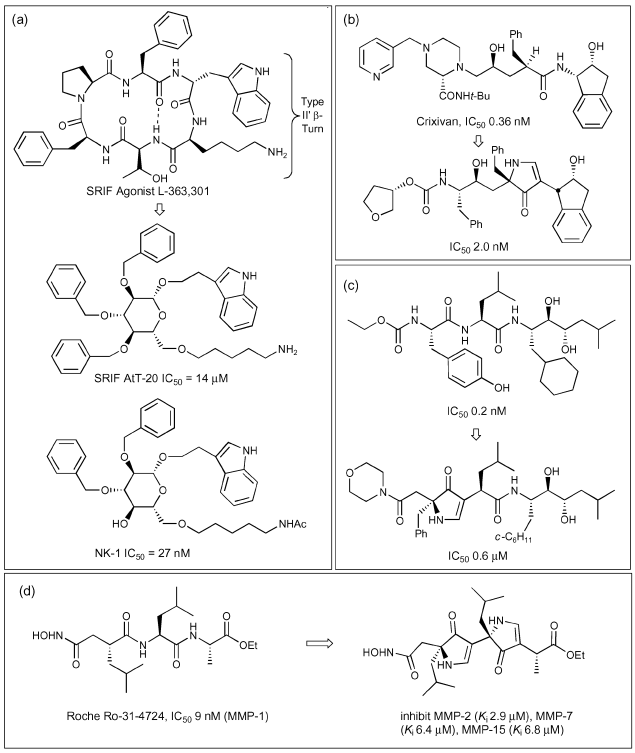



**Figure 3.** (a) β-D-glucose scaffold mimicking the β turn of the cyclic hexapeptide L 363,301. (b) Peptidal HIV-1 protease inhibitor and pyrrolinone-based inhibitor. (c) Peptidal inhibitor of renin developed by Abbott and pyrrolinone-based inhibitor. (d) Peptidyl inhibitor of MMP developed by Roche and pyrrolinone-based inhibitor.

non-peptide–peptide hybrid ligands for the human class II MHC protein HLA-DR1[18i] (Fig. 3).

Given these successes, we sought to develop a suitable scaffold to replace the 16-membered macrolide ring of cryptophycin-1 while maintaining the required spatial orientation of the side chains to mimic the conformation of the natural product. A serious caveat to this strategy was that modification of the macrolide ring might result in a conformational change of the side chains, and thereby significantly reduce the cytotoxicity.[4,5a] Since little was known about the bioactive conformations of the cryptophycins, our initial working hypothesis was that the available X-ray structure of (+)-cryptophycin-3[4] (**5**, Fig. 4) would reasonably represent the solution conformation permitting a template for scaffold design. Subsequently, NOE studies reported by Moore and co-workers have shown that the preferred side chain conformations of (+)-cryptophycin-3 in DMSO appear to be identical with those shown in the crystal structure.[4]

Early computer modeling studies suggested that a 7-membered ring could function as a viable depsipeptide ring surrogate. Compounds possessing 7-membered rings are quite prevalent as privileged structures[19] in pharmaceuticals (e.g. benzodiazepines). The efficacy of the 7-membered ring is attributed to the puckered conformation, in conjunction with a modest degree of flexibility to permit induced fit into the receptor.

With these design criteria in mind, we chose the azepine

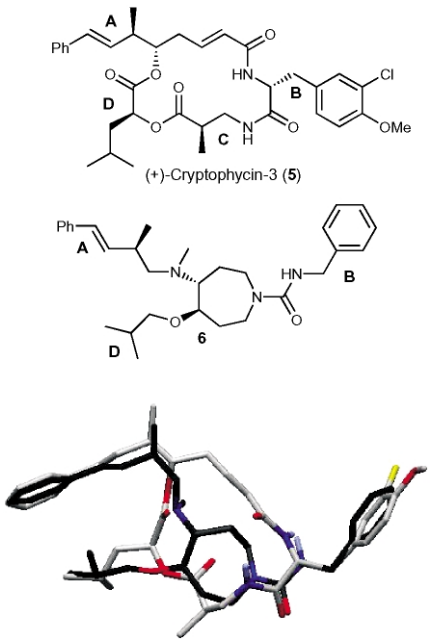



**Figure 4.** Overlay of the X-ray structure of (+)-cryptophycin-3 (**5**) and the simplified model of analogue (**6**) utilizing an azepine-based scaffold.

ring as a scaffold, reasoning that a benzyl substituent on the ring nitrogen would nicely overlay the substituted tyrosine moiety in unit B (Fig. 4). To alleviate the possibility of hydrophobic collapse induced by van der Waals interactions between the two phenyl groups, a problem observed in our initial modeling studies, we incorporated a urea subunit into the side chain. An additional advantage of the urea moiety is that it has the potential to mimic the carbonyl and NH groups in the macrolide ring of the cryptophycins. Addition of the remaining cryptophycin side chains onto the azepine scaffold completed the model for the Monte Carlo conformational analysis.[20] To simplify the calculation, we omitted the epoxide of unit A, as well as the chloro and methoxy substituents of unit B as shown in Figure 4. In addition, the relative disposition of the side chains in the crystal structure of (+)-cryptophycin-3 (**5**) was used as a constraint in the conformational search. The analysis located the global minimum for model structure **6**, in which the 7-membered ring adopted a bent half-chair conformation. The results identified a conformer (Fig. 4) displaying a similar chain topology at reasonably low

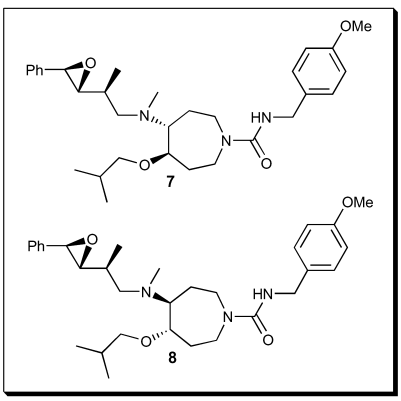
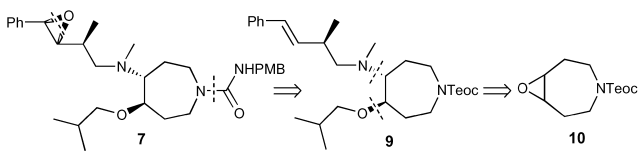



**Figure 5.** Proposed azepine-based cryptophycin analogues.

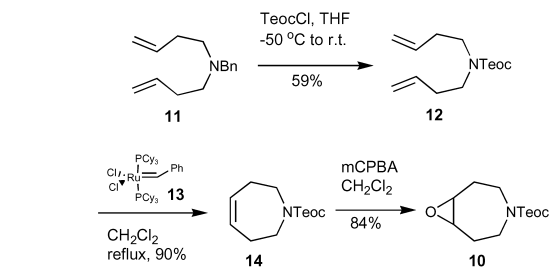
energy costs, considering the flexibility of the model structure. With this structural model available, we designed compounds **7** and **8** as potential mimics of the cryptophycins (Fig. 5). The synthetic plan permitted construction of **8**, a diastereomer of **7**, through a parallel synthesis.

### 2.2. First generation analogues: synthesis

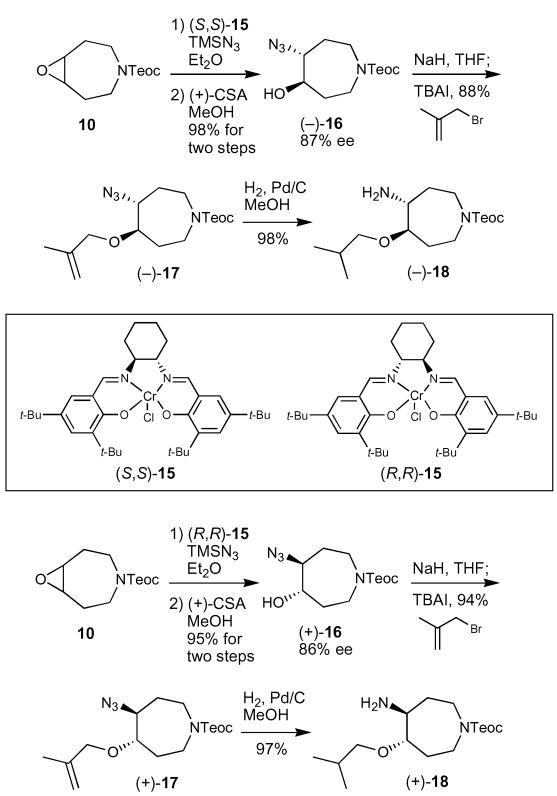
From the retrosynthetic perspective, we chose to install the epoxide at the final stage of the synthesis (Scheme 1), permitting an olefin precursor of **7**, which would mimic (+)-cryptophycin-3 (**5**), to be available for bioassay. Disconnection of the side chains led to the azepine framework **10**.




**Scheme 1.**




**Scheme 2.**

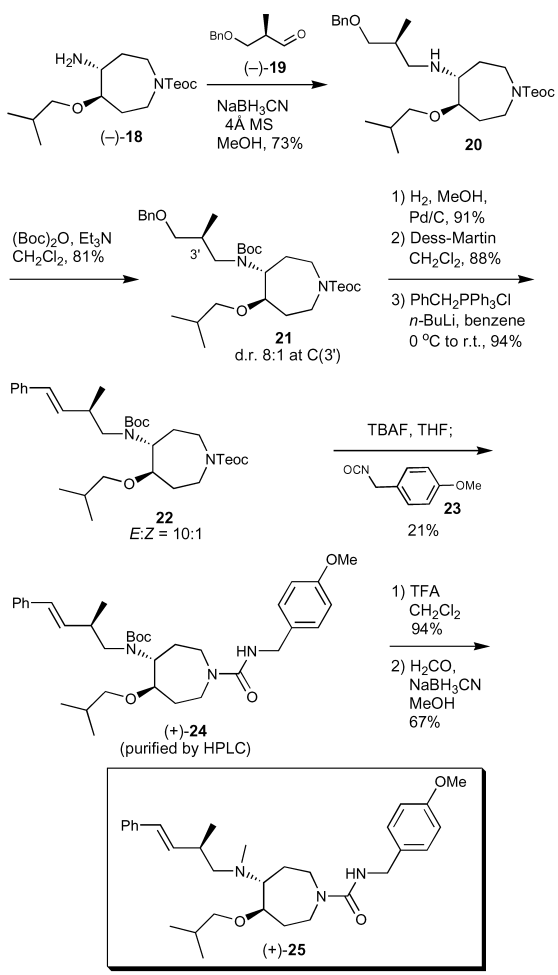



**Scheme 3.**

The synthesis of **7** and **8** began by converting known amine **11** to **12** (Scheme 2).[21] Ring-closing metathesis using Grubbs catalyst **13** led to olefin **14** in 90% yield,[22] which was epoxidized to furnish meso epoxide **10**.

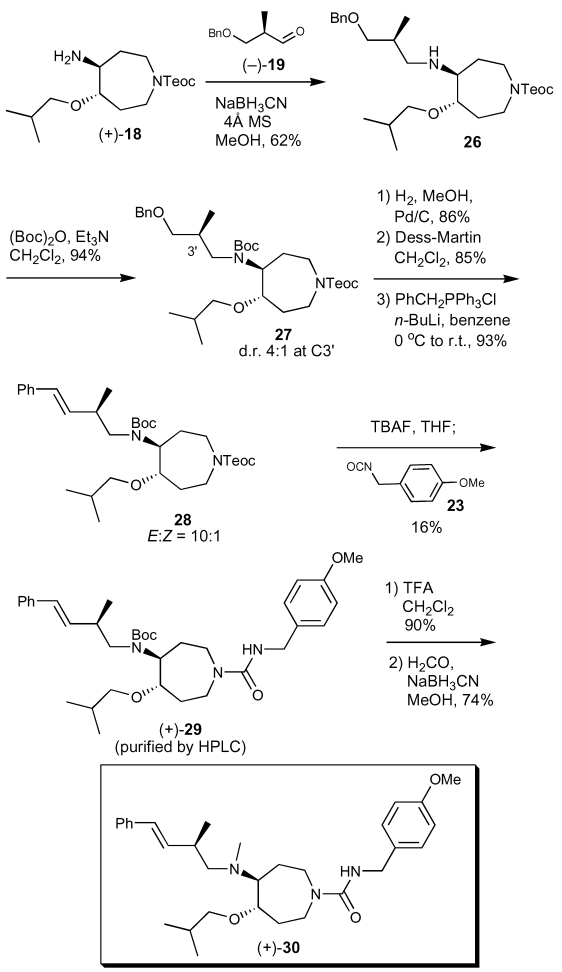
In 1995, Jacobsen reported that the chromium–salen complex was a highly effective catalyst for the enantioselective ring opening of epoxides with azidotrimethylsilane.[23] We adopted this chiral aminoalcohol synthesis to introduce functionality in an enantioselective fashion onto the azepine ring. Epoxide **10** was treated with trimethylsilyl azide in the presence of the Jacobsen Cr(salen) catalyst (*S*,*S*)-**15**[23a] (Scheme 3); reaction of the resultant azido silyl ether with camphorsulfonic acid then provided hydroxy azide (−)-**16** in 98% yield and 87% ee (two steps). Subsequent alkylation of the hydroxyl, followed by simultaneous reduction of the azide and olefin afforded amino ether (−)-**18**. The same sequence of reactions with (+)-**16** furnished the enantiomer (+)-**18**.

With both antipodes of the amino ether **18** in hand, the stage was set for incorporation of the remaining side chains. Coupling of amine (−)-**18** with aldehyde (−)-**19**[24] via reductive amination (Scheme 4) led to the corresponding secondary amine **20**,[25] which was protected as the *tert*-butyl carbamate to furnish **21** in 59% yield over the two steps. Unfortunately, NMR analysis indicated that partial




**Scheme 4.**

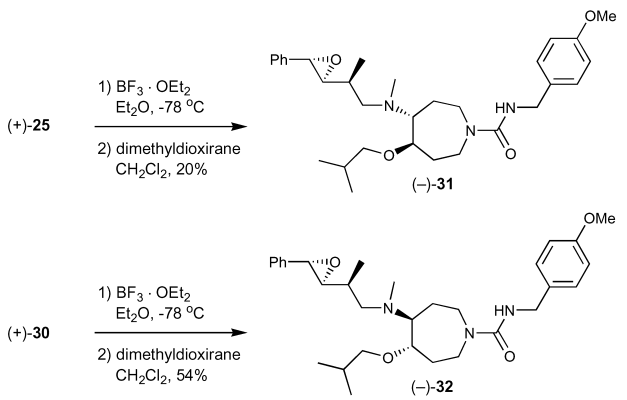
epimerization of the methyl group at C(3′) had occurred during the reductive amination; the desired compound **21** however was the major component of an 8:1 mixture of epimers determined by $^1$H NMR integration. Protection of the amine with the bulky Boc group enabled separation via HPLC later in the synthesis (vide infra). Hydrogenolysis of the benzyl ether followed by oxidation to the corresponding aldehyde and olefination utilizing the Wittig protocol[26] provided olefin **22** in 75% yield for three steps as a 10:1 mixture of *E*- and *Z*-isomers. The Teoc group was then removed with TBAF,[27] and the resulting amine coupled with commercially available 4-methoxybenzyl isocyanate **23** to furnish urea (+)-**24**.[28] At this juncture, purification by




**Scheme 5.**

reverse-phase HPLC led to (+)-**24** (>98% purity). Removal of the Boc group (TFA) and subsequent reductive N-methylation (HCHO, $NaBH_4$)[25] completed the synthesis of (+)-**25**. The same sequence of events was employed to convert (+)-**18** to (+)-**30** (Scheme 5).

Attempts to install the epoxide in the presence of the tertiary amine proved difficult, due to the high tendency of the nitrogen to undergo oxidation. Protection of the tertiary amine prior to epoxidation was therefore necessary. Messeguer and co-workers reported that a tertiary amine could be protected with a non-protic Lewis acid and that such adducts possessing olefins could be epoxidized with dimethyl dioxirane without the occurrence of oxidation at




**Scheme 6.**

nitrogen.[29] A one-pot procedure involving $BF_3$·amine complexation and epoxidation was applied to both (+)-**25** and (+)-**30** (Scheme 6). Unfortunately, only the undesired α-epoxides (−)-**31** and (−)-**32** were isolated after purification using preparative TLC.[30] We surmised that the desired β-epoxides reacted intra-molecularly with the tertiary amine either during the reaction or upon the purification to generate a 5-membered ring, whereas the undesired α-epoxides did not undergo this transformation.

### 2.3. First generation analogues: biological evaluation

Compounds (+)-**25**, (+)-**30**, (−)-**31**, and (−)-**32** (Fig. 6) were tested for in vitro cytotoxicity against six human cancer cell lines.[31] Mimic (+)-**25** displayed modest activity against four human cell lines (Table 1), suggesting that the side chains indeed occupied spatial orientation suitable for activity. Compound (+)-**30**, which differed from (+)-**25** in the stereochemistry at the junction of the side chains and the azepine ring, showed modest cytotoxicity against only two human cancer cell lines. These data suggest that the preferred trajectory of the side chains for activity was

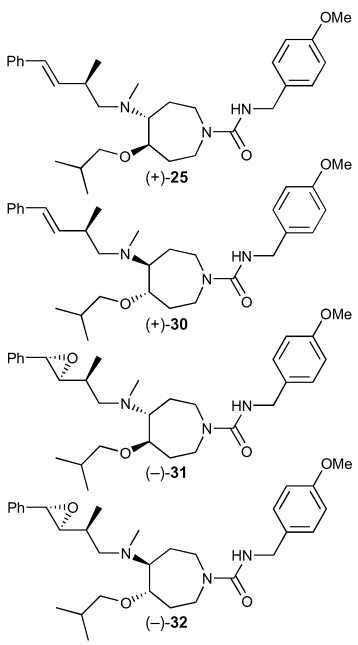



**Figure 6.** First generation analogues of cryptophycin.

**Table 1**. Biological evaluation of analogues, $GI_{50}$ (μM)

| Cell type | Cell-line | **25** | **30** | **31** | **32** |
|---|---|---|---|---|---|
| Pancreas-a | BXPC-3 | 4.8 | >10 | >10 | >10 |
| Breast adn | MCF-7 | >10 | >10 | >10 | >10 |
| CNS gliobl | SF268 | 6.8 | >10 | 10.2 | >10 |
| Lung-NSC | NCI-H460 | 3.7 | 13.2 | >10 | >10 |
| Colon | KM20L2 | 2.1 | 2.5 | >10 | >10 |
| Prostate | DU-145 | >10 | >10 | >10 | 40.3 |

obtained in (+)-**25** rather than in (+)-**30**. Lack of activity for epoxides (−)-**31**, and (−)-**32** was expected as synthetic cryptophycins with α-epoxides showed no biological activity.

We also suspect that the low potency of the analogues may result from facile protonation of the tertiary amine, which in turn would significantly change the orientation of the side chain, as well as the ability of the compounds to cross the cellular membrane. Although the analogues displayed only modest or poor cytotoxicity compared to the extraordinarily potent cryptophycins,[32] we were encouraged by the initial results which validated the utility of the azepine ring as an analogue scaffold. To enhance the biological activity of the analogues, we decided to redesign the side chains.

### 2.4. A second generation design strategy

Having demonstrated that incorporation of a tertiary amine (**6**, Fig. 4) permitted excellent overlap with cryptophycin-3 (**5**), but that installation of the β-epoxide, required for potent activity, was problematic due to the nucleophilic nitrogen, we reasoned that an ether linkage between the functional groups (Fig. 7) might enable us to install the desired epoxide with the requisite stereochemistry mimicking the cryptophycins.

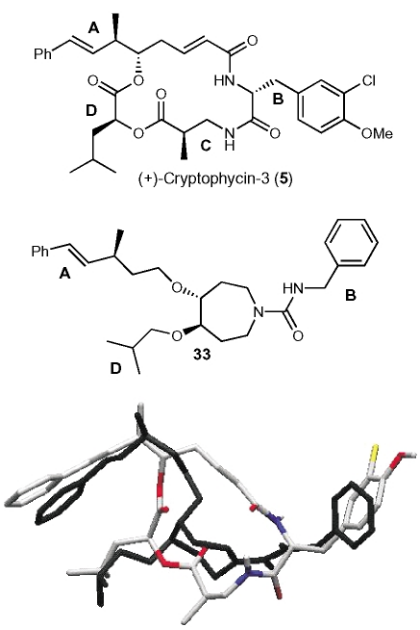



**Figure 7.** Overlay of the X-ray structure of (+)-cryptophycin-3 (**5**) and the simplified model of analogue (**33**) utilizing an azepine-based scaffold.

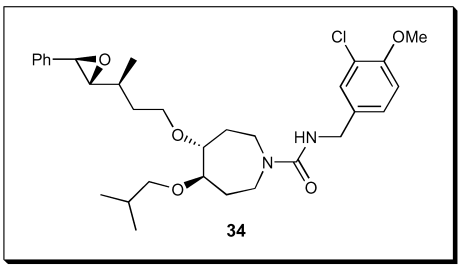


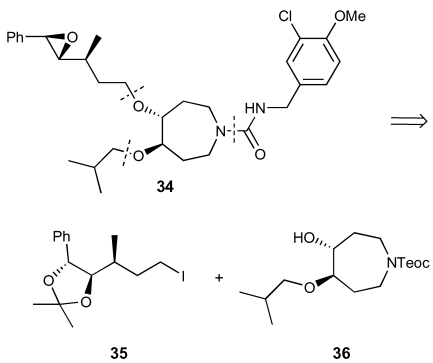

**Figure 8.** Proposed analogue **34**.

However, to obtain optimal overlap between the side chains of (+)-cryptophycin-3 (**5**) and the model (**33**), one additional carbon in the epoxide side chain would be required.

Grafting the required functional groups onto the simplified model **33** gave proposed analogue **34** as shown in Figure 8.

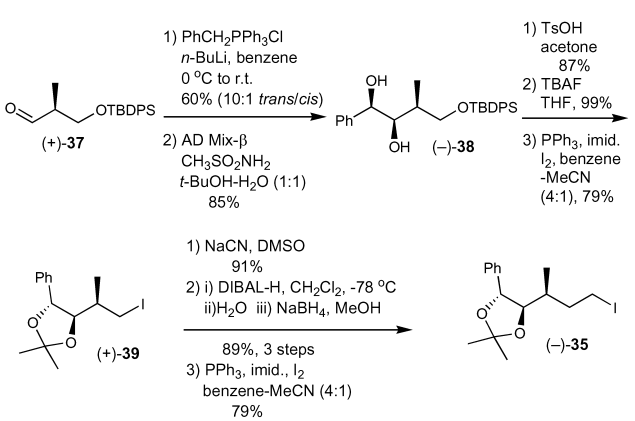
### 2.5. Synthesis of a second generation analogue of cryptophycin-1

With new structural constraints in mind, we turned to the synthesis of analogue **34** as outlined retrosynthetically in Scheme 7. In this approach, we would introduce the β-epoxide via the Sharpless 'one-pot' conversion of vicinal diols to epoxides.[33]




**Scheme 7.**

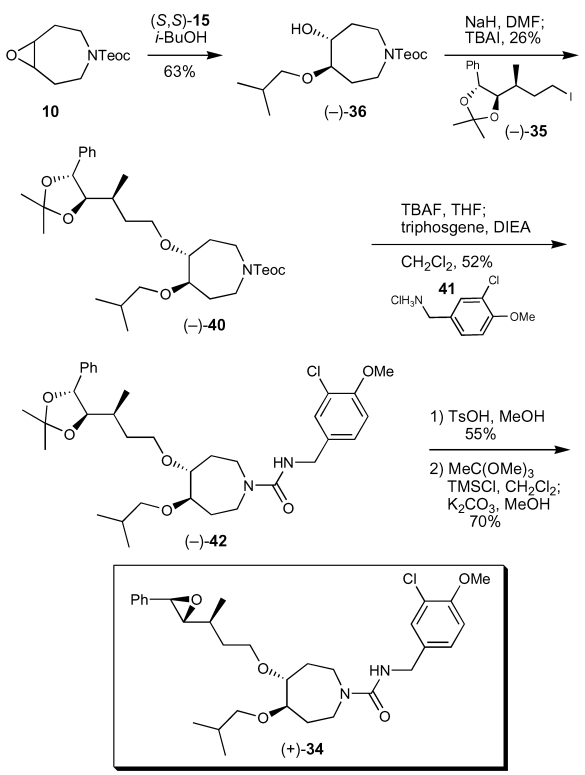
Preparation of iodide (−)-**35**, a precursor of the side chain, began with the Wittig olefination of aldehyde (+)-**37** (Scheme 8), followed by Sharpless dihydroxylation to




**Scheme 8.**

furnish diol (−)-**38**.[34] Protection of (−)-**38** as the acetonide, removal of the silyl protecting group and conversion of the resultant alcohol to the iodide furnished (+)-**39**. Homologation proceeded smoothly via cyanide displacement to give the desired nitrile, which in turn was subjected to a two-step reduction sequence followed by iodination.

Again, we employed the Jacobsen metal–salen catalyst to install functional groups on the azepine ring enantioselectively. Epoxide ring opening with iso-butanol in the presence of (*S*,*S*)-**15** afforded alcohol (−)-**36** (Scheme 9).[35] Although this operation proceeded with only modest selectivity (25% ee), alkylation of the resulting alcohol (−)-**36** with iodide (−)-**35** provided (−)-**40** in 26% yield as the major diastereomer (d.r.=20:1). The side product [60% yield from (−)-**35**] resulted from elimination of the iodide to give an olefin. We speculated that a kinetic resolution worked in our favor since the recovered starting alcohol **36** proved to be racemic. Removal of the Teoc protecting group with TBAF,[29,33] followed by reaction with 3-chloro-4-methoxybenzyl isocyanate, generated in situ from **41**,[36] provided acetonide (−)-**42**.[37] Hydrolysis of the acetonide and treatment of the resulting diol with trimethyl orthoacetate and TMSCl, followed by saponification of the acetate intermediate completed the synthesis of β-epoxide (+)-**34**.[33]




**Scheme 9.**

## 2.6. Biological evaluation of (+)-34

Mimic (+)-**34** was submitted to in vitro cytotoxicity tests against six human cancer cell lines (Table 2). Although we had anticipated better activity from (+)-**34** due to the presence of the β-epoxide in unit A and the chloride in unit B, compound (+)-**34** displayed the same levels of modest activity.

**Table 2**. Biological evaluation of analogue (+)-**34**; $GI_{50}$ (μM)

| Cell type | Cell-line | (+)-**34** |
|---|---|---|
| Pancreas-a | BXPC-3 | 3.2 |
| Breast adn | MCF-7 | 5.4 |
| CNS gliobl | SF268 | >10 |
| Lung-NSC | NCI-H460 | >10 |
| Colon | KM20L2 | 7.8 |
| Prostate | DU-145 | >10 |

The poor activity of the second generation analogues may be due to the flexibility of the azepine core compared to the cryptophycins leading to increased conformational mobility of the side chains. The longer side chains needed to correctly position the requisite substituents in the oxygen analogue may also have resulted in a conformational change.

## 3. Summary

We have designed and synthesized a series of azepine-based cryptophycin analogues. Although only modest activities were observed, these results hold the promise for a new series of cryptophycin analogues with improved cytotoxicity and pharmacokinetic properties available from a scaffold which appropriately orients the cryptophycin side chains, as has been achieved with the β-D-glucose scaffold for the somatostatin (SRIF) and substance P (NK-1) receptors.[18a–c]

## 4. Experimental

### 4.1. Materials and methods

All reactions were carried out under argon with dry, freshly distilled solvents, oven- or flame-dried glassware, and magnetic stirring, unless otherwise stated. All solvents were reagent grade or HPLC grade. Diethyl ether ($Et_2O$) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under argon; benzene and toluene were distilled from sodium, and dichloromethane ($CH_2Cl_2$) from calcium hydride. Triethylamine ($Et_3N$) and diisopropylethylamine (DIEA) were distilled from calcium hydride and stored over potassium hydroxide (KOH). Hexamethylphosphoramide was freshly distilled from calcium hydride. Anhydrous pyridine, dimethylformamide and dimethyl sulfoxide were purchased from Aldirich and used without purification. *n*-Butyllithium and *t*-butyllithium were purchased from Aldrich and used without purification.

Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using 0.25-mm E. Merck pre-coated silica gel plates. Flash chromatography was performed with the indicated solvents and E. Merck silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated.

All melting points were obtained on a Thomas–Hoover apparatus. Infrared spectra were recorded on a Perkin–Elmer Model 283B spectrophotometer. Proton and carbon

NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported in $\delta$ values relative to chloroform ($\delta$ 7.24 for proton and $\delta$ 77.0 for carbon NMR), benzene ($\delta$ 7.15 for proton and $\delta$ 128.0 for carbon NMR), methanol ($\delta$ 4.78 for proton and $\delta$ 49.0 for carbon NMR), and dimethyl sulfoxide ($\delta$ 2.49 for proton and $\delta$ 39.5 for carbon NMR). Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter in the solvent indicated. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Center by Dr Rakesh Kohli or Mr John Dykins on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed at the University of Pennsylvania elemental analysis center by Dr Rakesh Kohli. Single-crystal X-ray structures were determined by Dr Patrick Carroll at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer.

All calculations were performed on a Silicon Graphics Iris 4D/440 VGX (Unix operating system). The MacroModel program [Version 6.5 (Iris)] was used for construction and analysis of all modeled structures. The 10, 000 step Monte Carlo conformational search in the gas phase was carried out using the MM2 force field implanted in MacroModel.

### 4.2. Preparative experiments

**4.2.1. Diene 12.** A solution of 2-(trimethylsilyl)ethoxycarbonyl chloride (8.96 g, 1.79 equiv.) in THF (20 mL) was cooled to −50°C and a solution of *N*-benzyl-*N*,*N*-bishomoallylamine (4.48 g, 20.8 mmol) in THF (20 mL) was added dropwise. The resultant mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was concentrated in vacuo and flash chromatography on silica gel (hexanes–ether 25:1→10:1→5:1) gave 3.26 g (59% yield) of diene **12** as a colorless oil: $R_f$ 0.35 (hexanes–EtOAc 10:1); IR ($CHCl_3$) 3680 (w, br), 3460 (w, br), 3080 (m), 3020 (s), 2980 (s), 1680 (s), 1480 (s), 1420 (s), 1370 (m), 1300 (m), 1230 (s), 1160 (m), 1080 (m), 1040 (m), 990 (m), 920 (s), 840 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.98 (m, 2H), 2.27 (br d, $J$=5.8 Hz, 4H), 3.26 (br s, 4H), 4.14 (m, 2H), 5.00 (m, 2H), 5.05 (dd, $J$=1.4, 17.1 Hz, 2H), 5.75 (m, 2H), ; $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.5, 135.4, 116.6, 63.3, 47.1, 46.7, 33.2, 32.7, 17.9, −1.5; HRMS (CI, methane) *m*/*z* 270.1887 [(M+H)$^+$; calcd for $C_{14}H_{28}NO_2Si$: 270.1889].

**4.2.2. Olefin 14.** A solution of diene **12** (3.78 g, 14.0 mmol) in $CH_2Cl_2$ (150 mL) was treated with the Grubbs catalyst **13** (0.233 g, 0.020 equiv.) and the resulting mixture was heated to reflux. After 24 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. Flash chromatography using hexanes–ether (8:1) as eluant afforded olefin **14** as a colorless oil (3.06 g, 90% yield): $R_f$ 0.60 (hexanes–EtOAc 3:1); IR ($CHCl_3$) 3780 (w, br), 3460 (w, br), 3000 (s), 2960 (s), 1770 (s), 1470 (s), 1430 (s), 1350 (m), 1310 (m), 1230 (s), 1110 (s), 1040 (m), 990 (m), 930 (s), 840 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.99 (m, 2H), 2.27 (br d, $J$=13.0 Hz, 4H), 3.47 (br dd, $J$=3.4, 12.8 Hz, 4H), 4.17 (m, 2H) 5.71 (br d, $J$=1.9 Hz, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.0, 129.9, 129.3, 63.3, 46.7, 29.9, 29.7, 17.9, −1.5; HRMS (CI, methane) *m*/*z* 242.1575 [(M+H)$^+$; calcd for $C_{12}H_{24}NO_2Si$: 242.1576].

**4.2.3. Epoxide 10.** A solution of olefin **14** (2.91 g, 12.0 mmol) in $CH_2Cl_2$ (100 mL) was cooled to 0°C and treated with *m*-chloroperbenzoic acid (8.64 g, 4.00 equiv.). The reaction mixture was stirred at 0°C for 12 h and poured into 10% $NaHSO_3$ (100 mL). The layers were separated and the aqueous phase was extracted with ether (3×150 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (hexanes–ether 3:1→1:1) gave epoxide **10** as a pale yellow oil (2.57 g, 84% yield): $R_f$ 0.32 (hexanes–EtOAc 3:1); IR ($CHCl_3$) 3680 (w, br), 3480 (w, br), 3000 (s), 2960 (s), 1670 (s), 1480 (s), 1420 (s), 1360 (m), 1300 (m), 1250 (s), 1210 (s), 1130 (m), 1100 (s), 1070 (s), 980 (m), 940 (s), 860 (s), 830 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.97 (t, $J$=8.4 Hz, 2H), 2.06 (m, 1H), 2.19 (m, 3H), 2.76 (m, 2H), 3.17 (br s, 2H), 3.76 (br d, $J$=14.6 Hz, 1H), 3.88 (br d, $J$=13.8 Hz, 1H), 4.13 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 155.6, 63.4, 56.0, 55.8, 43.6, 43.0, 29.0, 28.3, 17.9, −1.5; HRMS (CI, methane) *m*/*z* 258.1523 [(M+H)$^+$; calcd for $C_{12}H_{24}NO_3Si$: 258.1525].

**4.2.4. Azido alcohol (−)-16.** To a suspension of catalyst (*S*,*S*)-**15** (52 mg, 0.03 equiv.) in ether (1.0 mL) was added epoxide **10** (746 mg, 2.90 mmol). After 15 min, azidotrimethylsilane (0.420 mL, 1.09 equiv.) was added. The reaction mixture was stirred for 6 days and then filtered through a plug of silica gel (10 mL) with 100 mL of 30% EtOAc–hexanes. The filtrate was concentrated in vacuo to give azido silyl ether as an oil.

To a solution of the unpurified azido silyl ether in MeOH (5.0 mL) was added 1*S*-(+)-10-camphorsulfonic acid (12 mg, 0.02 equiv.). The reaction mixture was stirred for 30 min and then concentrated to remove MeOH. The residue was purified by flash chromatography on silica gel using hexanes–ether (1:1) as eluant, to afford azido alcohol (−)-**16** as a colorless oil (647 mg, 98% yield): $R_f$ 0.23 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=-12.5°$ (*c* 2.94, $CHCl_3$); IR ($CHCl_3$) 3560 (w, br), 3440 (w, br), 3000 (s), 2960 (s), 2890 (s), 2100 (s), 1680 (s), 1420 (s), 1350 (w), 1250 (s), 1200 (s), 1130 (w), 1050 (m), 930 (w), 840 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.99 (m, 2H), 1.75 (m, 2H), 2.09 (m, 2H), 2.34 (d, $J$=32.7 Hz, 1H), 3.24–3.41 (m, 3H), 3.57 (m, 1H), 3.68 (m, 1H), 4.16 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.2, 74.0, 73.8, 67.7, 63.8, 41.3, 41.2, 40.9, 32.7, 32.6, 29.8, 29.6, 17.9, −1.5; HRMS (ESI) *m*/*z* 323.1523 [(M+Na)$^+$; calcd for $C_{12}H_{24}N_4O_3NaSi$: 323.1515].

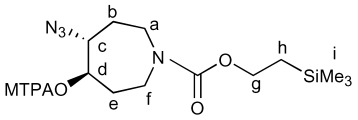
*Determination of enantiomeric purity of* (−)-**16**. HPLC conditions: CHIRALPAK AD, hexanes–*i*-propanol 95:5, 1.0 mL/min, 25°C, λ=210 nm.

| | | | | |
|---|---|---|---|---|
| (−)-**16** | 13.525 min | 93.5% | 18.472 min | 6.5% |
| Racemic | 13.699 min | 50.4% | 18.481 min | 49.6% |

*Determination of stereochemistry of* (−)-**16**. (*R*)-(−)-α-methoxy-α-trifluoromethylphenyl-acetyl chloride [(*R*)-MTPACl, 7.9 μL, 1.2 equiv.] was added to a solution of (−)-**16** (10.2 mg, 0.0340 mmol), 4-(*N*,*N*, -dimethylamino)-pyridine (DMAP, 5 mg), and triethylamine (10 μL, 2.1 equiv.) in $CH_2Cl_2$ (0.7 mL) at room temperature. The

reaction mixture was stirred for 3 h at room temperature and concentrated in vacuo. Flash chromatography, using $CH_2Cl_2$–MeOH (70:1) as eluant, gave 10.5 mg (60% yield) of the (*S*)-MTPA ester of (−)-**16** as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.97 (t, $J$=8.4 Hz, 2H), 1.80–1.94 (m, 2H), 2.02 (m, 1H), 2.16 (m, 1H), 3.32–3.45 (m, 2H), 3.54 (s, 3H), 3.48–3.58 (m, 1H), 3.67 (m, 2H), 4.15 (dd, $J$=7.5, 16.3 Hz, 2H), 5.08 (m, 1H), 7.40 (m, 3H), 7.51 (m, 2H).

In similar fashion, the (*R*)-MTPA ester of (−)-**16** was obtained in 64% yield as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.96 (m, 2H), 1.80 (m, 1H), 1.89 (m, 1H), 2.08 (m, 2H), 3.29–3.51 (m, 3H), 3.55 (s, 3H), 3.58–3.69 (m, 2H), 4.15 (t, $J$=8.4 Hz, 2H), 5.02 (br m, 1H), 7.40 (m, 3H), 7.51 (m, 2H).




| | (*S*)-MTPA ester | (*R*)-MTPA ester | (*S*)−(*R*) |
|---|---|---|---|
| b1/b2 | 1.82/2.02 | 1.89/2.08 | −0.07/−0.06 |
| c | 3.67 | 3.69 | −0.02 |
| e1/e2 | 1.91/2.16 | 1.80/2.08 | +0.11/+0.08 |
| g | 4.153 | 4.151 | +0.002 |
| h | 0.973 | 0.962 | +0.011 |
| i | 0.022 | 0.019 | +0.003 |

**4.2.5. Azido ether (−)-17.** To a suspension of NaH (95%, 170 mg, 5.35 equiv.) in THF (10 mL) was added a solution of azido alcohol (−)-**16** (398 mg, 1.32 mmol) in THF (3 mL) at room temperature. After 30 min, when gas evolution had ceased, tetrabutylammonium iodide (TBAI, 48.9 mg, 0.10 equiv.) was added followed by dropwise addition of methallyl bromide (0.72 mL, 5.4 equiv.). The resulting mixture was stirred for 30 min at room temperature, quenched by addition of water (10 mL), and diluted with ether (30 mL). The layers were separated and the aqueous phase was further extracted with ether (2×30 mL). Combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexanes–ether 5:1) gave azido ether (−)-**17** as a pale yellow oil (413 mg, 88% yield): $R_f$ 0.47 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}$=−3.5° (*c* 2.67, $CHCl_3$); IR ($CHCl_3$) 3680 (w, br), 3620 (w, br), 3020 (s), 2960 (s), 2100 (s), 1680 (s), 1420 (s), 1350 (m), 1220 (s), 1100 (s), 1060 (s), 910 (m), 840 (s) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.98 (t, $J$=8.5 Hz, 2H), 1.75 (s, 3H), 1.68–1.83 (m, 2H), 2.04 (m, 2H), 3.28 (m, 1H), 3.42 (m, 2H), 3.49 (m, 1H), 3.59 (m, 1H), 3.65 (m, 1H), 3.94 (m, 2H), 4.15 (m, 2H), 4.92 (d, $J$=43.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.2, 141.9, 112.6, 80.1, 80.0, 73.5, 64.6, 64.4, 63.6, 41.0, 40.9, 40.7, 29.7, 29.6, 20.3, 29.1, 19.5, 17.9, −1.5; HRMS (CI, methane) *m*/*z* 355.2178 [(M+H)$^+$; calcd for $C_{16}H_{31}N_4O_3Si$: 355.2165].

**4.2.6. Amine (−)-18.** To a solution of azido ether (−)-**17** (406 mg, 1.15 mmol) in MeOH (15 mL) was added Pd/C (10%, 57.4 mg) and the reaction flask was charged with $H_2$. The reaction mixture was stirred for 12 h at room temperature and filtered through a celite plug, then concentrated in vacuo. Flash chromatography ($CH_2Cl_2$–MeOH 8:1→4:1) afforded 372 mg (98% yield) of amine (−)-**18** as a colorless oil: $R_f$ 0.22 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=−3.6° (*c* 2.1, $CHCl_3$); IR (neat) 3540 (m, br), 3360 (m), 2940 (s), 2860 (s), 1690 (s), 1460 (s), 1420 (s), 1340 (m), 1280 (m), 1240 (s), 1180 (m), 1090 (s), 850 (s), 830 (s) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ −0.00 (s, 9H), 0.87 (d, $J$=6.8 Hz, 3H), 0.88 (d, $J$=7.4 Hz, 3H), 0.96 (m, 2H), 1.48–1.86 (m, 6H), 2.02 (m, 1H), 2.81 (m, 1H), 2.91 (m, 1H), 3.07 (m, 1H), 3.31 (dd, $J$=6.4, 8.6 Hz, 1H), 3.14–3.36 (m, 2H), 3.54 (m, 2H), 3.64 (m, 1H), 4.13 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 84.8, 84.6, 76.2, 76.1, 63.4, 56.1, 55.7, 41.9, 41.8, 41.2, 41.0, 32.9, 32.5, 30.1, 29.8, 28.8, 19.5, 19.4, 17.8, −1.5; HRMS (ESI) *m*/*z* 331.2402 [(M+H)$^+$; calcd for $C_{16}H_{35}N_2O_3Si$: 331.2417].

**4.2.7. Azido alcohol (+)-16.** To a suspension of catalyst (*R*,*R*)-**15** (52 mg, 0.03 equiv.) in ether (1.0 mL) was added epoxide **10** (694 mg, 2.69 mmol). After 15 min, azidotrimethylsilane (0.420 mL, 1.17 equiv.) was added. The reaction mixture was stirred for 6 days and then filtered through a plug of silica gel (10 mL) with 100 mL of 30% EtOAc–hexanes. The filtrate was concentrated in vacuo to give azido silyl ether as an oil.

To a solution of the unpurified azido silyl ether in MeOH (5.0 mL) was added 1*S*-(+)-10-camphorsulfonic acid (13 mg, 0.03 equiv.). The reaction mixture was stirred for 30 min and then concentrated to remove MeOH. The residue was purified by flash chromatography on silica gel using hexanes–ether (1:1) as eluant, to afford azido alcohol (+)-**16** (605 mg, 95% yield) as a colorless oil: $R_f$ 0.23 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}$=+12.4° (*c* 2.85, $CHCl_3$); IR ($CHCl_3$) 3580 (w, br), 3460 (w, br), 3010 (s), 2960 (s), 2900 (s), 2100 (s), 1670 (s), 1430 (s), 1350 (m), 1250 (s), 1210 (s), 1140 (m), 1050 (s), 930 (m), 840 (s) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.03 (s, 9H), 0.99 (m, 2H), 1.75 (m, 2H), 2.09 (m, 2H), 2.33 (d, $J$=34.2 Hz, 1H), 3.24–3.41 (m, 3H), 3.56 (m, 2H), 3.68 (m, 1H), 4.17 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.2, 74.0, 73.8, 67.7, 63.7, 41.3, 41.2, 40.9, 32.7, 32.6, 29.8, 29.6, 17.9, −1.5; HRMS (ESI) *m*/*z* 323.1517 [(M+Na)$^+$; calcd for $C_{12}H_{24}N_4O_3NaSi$: 323.1515].

*Determination of enantiomeric purity of* (+)-**16**. HPLC conditions: CHIRALPAK AD, hexanes–*i*-propanol 95:5, 1.0 mL/min, 25°C, $\lambda$=210 nm.

| | | | | |
|---|---|---|---|---|
| (+)-**16** | 13.653 min | 7.3% | 18.068 min | 92.7% |
| Racemic | 13.699 min | 50.4% | 18.481 min | 49.6% |

**4.2.8. Azido ether (+)-17.** To a suspension of NaH (95%, 138 mg, 5.68 equiv.) in THF (10 mL) was added a solution of azido alcohol (+)-**16** (335 mg, 1.01 mmol) in THF (3 mL) at room temperature. After 30 min, when gas evolution had ceased, tetrabutylammonium iodide (TBAI, 42.3 mg, 0.11 equiv.) was added followed by dropwise addition of methallyl bromide (0.61 mL, 6.0 equiv.). The resulting mixture was stirred for 30 min at room temperature, quenched by addition of water (10 mL), and diluted with ether (30 mL). The layers were

separated and the aqueous phase was further extracted with ether (2×30 mL). Combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexanes–ether 5:1) gave azido ether (+)-**17** as a pale yellow oil (336 mg, 94% yield): $R_f$ 0.47 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=+3.3°$ (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3680 (w, br), 3600 (w, br), 3020 (s), 2960 (m), 2100 (s), 1680 (s), 1420 (s), 1360 (m), 1220 (s), 1090 (m), 1050 (m), 900 (s), 830 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.99 (t, *J*=8.4 Hz, 2H), 1.75 (s, 3H), 1.68–1.83 (m, 2H), 2.04 (m, 2H), 3.28 (m, 1H), 3.42 (m, 2H), 3.49 (m, 1H), 3.59 (m, 1H), 3.65 (m, 1H), 3.94 (m, 2H), 4.16 (m, 2H), 4.92 (d, *J*=42.9 Hz, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.2, 141.9, 112.6, 80.1, 80.0, 73.5, 64.6, 64.4, 63.6, 41.0, 40.9, 40.7, 29.7, 29.6, 29.3, 29.2, 19.5, 17.9, −1.5; HRMS (CI, methane) *m/z* 355.2164 [$(M+H)^+$; calcd for $C_{16}H_{31}N_4O_3Si$: 355.2165].

**4.2.9. Amine (+)-18.** To a solution of azido ether (+)-**17** (336 mg, 0.948 mmol) in MeOH (15 mL) was added Pd/C (10%, 29.1 mg) and the reaction flask was charged with $H_2$. The reaction mixture was stirred for 12 h at room temperature and filtered through a celite plug, then concentrated in vacuo. Flash chromatography ($CH_2Cl_2$–MeOH 8:1→4:1) afforded 328 mg (97% yield) of amine (+)-**18** as a colorless oil: $R_f$ 0.22 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}=+2.8°$ (*c* 1.7, $CHCl_3$); IR (neat) 3540 (m, br), 3360 (m), 2940 (s), 2860 (s), 1690 (s), 1460 (s), 1420 (s), 1340 (m), 1280 (m), 1240 (s), 1170 (m), 1090 (s), 850 (s), 830 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.89 (d, *J*=6.8 Hz, 3H), 0.90 (d, *J*=7.3 Hz, 3H), 0.98 (m, 2H), 1.51–1.87 (m, 6H), 2.04 (m, 1H), 2.84 (m, 1H), 2.94 (m, 1H), 3.09 (m, 1H), 3.33 (dd, *J*=6.4, 8.6 Hz, 1H), 3.17–3.37 (m, 2H), 3.55 (m, 1H), 3.66 (m, 1H), 4.15 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 84.8, 84.5, 76.3, 76.2, 63.4, 56.2, 55.8, 42.0, 41.8, 41.2, 41.0, 32.9, 32.5, 30.2, 29.9, 28.9, 19.5, 17.9, −1.5; HRMS (CI, methane) *m/z* 331.2412 [$(M+H)^+$; calcd for $C_{16}H_{35}N_2O_3Si$: 331.2417].

**4.2.10. Benzyl ether 20.** To a solution of aldehyde (−)-**19** (168 mg, 2.97 equiv.) and amine (−)-**18** (105 mg, 0.318 mmol) in MeOH (8 mL) were added crushed 4 Å molecular sieves (2 mL) and $NaBH_3CN$ (38.6 mg, 1.93 equiv.). The pH was adjusted to 6–7 with glacial AcOH and the resultant mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through a silica gel plug and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$–MeOH 40:1→10:1) afforded 114 mg (73% yield) of secondary amine **20** as a colorless oil: $R_f$ 0.33 ($CH_2Cl_2$–MeOH 10:1); IR (neat) 3320 (w), 2960 (s), 2860 (s), 1690 (s), 1470 (s), 1410 (s), 1350 (m), 1240 (s), 1200 (m), 1090 (s), 990 (w), 930 (w), 850 (s), 830 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.01 (s, 9H), 0.86 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H), 0.89 (d, *J*=7.8 Hz, 3H), 0.97 (t, *J*=8.4 Hz, 2H), 1.49 (m, 1H), 1.63 (m, 1H), 1.78 (m, 1H), 1.90–2.05 (m, 3H), 2.17 (br s, 1H), 2.32* [dd, *J*=6.9, 11.3 Hz, 1H, minor diastereomer at C(3)], 2.54 (m, 3H), 2.73* (dd, *J*=6.1, 11.3 Hz, 1H), 3.05 (m, 1H), 3.14 (m, 1H), 3.19 (m, 1H), 3.28–3.38 (m, 4H), 3.56 (m, 2H), 4.14 (t, *J*=8.4 Hz, 2H), 4.47 (s, 2H), 7.22–7.33 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 138.6, 128.3, 128.2, 127.5, 127.4, 81.9, 81.7, 76.0, 75.9, 74.4, 73.0, 63.3, 62.1, 61.6, 50.8, 42.2, 42.0, 40.6, 40.4, 34.0, 30.5, 30.2, 28.8, 28.4, 19.4, 17.9, 15.6, −1.5; HRMS (ESI) *m/z* found 493.3453 [$(M+H)^+$; calcd for $C_{27}H_{49}N_2O_4Si$: 493.3462].

**4.2.11. *tert*-Butyl carbamate 21.** 8:1 Mixture at C3′. A solution of secondary amine **20** (114 mg, 0.232 mmol) in $CH_2Cl_2$ (5 mL) was treated with $Et_3N$ (37 μL, 1.1 equiv.) and $(Boc)_2O$ (59 μL, 1.1 equiv.) and the resulting mixture was stirred for 12 h at room temperature. The reaction mixture was quenched by addition of 10% $NaHSO_4$ (10 mL) and extracted with ether (3×20 mL). Combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (hexanes–EtOAc 13:1→4:1) afforded 111 mg (81% yield) of *tert*-butyl carbamate **21** as a colorless oil: $R_f$ 0.5 (hexanes–EtOAc 3:1); IR (neat) 2940 (s), 2860 (s), 1690 (s), 1460 (m), 1420 (m), 1360 (m), 1320 (w), 1290 (w), 1240 (m), 1170 (m), 1150 (m), 1090 (m), 850 (m), 830 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.84, (d, *J*=6.5 Hz, 3H), 0.85 (d, *J*=6.4 Hz, 3H), 0.93 (d, *J*=6.6 Hz, 3H), 0.97 (t, *J*=8.4 Hz, 2H), 1.40 (d, *J*=8.5 Hz, 9H), 1.53 (m, 1H), 1.68–2.28 (m, 5H), 2.92–3.85 (m, 12H), 4.13 (m, 2H), 4.48 (m, 2H), 7.22–7.35 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 155.5, 155.2, 138.8, 138.6, 128.9, 128.8, 128.4, 128.3, 127.5, 80.5, 80.4, 79.5, 79.4, 79.2, 79.1, 77.7, 77.6, 77.5, 76.9, 76.6, 73.7, 73.6, 73.1, 73.0, 65.7, 65.5, 65.4, 63.4, 54.1, 54.0, 53.7, 43.4, 43.3, 41.0, 40.9, 34.1, 33.8, 32.2, 32.1, 31.9, 31.7, 31.6, 31.4, 30.8, 30.6, 28.9, 28.7, 28.6, 28.5, 19.5, 17.9, 15.7, 15.4, −1.5; HRMS (ESI) *m/z* found 615.3823 [$(M+Na)^+$; calcd for $C_{32}H_{56}N_2O_6$ NaSi: 615.3805].

**4.2.12. Olefin 22.** *trans*–*cis*=10:1. To a solution of *tert*-butyl carbamate **21** (696 mg, 1.17 mmol) in MeOH (20 mL) was added Pd/C (10%, 41.3 mg) and the reaction flask was charged with $H_2$. The reaction mixture was stirred for 12 h at room temperature, filtered through a celite plug, and then concentrated in vacuo. Flash chromatography (hexanes–EtOAc 4:1) gave 537 mg (91% yield) of alcohol as a colorless oil: $R_f$ 0.28 (hexanes–EtOAc 2:1); IR (neat) 3460 (m, br), 2940 (s), 2860 (s), 1690 (s), 1470 (m), 1420 (m), 1360 (m), 1250 (m), 1170 (m), 1090 (m), 1040 (w), 990 (w), 930 (w), 850 (m), 830 (w) $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 0.07 (s, 9H), 0.90 (d, *J*=6.7 Hz, 6H), 0.94 (d, *J*=6.8 Hz, 3H), 1.03 (t, *J*=8.2 Hz, 2H), 1.47 (br s, 9H), 1.62 (m, 1H), 1.77 (m, 1H), 1.88 (m, 2H), 2.13 (m, 1H), 2.25 (m, 1H), 2.96 (m, 1H), 3.08 (m, 2H), 3.30–3.85 (m, 9H), 4.78 (m, 2H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$ 158.0, 157.7, 156.9, 81.5, 81.4, 81.3, 80.7, 80.5, 80.4, 79.4, 77.5, 66.6, 66.3, 65.5, 64.8, 54.5, 54.4, 43.9, 43.5, 42.5, 37.3, 36.4, 32.7, 32.6, 32.5, 32.4, 32.3, 32.2, 32.1, 31.7, 31.4, 30.1, 28.9, 23.7, 19.9, 18.7, 15.8, 15.7, 15.6, −1.4; HRMS (CI, methane) *m/z* found 503.3505 [$(M+H)^+$; calcd for $C_{25}H_{51}N_2O_6Si$: 503.3516].

A solution of alcohol (519 mg, 1.03 mmol) in $CH_2Cl_2$ (20 mL) was treated with pyridine (0.28 mL, 3.4 equiv.) and Dess–Martin periodinane (527 mg, 1.1 equiv.), then the resultant mixture was stirred for 30 min at room temperature. The reaction mixture was poured into 20% $Na_2S_2O_3$-saturated $NaHCO_3$ (1:1=V:V, 60 mL) and after separation, the aqueous phase was extracted with ether (3×80 mL). Combined extracts were washed with saturated $CuSO_4$ (3×60 mL), water (60 mL), and brine (60 mL), dried

($MgSO_4$), filtered, then concentrated in vacuo. Flash chromatography (hexanes–ether 4:1→1:1) afforded aldehyde as a colorless oil (470 mg, 88% yield): $R_f$ 0.30 (hexanes–EtOAc 2:1); IR (neat) 2960 (s), 2860 (s), 2720 (w), 1690 (s), 1460 (m), 1420 (m), 1360 (m), 1310 (w), 1250 (m), 1170 (m), 1090 (m), 930 (w), 860 (m), 830 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.00 (s, 9H), 0.83 (d, $J$=3.5, 6.7 Hz, 3H), 0.84 (d, $J$=6.7 Hz, 3H), 0.96 (t, $J$=8.4 Hz, 2H), 1.04* [d, $J$=7.2 Hz, 3H, minor diastereomer at C(3′)], 1.05 (d, $J$=7.0 Hz, 3H), 1.40 (br s, 9H), 1.51 (m, 1H), 1.72 (m, 1H), 1.83 (m, 1H), 2.05 (m, 1H), 2.27 (m, 1H), 2.57 (m, 1H), 3.25 (dd, $J$=6.4, 8.7 Hz, 1H), 2.95–3.37 (m, 6H), 3.51–3.71 (m, 3H), 3.84 (m, 1H),.4.13 (t, $J$=8.4 Hz, 2H), 9.59 (br s, 1H), 9.65* (d, $J$=1.6 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 203.7, 203.5, 156.2, 155.3, 154.4, 80.4, 80.2, 80.1, 80.0, 79.2, 79.1, 76.6, 76.4, 65.7, 65.5, 63.4, 51.7, 51.4, 46.9, 46.8, 43.2, 42.9, 41.0, 40.8, 32.2, 32.1, 31.8, 31.4, 31.2, 30.6, 30.3, 28.8, 28.5, 28.4, 19.4, 17.8, 12.0, 11.8, −1.5; HRMS (ESI) $m/z$ found 523.3181 [$(M+Na)^+$; calcd for $C_{25}H_{48}N_2O_6$ NaSi: 523.3179].

To a solution of benzyltriphenylphosphonium chloride (435 mg, 1.19 equiv.) in benzene (10 mL) at 0°C was added $n$-BuLi (0.79 mL, 1.2 equiv.) in hexanes (1.4 M) dropwise and the resulting solution was warmed to room temperature then stirred for 1 h. The solution was cooled to 0°C and treated with a solution of aldehyde (470 mg, 0.939 mmol) in benzene (5 mL). The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched with saturated $NH_4Cl$ (50 mL) and extracted with ether (4×50 mL). Combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexanes–ether 5:1→4:1→2:1) afforded olefin **22** as a pale yellow oil (507 mg, 94% yield): $R_f$ 0.42 (hexanes–EtOAc 3:1); IR (neat) 2960 (s), 1680 (s), 1470 (m), 1420 (m), 1360 (m), 1250 (m), 1170 (m), 1090 (m), 960 (m), 930 (m), 850 (m), 830 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.01* [s, 9H, minor diastereomer at C(3′)], 0.02 (s, 9H), 0.85 (m, 6H), 0.97 (t, $J$=8.4 Hz, 2H), 1.04 (m, 3H), 1.37 (s, 9H), 1.42* (s, 9H), 1.52 (m, 1H), 1.73 (m, 1H), 1.81–2.29 (m, 3H), 2.57 (m, 1H), 2.94–3.22 (m, 5H), 3.27 (m, 1H), 3.39–3.88 (m, 4H), 4.11* (t, $J$=8.3 Hz, 2H), 4.14 (t, $J$=8.3 Hz, 2H), 6.08 (m, 1H), 6.31 (d, $J$=15.9 Hz, 1H), 6.36* (d, $J$=15.9 Hz, 1H), 7.15–7.30 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 156.2, 155.3, 154.9, 137.7, 137.4, 134.6, 134.5, 134.1, 134.0, 129.8, 129.4, 129.3, 128.5, 128.4, 128.3, 128.2, 127.1, 127.0, 126.8, 126.0, 125.9, 80.6, 80.5, 79.4, 79.2, 79.0, 76.9, 76.6, 70.5, 65.2, 63.4, 56.4, 56.3, 43.4, 43.3, 40.9, 40.7, 40.6, 40.5, 37.6, 32.5, 32.4, 32.2, 32.0, 31.7, 30.9, 30.5, 28.8, 28.5, 28.4, 19.4, 18.2, 17.8, −1.5; HRMS (ESI) $m/z$ found 597.3707 [$(M+Na)^+$; calcd for $C_{32}H_{54}N_2O_5NaSi$: 597.3700].

**4.2.13. Urea (+)-24.** Under argon, TBAF (1.6 equiv.) in THF (1.2 mL, 1.0 M) was added to a solution of **22** (425 mg, 0.740 mmol) in THF (20 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then treated with 4-methoxybenzyl isocyanate **23** (318 mg, 2.6 equiv.). The resulting mixture was then stirred for 2 h, and quenched with MeOH (0.5 mL). The solution was concentrated in vacuo and purified by flash chromatography using $CH_2Cl_2$–MeOH (40:1) as eluant, to furnish **24** as a mixture (356 mg, 81% yield). The mixture was further purified by preparative HPLC using a reverse phase DYNAMAX® $C_{18}$ column [21.1 mm, MeCN–0.1% TFA in water (3:1), 4.0 mL/min] to give (+)-**24** (92.8 mg, 21% yield) as a colorless oil: $R_f$ 0.40 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=+56.5° ($c$ 1.30, $CHCl_3$); IR (neat) 3340 (m, br), 2960 (s), 1690 (s), 1630 (s), 1510 (s), 1460 (m), 1360 (m), 1240 (s), 1170 (s), 1090 (m), 1030 (m), 910 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.85 (d, $J$=6.4 Hz, 3H), 0.86 (d, $J$=6.1 Hz, 3H), 1.06 (d, $J$=6.7 Hz, 3H), 1.39 (s, 9H), 1.52 (m, 1H), 1.73 (m, 2H), 1.90 (m, 1H), 2.09–2.35 (m, 2H), 2.56 (m, 1H), 2.99–3.06 (m, 4H), 3.13 (m, 1H), 3.27 (m, 1H), 3.49 (m, 2H), 3.62 (m, 1H), 3.73 (m, 1H), 3.77 (s, 9H), 3.86 (m, 1H), 4.31 (m, 2H), 4.43 (m, 1H), 6.10 (m 1H), 6.31 (d, $J$=15.9 Hz, 1H), 6.84 (d, $J$=8.6 Hz, 2H), 7.12–7.30 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.9, 157.5, 155.4, 155.1, 137.7, 137.5, 134.6, 134.1, 131.7, 129.3, 129.1, 129.0, 128.5, 128.4, 127.0, 126.8, 126.0, 125.9, 114.0, 113.9, 80.6, 79.5, 79.3, 79.1, 76.6, 65.5, 56.5, 55.3, 44.5, 43.0, 40.1, 37.6, 37.5, 32.3, 32.1, 31.5, 30.7, 28.8, 28.5, 28.4, 19.5, 19.4, 18.0; HRMS (ESI) $m/z$ found 616.3733 [$(M+Na)^+$; calcd for $C_{35}H_{51}N_3O_5Na$: 616.3726].

**4.2.14. Analogue (+)-25.** To a solution of urea (+)-**24** (15.0 mg, 0.0253 mmol) in $CH_2Cl_2$ (1.2 mL) was added trifluoroacetic acid (TFA, 0.65 mL) and the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL), washed with water (30 mL), and saturated $NaHCO_3$ (30 mL), dried ($Na_2SO_4$), filtered then concentrated in vacuo. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$-(saturated with $NH_3$)–MeOH (10:1)] afforded 11.7 mg (94% yield) of secondary amine as a colorless oil: $R_f$ 0.35 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=+25.0° ($c$ 0.585, $CHCl_3$); IR (neat) 3320 (m, br), 2940 (s), 1620 (s), 1500 (s), 1460 (m), 1360 (m), 1350 (w), 1290 (w), 1240 (m), 1170 (m), 1090 (m), 1030 (m), 960 (m), 800 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.66 (d, $J$=6.7 Hz, 3H), 0.67 (d, $J$=6.7 Hz, 3H), 1.09 (d, $J$=6.7 Hz, 3H), 1.48–1.65 (m, 3H), 2.05 (m, 2H), 2.37 (dd, $J$=9.0, 10.8 Hz, 2H), 2.50 (m, 1H), 2.56 (m, 1H), 2.73 (dd, $J$=5.0, 10.8 Hz, 1H), 2.98 (dd, $J$=6.3, 8.7 Hz, 1H), 3.10–3.25 (m, 4H), 3.57 (m, 1H), 3.64 (m, 1H), 3.77 (s, 3H), 4.32 (m, 2H), 4.49 (t, $J$=5.2 Hz, 1H), 6.01 (dd, $J$=8.5, 15.8 Hz, 1H), 6.45 (d, $J$=15.8 Hz, 1H), 6.84 (d, $J$=8.6 Hz, 2H), 7.15–7.35 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.9, 157.5, 137.2, 133.8, 131.7, 130.7, 129.1, 128.4, 127.1, 126.1, 114.0, 82.1, 76.9, 76.2, 62.9, 55.3, 53.3, 44.6, 41.8, 39.9, 38.1, 30.7, 28.8, 28.7, 19.3, 19.2, 19.0; HRMS (ESI) $m/z$ found 494.3378 [$(M+H)^+$; calcd for $C_{30}H_{44}N_3O_3$: 494.3383].

To a solution of secondary amine (11.7 mg, 0.0237 mmol) and 37% formaldehyde (5.1 mg, 2.6 equiv.) in MeOH (1 mL) were added crushed 4 Å molecular sieves (0.3 mL) and $NaBH_3CN$ (4.2 mg, 2.8 equiv.). The pH was adjusted to 6–7 with glacial AcOH and the resultant mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through a silica gel plug and concentrated in vacuo. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$-(saturated with $NH_3$)–MeOH (10:1)] afforded 9.8 mg (67% yield) of amine (+)-**25** as a colorless oil: $R_f$ 0.33 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=+17° ($c$ 0.55, $CHCl_3$); IR

(neat) 3340 (m, br), 2940 (s), 1630 (s), 1500 (s), 1460 (m), 1390 (w), 1350 (w), 1290 (w), 1240 (m), 1170 (m), 1080 (m), 1030 (m), 950 (m), 810 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.858 (d, $J$=6.7 Hz, 3H), 0.862 (d, $J$=6.6 Hz, 3H), 1.05 (m, 3H), 1.61 (m, 1H), 1.69–1.81 (m, 2H), 1.89 (m, 1H), 1.97 (m, 1H), 2.28 (br s, 3H), 2.48 (br s, 3H), 2.62 (br s, 1H), 3.10–3.17 (m, 2H), 3.19–3.26 (m, 2H), 3.38 (dt, $J$=3.0, 8.1 Hz, 1H), 3.54 (m, 1H), 3.61 (m, 1H), 3.77 (s, 3H), 4.33 (d, $J$=5.3 Hz, 2H), 4.49 (br s, 1H), 6.15 (dd, $J$=6.4, 16.0 Hz, 1H), 6.35 (d, $J$=16.0 Hz, 1H), 6.84 (d, $J$=8.6 Hz, 2H), 7.14–7.32 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.9, 157.6, 138.0, 131.8, 129.1, 128.4, 128.3, 126.8, 126.0, 114.0, 79.9, 75.9, 68.0, 61.9, 55.3, 44.6, 42.5, 40.6, 38.0, 35.8, 30.9, 29.0, 28.3, 19.6, 18.3; HRMS (ESI) $m/z$ found 508.3525 [$(M+H)^+$; calcd for $C_{31}H_{46}N_3O_3$: 508.3539].

**4.2.15. Benzyl ether 26.** To a solution of aldehyde (−)-**19** (664 mg, 1.49 equiv.) and amine (+)-**18** (826 mg, 2.50 mmol) in MeOH (8 mL) were added crushed 4 Å molecular sieves (3 mL) and $NaBH_3CN$ (32.9 mg, 2.10 equiv.). The pH was adjusted to 6–7 with glacial AcOH and the resultant mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through a silica gel plug and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$–MeOH 40:1→10:1) afforded 763 mg (62% yield) of benzyl ether **26** as a colorless oil: $R_f$ 0.33 ($CH_2Cl_2$–MeOH 10:1); IR (neat) 3320 (w), 2940 (s), 2860 (s), 1690 (s), 1470 (s), 1420 (s), 1360 (m), 1250 (s), 1200 (m), 1090 (s), 990 (w), 940 (w), 860 (s), 830 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.01 (s, 9H), 0.87 (d, $J$=6.6 Hz, 3H), 0.88 (d, $J$=6.5 Hz, 3H), 0.94 (d, $J$=6.8 Hz, 3H), 0.97 (t, $J$=8.4 Hz, 2H), 1.49 (m, 1H), 1.63 (m, 1H), 1.78 (m, 1H), 1.90–2.05 (m, 3H), 2.17 (br s, 1H), 2.32 (dd, $J$=6.9, 11.3 Hz, 1H), 2.55 (m, 1H), 2.72 (dd, $J$=6.1, 11.3 Hz, 1H), 3.04 (m, 1H), 3.14 (m, 1H), 3.20 (m, 1H), 3.32 (m, 3H), 3.38 (dd, $J$=6.3, 9.2 Hz, 1H), 3.57(m, 2H), 4.14 (m, 2H), 4.47 (s, 2H), 7.22–7.33 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 138.6, 128.3, 127.5, 127.4, 81.9, 81.7, 76.0, 75.9, 74.3, 73.1, 73.0, 63.3, 62.5, 61.9, 50.8, 42.2, 42.1, 40.6, 40.4, 34.2, 30.4, 30.2, 29.0, 28.8, 28.6, 19.5, 19.4, 17.9, 15.6, −1.5; HRMS (ESI) $m/z$ found 493.3464 [$(M+H)^+$; calcd for $C_{27}H_{49}N_2O_4Si$: 493.3462].

**4.2.16. *tert*-Butyl carbamate 27.** 4:1 Mixture at C3′. A solution of benzyl ether **26** (676 mg, 1.37 mmol) in $CH_2Cl_2$ (15 mL) was treated with $Et_3N$ (0.21 mL, 1.1 equiv.) and $(Boc)_2O$ (0.34 mL, 1.1 equiv.) and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was quenched by addition of 10% $NaHSO_4$ (60 mL) and extracted with ether (3×50 mL). Combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (hexanes–ether 5:1→4:1→3:1→2:1) afforded 765 mg (94% yield) of *tert*-butyl carbamate **27** as a colorless oil: $R_f$ 0.5 (hexanes–EtOAc 3:1); IR (neat) 2940 (s), 2860 (s), 1690 (s), 1450 (m), 1420 (m), 1360 (m), 1320 (w), 1290 (w), 1250 (m), 1170 (m), 1150 (m), 1090 (m), 850 (m), 830 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 9H), 0.85 (d, $J$=6.6 Hz, 3H), 0.86 (d, $J$=6.3 Hz, 3H), 0.92 (d, $J$=6.7 Hz, 3H), 0.97 (t, $J$=8.4 Hz, 2H), 1.48 (d, $J$=5.0 Hz, 9H), 1.53 (m, 1H), 1.70–2.30 (m, 5H), 3.01–3.85 (m, 12H), 4.13 (t, $J$=8.8 Hz, 2H), 4.48 (m, 2H), 7.25 (m, 1H), 7.30 (br s, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 155.6, 155.3, 138.7, 128.3, 127.5, 79.4, 79.3, 79.2, 79.1, 77.6, 77.5, 77.4, 73.7, 73.1, 65.7, 65.6, 65.4, 63.4, 54.2, 43.3, 41.0, 40.9, 34.3, 34.2, 34.1, 33.8, 32.2, 32.0, 31.9, 31.6, 31.1, 30.8, 30.7, 28.9, 28.6, 28.5, 19.5, 17.9, 15.5, 15.4, −1.5; HRMS (CI, methane) $m/z$ found 593.3972 [$(M+H)^+$; calcd for $C_{32}H_{57}N_2O_6Si$: 593.3986].

**4.2.17. Olefin 28.** *trans*–*cis*=10:1. To a solution of *tert*-butyl carbamate **27** (765 mg, 1.29 mmol) in MeOH (20 mL) was added Pd/C (10%, 34.0 mg) and the reaction flask was charged with $H_2$. The reaction mixture was stirred for 17 h at room temperature, filtered through a celite plug, and then concentrated in vacuo. Flash chromatography (hexanes–EtOAc 5:1→2:1→1:1) gave 558 mg (86% yield) of alcohol as a colorless oil: $R_f$ 0.28 (hexanes–EtOAc 2:1); IR (neat) 3440 (m, br), 2940 (s), 2860 (s), 1690 (s), 1460 (m), 1410 (m), 1360 (m), 1240 (m), 1170 (m), 1090 (m), 1030 (w), 990 (w), 930 (w), 850 (m), 830 (w) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.01 (s, 9H), 0.84 (d, $J$=6.7 Hz, 6H), 0.89 (d, $J$=7.0 Hz, 3H), 0.97 (t, $J$=8.4 Hz, 2H), 1.43 (s, 9H), 1.56 (m, 1H), 1.69 (s, 1H), 1.70–2.02 (m, 3H), 2.05 (m, 2H), 3.03–3.33 (m, 7H), 3.51–3.68 (m, 4H), 3.84 (m, 1H), 4.14 (t, $J$=8.3 Hz, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 157.0, 156.2, 80.6, 80.4, 79.9, 79.7, 78.0, 77.4, 76.6, 76.4, 65.5, 65.4, 65.3, 63.7, 63.5, 43.1, 43.0, 41.3, 41.1, 35.7, 35.6, 31.6, 31.4, 31.3, 31.1, 28.8, 28.5, 19.5, 19.4, 19.3, 17.9, 15.0, −1.5; HRMS (ESI) $m/z$ found 525.3356 [$(M+Na)^+$; calcd for $C_{25}H_{50}N_2O_6NaSi$: 525.3336].

A solution of alcohol (446 mg, 0.887 mmol) in $CH_2Cl_2$ (10 mL) was treated with pyridine (0.28 mL, 3.9 equiv.) and Dess–Martin periodinane (376 mg, 1.00 equiv.), and the resultant mixture was stirred for 30 min at room temperature. The reaction mixture was poured into 20% $Na_2S_2O_3$–saturated $NaHCO_3$ (1:1=V:V, 60 mL) and after separation, the aqueous phase was extracted with ether (4×80 mL). Combined extracts were washed with saturated $CuSO_4$ (3×80 mL), water (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, then concentrated in vacuo. Flash chromatography (hexanes–ether 4:1→1:1) afforded aldehyde as a colorless oil (377 mg, 85% yield): $R_f$ 0.30 (hexanes–EtOAc 2:1); IR (neat) 2960 (s), 2860 (s), 2700 (w), 1690 (s), 1470 (m), 1420 (m), 1360(m), 1320 (w), 1250 (m), 1180 (m), 1090 (m), 930 (w), 850 (m), 830(m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.00 (s, 9H), 0.83 (d, $J$=6.7 Hz, 3H), 0.84 (d, $J$=6.6 Hz, 3H), 0.96 (t, $J$=8.4 Hz, 2H), 1.00* [d, $J$=7.2 Hz, 1H, minor diastereomer at C(3′)] 1.04 (d, $J$=7.2 Hz, 1H), 1.40 (s, 9H), 1.54 (m, 1H), 1.72 (m, 1H), 1.81 (m, 1H), 2.06 (m, 1H), 2.20 (m, 1H), 2.55–2.75 (m, 1H), 2.98–3.42 (m, 7H), 3.52–3.77 (m, 3H), 4.13 (t, $J$=8.4 Hz, 2H), 9.59* (br s, 1H), 9.66 (br s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 203.7, 203.5, 156.3, 155.5, 154.7, 80.2, 80.0, 79.1, 78.9, 76.5, 76.3, 65.8, 65.7, 65.6, 63.5, 51.0, 50.9, 47.1, 46.9, 43.1, 41.0, 31.8, 31.6, 31.4, 30.9, 30.6, 28.8, 28.5, 28.4, 19.4, 17.9, 12.0, 11.9, 11.8, −1.5; HRMS (CI, methane) $m/z$ found 501.3350 [$(M+H)^+$; calcd for $C_{25}H_{49}N_2O_6Si$: 501.3360].

To a solution of benzyltriphenylphosphonium chloride (510 mg, 1.21 equiv.) in benzene (10 mL) at 0°C was added *n*-BuLi (0.85 mL, 1.1 equiv.) in hexanes (1.4 M) dropwise and the resulting solution was warmed to room temperature then stirred for 1 h. The solution was cooled to

0°C and treated with a solution of aldehyde (543 mg, 1.08 mmol) in benzene (5 mL). The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched with saturated $NH_4Cl$ (50 mL) and extracted with ether (4×50 mL). Combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexanes–ether 5:1→4:1→2:1) afforded olefin **28** as a pale yellow oil (580 mg, 93% yield): $R_f$ 0.42 (hexanes–EtOAc 3:1); IR (neat) 2940 (s), 1690 (s), 1460 (m), 1420 (m), 1360 (m), 1250 (m), 1170 (m), 1090 (m), 960 (m), 930 (m), 860 (m), 830 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.01 (s, 9H), 0.02* [s, 9H, minor diastereomer at C(3′)], 0.85 (m, 6H), 0.96 (m, 2H), 1.04 (d, $J$=6.7 Hz, 3H), 1.37* (s, 9H), 1.43 (s, 9H), 1.52 (m, 1H), 1.73 (m, 1H), 1.86 (m, 1H), 2.01–2.30 (m, 2H), 2.57 (m, 1H), 2.94–3.21 (m, 5H), 3.26 (m, 1H), 3.36–3.84(m, 4H), 4.13 (m, 2H), 6.06 (m, 1H), 6.32* (d, $J$=15.9 Hz, 1H), 6.37 (d, $J$=15.9 Hz, 1H), 7.17–7.32 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.2, 155.4, 155.1, 137.5, 137.3, 134.3, 134.1, 133.8, 133.6, 129.8, 128.5, 128.3, 128.2, 127.1, 127.0, 125.9, 80.7, 80.6, 79.5, 79.3, 79.1, 66.4, 66.2, 63.4, 63.3, 57.5, 57.4, 43.5, 43.3, 40.7, 38.1, 37.8, 37.7, 37.6, 32.1, 31.7, 31.5, 31.0, 30.7, 28.8, 28.6, 28.5, 28.3, 19.4, 18.2, 17.9, −1.5; HRMS (ESI) $m/z$ found 597.3693 [$(M+Na)^+$; calcd for $C_{32}H_{54}N_2O_5NaSi$: 597.3700].

**4.2.18. Urea (+)-29.** Under argon, TBAF (1.0 mL, 1.3 equiv.) in THF (1.0 M) was added to a solution of olefin **28** (464 mg, 0.807 mmol) in THF (40 mL) at room temperature. The reaction mixture was stirred for 18 h at room temperature, and then treated with 4-methoxybenzyl isocyanate (420 mg, 3.2 equiv.). The resulting mixture was then stirred for 2 h, and quenched with MeOH (0.2 mL). The solution was concentrated in vacuo and purified by flash chromatography using $CH_2Cl_2$–MeOH (40:1) as eluant, to furnish urea (+)-**29** as a mixture (307 mg, 64% yield). The mixture was further purified by preparative HPLC using a reverse phase DYNAMAX® $C_{18}$ column [21.1 mm, MeCN–0.1% TFA in water (3:1), 4.0 mL/min] to give (+)-**29** (75.3 mg, 16% yield) as a colorless oil: $R_f$ 0.40 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=+59.0° ($c$ 1.36, $CHCl_3$); IR (neat) 3340 (m, br), 2940 (s), 1680 (s), 1630 (s), 1500 (s), 1460 (m), 1360 (m), 1240 (s), 1170 (s), 1090 (m), 1030 (m), 960 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.84 (d, $J$=6.7 Hz, 3H), 0.85 (d, $J$=6.4 Hz, 3H), 1.01 (d, $J$=6.7 Hz, 3H), 1.38 (m, 1H), 1.44 (s, 9H), 1.72 (m, 1H), 1.81 (m, 1H), 2.05–2.39 (m, 2H), 2.55 (m, 1H), 2.62 (m, 1H), 2.76–2.99 (m, 3H), 3.02 (m, 2H), 3.26 (m, 1H), 3.57 (m, 1H), 3.77 (s, 3H), 3.73–3.89 (m, 1H), 3.90 (m, 1H), 4.06 (m, 1H), 4.18 (dd, $J$=5.1, 14.4 Hz, 1H), 4.28 (dd, $J$=5.6, 14.4, 1H), 6.02 (m, 1H), 6.34 (d, $J$=15.8 Hz, 1H), 6.85 (d, $J$=8.7 Hz, 2H), 6.98–7.32 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.8, 157.4, 155.2, 154.9, 137.5, 137.3, 134.9, 134.3, 131.9, 129.8, 129.7, 128.9, 128.5, 128.4, 128.2, 127.1, 127.0, 125.8, 113.9, 80.5, 79.6, 79.1, 76.8, 67.2, 58.7, 55.2, 44.3, 43.3, 38.7, 38.4, 32.8, 32.6, 31.3, 30.5, 28.8, 28.7, 28.6, 28.5, 19.4, 18.0, 17.9; HRMS (ESI) $m/z$ found 616.3716 [$(M+Na)^+$; calcd for $C_{35}H_{51}N_3O_5Na$: 616.3726].

**4.2.19. Analogue (+)-30.** To a solution of urea (+)-**29** (18.2 mg, 0.0306 mmol) in $CH_2Cl_2$ (2.0 mL) was added trifluoroacetic acid (TFA, 1.0 mL) and the resulting mixture was stirred at room temperature for 14 min. The reaction mixture was diluted with $CH_2Cl_2$ (200 mL), washed with water (40 mL), and saturated $NaHCO_3$ (40 mL), dried ($Na_2SO_4$), filtered then concentrated in vacuo. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$ (saturated with $NH_3$)–MeOH (10:1)] afforded 13.6 mg (90% yield) of secondary amine as a colorless oil: $R_f$ 0.35 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=+51.5° ($c$ 0.635, $CHCl_3$); IR (neat) 3320 (m, br), 2980 (s), 1640 (s), 1500 (s), 1460 (m), 1380 (m), 1340 (w), 1290 (w), 1240 (s), 1170 (m), 1080 (m), 1030 (m), 960 (m), 810 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.82 (d, $J$=6.7 Hz, 6H), 1.09 (d, $J$=6.3 Hz, 3H), 1.53–1.69 (m, 2H), 1.72 (m, 1H), 2.03 (m, 3H), 2.48 (m, 2H), 2.66 (m, 2H), 3.04 (dd, $J$=6.6, 8.7 Hz, 1H), 3.15–3.24 (m, 3H), 3.28 (dd, $J$=6.4, 8.7 Hz, 1H), 3.55 (m, 1H), 3.61 (m, 1H), 3.77 (s, 3H), 4.30 (m, 2H), 4.49 (t, $J$=5.2 Hz, 1H), 6.09 (dd, $J$=7.3, 15.9 Hz, 1H), 6.39 (d, $J$=15.9 Hz, 1H), 6.83 (d, $J$=8.5 Hz, 2H), 7.15–7.32 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.9, 157.6, 137.5, 134.2, 131.8, 129.7, 129.1, 128.4, 127.0, 126.1, 114.0, 81.6, 76.6, 76.0, 61.8, 55.3, 53.0, 44.5, 41.7, 39.8, 37.5, 30.4, 28.8, 28.7, 19.4, 18.4; HRMS (ESI) $m/z$ found 494.3393 [$(M+H)^+$; calcd for $C_{30}H_{44}N_3O_3$: 494.3383].

To a solution of secondary amine (12.7 mg, 0.0257 mmol) and 37% formaldehyde (4.1 mg, 2.0 equiv.) in MeOH (2.0 mL) were added crushed 4 Å molecular sieves (0.5 mL) and $NaBH_3CN$ (3.2 mg, 2.0 equiv.). The pH was adjusted to 6–7 with glacial AcOH and the resultant mixture was stirred for 16 h at room temperature. The reaction mixture was filtered through a silica gel plug and concentrated in vacuo. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$(saturated with $NH_3$)–MeOH (10:1)] afforded 9.7 mg (74% yield) of analogue (+)-**30** as a colorless oil: $R_f$ 0.33 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}$=+18° ($c$ 0.46, $CHCl_3$); IR (neat) 3320 (m, br), 2940 (s), 1620 (s), 1500 (s), 1460 (m), 1380 (w), 1340 (w), 1290 (w), 1240 (w), 1160 (m), 1080 (m), 1030 (m), 960 (m), 810 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (d, $J$=6.7 Hz, 6H), 1.04 (d, $J$=6.5 Hz, 3H), 1.58–1.82 (m, 4H), 1.89 (m, 1H), 1.95 (m, 1H), 2.29 (br s, 3H), 2.40 (m, 1H), 2.47 (m, 1H), 2.54 (m, 1H), 2.60 (m, 1H), 3.08 (m, 1H), 3.14 (dd, $J$=6.4, 8.6 Hz, 1H), 3.21 (dd, $J$=6.6, 8.6 Hz, 1H), 3.24 (m, 1H), 3.38 (dt, $J$=2.9, 8.1 Hz, 1H), 3.53 (m, 1H), 3.61 (m, 1H), 3.77 (s, 3H), 4.32 (d, $J$=5.3 Hz, 2H), 4.48 (t, $J$=5.0 Hz, 1H), 6.16 (dd, $J$=7.0, 16.0 Hz, 1H), 6.36 (d, $J$=16.0 Hz, 1H), 6.84 (d, $J$=8.7 Hz, 2H), 7.13–7.35 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.9, 157.6, 138.0, 135.6, 131.8, 129.1, 128.4, 126.8, 125.9, 114.0, 79.9, 75.8, 68.3, 61.9, 55.3, 44.6, 42.4, 40.6, 38.1, 35.8, 30.9, 29.0, 28.6, 19.6, 18.0; HRMS (ESI) $m/z$ found 508.3542 [$(M+H)^+$; calcd for $C_{31}H_{46}N_3O_3$: 508.3539].

**4.2.20. α-Epoxide (−)-31.** To a solution of olefin (+)-**25** (12.4 mg, 0.0244 mmol) in ether (5.0 mL) at −78°C was added $BF_3{\cdot}OEt_2$ (6.2 μL, 2.0 equiv.) and the resulting mixture was warmed to room temperature, then stirred for 16 h. The reaction mixture was concentrated in vacuo, dissolved in $CH_2Cl_2$ (0.5 mL), and cooled to 0°C. A solution of dimethyldioxirane in acetone (9 mL) was added to the reaction mixture and the resulting mixture was stirred at 0°C for 1.5 h. The reaction mixture was concentrated in vacuo, diluted with $CH_2Cl_2$ (170 mL), washed with 10% $NaHSO_3$

(3×30 mL), and saturated $NaHCO_3$ (40 mL), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$(saturated with $NH_3$)-MeOH (9:1)] afforded epoxide (−)-**31** (2.5 mg, 20% yield) as a colorless oil: $R_f$ 0.27 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}=-9.6°$ (*c* 0.49, $CHCl_3$); IR (neat) 3340 (m, br), 2960 (s), 1620 (s), 1510 (s), 1460 (m), 1390 (w), 1350 (w), 1290 (w), 1240 (s), 1170 (m), 1090 (m), 1030 (m), 880 (m), 810 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.879 (d, *J*=6.7 Hz, 3H), 0.883 (d, *J*=6.7 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 1.58–1.81 (m, 5H), 1.89 (m, 1H), 1.96 (m, 1H), 2.27 (s, 3H), 2.55 (dd, *J*=7.6, 12.7 Hz, 1H), 2.61 (m, 1H), 2.66 (dd, *J*=6.5, 12.8 Hz, 1H), 2.83 (dd, *J*=2.1, 6.6 Hz, 1H), 3.11 (m, 1H), 3.15 (dd, *J*=6.4, 8.7 Hz, 1H), 3.21 (dd, *J*=6.7, 8.4 Hz, 1H), 3.23 (m, 1H), 3.38 (dt, *J*=3.0, 8.2 Hz, 1H), 3.55 (m, 1H), 3.61 (m, 1H), 3.64 (d, *J*=2.0 Hz, 1H), 3.66 (s, 3H), 4.33 (t, *J*=5.3 Hz, 2H), 4.50 (t, *J*=5.2 Hz, 1H), 6.83 (d, *J*=8.6 Hz, 2H), 7.16–7.31 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta\delta$ 158.9, 157.6, 138.1, 131.8, 129.1, 128.4, 127.9, 125.6, 114.0, 79.9, 75.9, 67.9, 66.3, 59.5, 56.6, 55.3, 44.6, 42.6, 40.6, 37.9, 35.0, 30.9, 29.0, 28.5, 19.7, 19.6, 14.5; HRMS (ESI) *m/z* found 524.3502 [(M+H)$^+$; calcd for $C_{31}H_{46}N_3O_4$: 524.3488].

**4.2.21. α-Epoxide (−)-32.** To a solution of olefin (+)-**30** (10.0 mg, 0.0197 mmol) in ether (10 mL) at −78°C was added $BF_3{\cdot}OEt_2$ (5.0 μL, 2.0 equiv.) and the resulting mixture was warmed to room temperature, then stirred for 16 h. The reaction mixture was concentrated in vacuo, dissolved in $CH_2Cl_2$ (0.5 mL), and cooled to 0°C. A solution of dimethyldioxirane in acetone (9 mL) was added to the reaction mixture and the resulting mixture was stirred at 0°C for 1.5 h. The reaction mixture was concentrated in vacuo, diluted with $CH_2Cl_2$ (180 mL), washed with 10% $NaHSO_3$ (3×30 mL), and saturated $NaHCO_3$ (50 mL), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$ (saturated with $NH_3$)–MeOH (9:1)] afforded α-epoxide (−)-**32** (5.6 mg, 54% yield) as a colorless oil: $R_f$ 0.27 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}=-14°$ (*c* 0.62, $CHCl_3$); IR (neat) 3340 (m, br), 2940 (s), 1620 (s), 1510 (s), 1460 (m), 1390 (w), 1350 (w), 1290 (w), 1240 (s), 1170 (m), 1080 (m), 103 (m), 880 (m), 820 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.89 (d, *J*=6.7 Hz, 6H), 0.97 (d, *J*=6.9 Hz, 3H), 1.62–1.84 (m, 4H), 1.89 (m, 1H), 1.98 (m, 1H), 2.29 (s, 3H), 2.48 (dd, *J*=7.9, 12.6 Hz, 1H), 2.61 (m, 1H), 2.74 (dd, *J*=6.1, 12.7 Hz, 1H), 2.88 (dd, *J*=2.1, 6.5 Hz, 1H), 3.08 (m, 1H), 3.14 (dd, *J*=6.3, 8.6 Hz, 1H), 3.22 (dd, *J*=6.6, 8.5 Hz, 1H), 3.25 (m, 1H), 3.39 (dt, *J*=2.9, 8.1 Hz, 1H), 3.54 (ddd, *J*=2.6, 6.8, 10.0 Hz, 1H), 3.64 (m, 1H), 3.67 (d, *J*=2.0 Hz, 1H), 3.78 (s, 3H), 4.35 (d, *J*=5.3 Hz, 2H), 4.54 (t, *J*=5.2 Hz, 1H), 6.85 (d, *J*=8.6 Hz, 2H), 7.22–7.33 (m, 7H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.8, 157.5, 138.0, 131.7, 129.0, 128.3, 127.8, 125.5, 114.0, 79.9, 75.8, 68.6, 66.2, 59.1, 56.6, 55.2, 44.5, 42.3, 40.6, 37.8, 34.7, 30.8, 28.9, 28.6, 19.6, 14.2; HRMS (ESI) *m/z* found 524.3479 [(M+H)$^+$; calcd for $C_{31}H_{46}N_3O_4$: 524.3488].

**4.2.22. Diol (−)-38.** *trans*–*cis*=10:1. Via the procedure described above for the preparation of **22**, reaction of benzyltriphenylphosphonium chloride (11.4 g, 1.05 equiv.) in benzene (200 mL) at 0°C with *n*-BuLi (20.2 mL, 1.01 equiv.) in hexanes (1.4 M), addition of aldehyde (+)-**37** (9.17 g, 28.1 mmol) in benzene (50 mL), workup, and flash chromatography (hexanes–ether 150:1→100:1→10:1) gave olefin as a colorless oil (6.70 g, 60% yield): $R_f$ 0.47 (hexanes–EtOAc 40:1); $[\alpha]_D^{20}=+11.1°$ (*c* 0.595, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2960 (m), 2940 (m), 2860 (m), 1430 (w), 1200 (s), 1120 (s), 960 (w), 920 (w) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.09 (s, 9H), 1.15 (d, *J*=2.4 Hz, 3H), 2.59 (m, 1H), 3.64 (m, 2H), 6.18 (dd, *J*=7.4, 16.0 Hz, 1H), 6.42 (d, *J*=16.0 Hz, 1H), 7.19–7.44 (m, 11H), 7.69 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 137.8, 135.67, 135.66, 134.0, 133.4, 129.5, 128.4, 127.6, 126.9, 126.0, 68.7, 39.8, 26.9, 19.3, 16.7. Anal. calcd for $C_{27}H_{32}OSi$: C, 80.95; H, 8.05. Found: C, 81.29; H, 8.12.

To a solution of olefin (1.51 g, 3.77 mmol) in *t*-BuOH–water (1:1, 32 mL) at 0°C were added methanesulfonamide (359 mg, 1.00 equiv.) and AD-mix-β (5.86 g). The resulting mixture was stirred at 0°C vigorously for 5 days. Solid $Na_2SO_3$ (6.5 g) was added and the mixture was warmed to room temperature with stirring then extracted with EtOAc (3×100 mL). Combined extracts were washed with 10% NaOH (100 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by flash chromatography (hexanes–ether 6:1→4:1→3:1→1:1) to give diol (−)-**38** as a colorless oil (1.40 g, 85% yield): $R_f$ 0.23 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=-4.2°$ (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3500 (w, br), 3020 (s), 2960 (s), 2940 (s), 2860 (m), 1430 (w), 1200 (s), 1110 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.92 (d, *J*=7.0 Hz, 3H), 1.03 (s, 9H), 1.54 (m, 1H), 2.92 (d, *J*=3.3 Hz, 1H), 3.00 (m, 1H), 3.56–3.63 (m, 2H), 3.97 (dt, *J*=2.9, 7.6 Hz, 1H), 4.64 (dd, *J*=2.6, 7.6 Hz, 1H), 7.24–7.40 (m, 11H), 7.55–7.62 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 140.9, 135.5, 135.4, 133.1, 129.7, 128.4, 127.9, 127.7, 127.0, 75.4, 67.6, 36.0, 26.8, 19.1, 10.2; HRMS (CI, methane) *m/z* 435.2343 [(M+H)+; calcd for $C_{27}H_{35}O_3Si$: 435.2355].

**4.2.23. Iodide (+)-39.** To a solution of diol (−)-**38** (1.40 g, 3.23 mmol) in acetone (80 mL) was added *p*-toluenesulfonic acid monohydrate (896 mg, 1.46 equiv.) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo to remove acetone and diluted with ether (300 mL), washed with saturated $NaHCO_3$ (2×50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexanes–ether 50:1→30:1→10:1) gave 1.33 g (87% yield) of acetonide as a white solid: mp 61–63 °C; $R_f$ 0.33 (hexanes–EtOAc 10:1); $[\alpha]_D^{20}=+4.88°$ (*c* 2.83, $CHCl_3$); IR ($CHCl_3$) 3020 (s), 2940 (s), 2860 (m), 1430 (w), 1380 (w), 1200 (s), 1110 (s), 1040 (s), 930 (w), 880 (w) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.96 (s, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 1.46 (s, 3H), 1.54 (s, 3H), 1.85 (m, 1H), 3.49 (dd, *J*=6.4 10.0 Hz, 1H), 3.59 (dd, *J*=7.4, 10.0 Hz, 1H), 4.10 (dd, *J*=3.0, 8.8 Hz, 1H), 4.70 (d, *J*=8.8 Hz, 1H), 7.29–7.40 (m, 11H), 7.51 (m, 2H), 7.58 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 138.3, 135.6, 135.5, 133.8, 129.5, 128.5, 128.1, 127.5, 127.0, 108.5, 82.5, 80.4, 66.3, 35.8, 27.2, 26.8, 19.2, 10.7. Anal. calcd for $C_{30}H_{38}O_3Si$: C, 75.90; H, 8.07. Found: C, 75.55; H, 8.21.

A solution of acetonide (1.33 g, 2.81 mmol) in THF (20 mL) was treated with TBAF (3.0 mL, 1.1 equiv.) in THF (1.0 M) and the resultant mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by

addition of saturated $NH_4Cl$ (70 mL) and extracted with ether (3×100 mL). Combined extracts were washed with saturated $NaHCO_3$ (70 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (hexanes–ether 5:1→3:1→1:1) to give alcohol as a colorless oil (658 mg, 99% yield): $R_f$ 0.23 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=-10.0°$ (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3520 (w, br), 2980 (s), 2940 (s), 2880 (s), 1450 (m), 1360 (m), 1220 (s), 1170 (m), 1110 (m), 1080 (m), 1040 (s), 910 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.05 (d, *J*=7.0 Hz, 3H), 1.47 (s, 3H), 1.54 (s, 3H), 1.85 (m, 1H), 1.92 (br s, 1H), 3.56 (d, *J*=5.3 Hz, 2H), 3.93 (dd, *J*=3.0, 8.9 Hz, 1H), 4.76 (d, *J*=8.9 Hz, 1H), 7.27–7.37 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 137.8, 128.6, 128.3, 126.8, 108.7, 84.5, 80.0, 66.6, 34.7, 27.2, 27.0, 10.7. Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.12; H, 8.60.

To a solution of alcohol (822 mg, 3.48 mmol) in benzene (40 mL)–$CH_3CN$ (10 mL) were added imidazole (1.23 g, 4.34 equiv.), $PPh_3$ (2.00 g, 2.19 equiv.), and $I_2$ (1.59 g, 1.86 equiv.) and the resulting mixture was stirred at room temperature for 20 min. The reaction mixture was poured into saturated $NaHCO_3$–20% $Na_2S_2O_3$ (1:1, 160 mL) and extracted with ether (3×160 mL). The combined extracts were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (hexanes–ether 50:1) to give alcohol iodide (+)-**39** as a colorless oil (942 mg, 79% yield): $R_f$ 0.30 (hexanes–EtOAc 10:1); $[\alpha]_D^{20}=+20.1°$ (*c* 2.15, $CHCl_3$); IR (neat) 3040 (m), 3010 (m), 2970 (s), 2910 (s), 2880 (s), 1480 (w), 1450 (m), 1370 (s), 1230 (s), 1160 (m), 1050 (s), 1020 (m), 980 (m), 880 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.15 (d, *J*=6.8 Hz, 3H), 1.46 (s, 3H), 1.53 (s, 3H), 1.89 (m, 1H), 3.01 (dd, *J*=8.0, 9.8 Hz, 1H), 3.22 (dd, *J*=5.7, 9.8 Hz, 1H), 3.90 (dd, *J*=3.6, 8.6 Hz, 1H), 4.69 (d, *J*=8.6 Hz, 1H), 7.29–7.36 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 137.6, 128.7, 128.5, 127.0, 108.8, 84.8, 80.7, 36.4, 27.2, 27.0, 15.1, 11.5. Anal. calcd for $C_{14}H_{19}O_2I$: C, 48.57; H, 5.53. Found: C, 48.29; H, 5.45.

**4.2.24. Iodide (−)-35.** A solution of iodide (+)-**39** (841 mg, 2.43 mmol) in DMSO (3 mL) was treated with NaCN (191 mg, 1.61 equiv.) and the resultant mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (3×70 mL). Combined extracts were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes–ether 16:1→5:1) afforded cyanide as a colorless oil (545 mg, 91% yield): $R_f$ 0.20 (hexanes–EtOAc 10:1); $[\alpha]_D^{20}=-1.8°$ (*c* 1.1, $CHCl_3$); IR (neat) 3080 (w), 3040 (m), 3020 (m), 2980 (s), 2920 (s), 2880 (s), 2240 (m), 1490 (m), 1450 (s), 1420 (m), 1370 (s), 1230 (s), 1160 (s), 1050 (s), 990 (m), 880 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.18 (d, *J*=6.8 Hz, 3H), 1.46 (s, 3H), 1.53 (s, 3H), 2.07 (m, 1H), 2.27 (dd, *J*=8.3, 16.8 Hz, 1H), 2.38 (dd, *J*=6.1, 16.8 Hz, 1H), 3.81 (dd, *J*=3.5, 8.7 Hz, 1H), 4.70 (d, *J*=8.7 Hz, 1H), 7.30–7.37 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 137.2, 128.8, 128.7, 126.9, 118.4, 109.0, 84.3, 80.2, 30.9, 27.1, 27.0, 22.3, 13.8. Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.54; H, 7.89; N, 5.65.

To a solution of cyanide (600 mg, 2.45 mmol) in $CH_2Cl_2$ (6 mL) at −78°C was added DIBAL-H (5.0 mL, 2.0 equiv.) in toluene (1.0 M) slowly and the resulting mixture was stirred for 5 h at −78°C. Saturated $NH_4Cl$ (60 mL) was added and the reaction mixture was stirred at room temperature for 1 h and the aqueous phase was extracted with EtOAc (4×80 mL). Combined extracts were washed with saturated $NaHCO_3$ (80 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was then dissolved in MeOH (20 mL) and treated with $NaBH_4$ (825 mg, 8.91 equiv.) portionwise at room temperature. After 30 min, the reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (4×80 mL). Combined extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes–ether 4:1→2:1→1:1) gave alcohol as a colorless oil (546 mg, 89% yield): $R_f$ 0.27 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=-12°$ (*c* 0.73, $CHCl_3$); IR (neat) 3420 (m, br), 2980 (m), 2900 (m), 2880 (m), 1490 (m), 1450 (s), 1370 (s), 1230 (s), 1170 (s), 1050 (s), 880 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.02 (d, *J*=6.9 Hz, 3H), 1.47 (s, 3H), 1.48–1.52 (m, 1H), 1.54 (s, 3H), 1.64–1.70 (m, 1H), 1.83 (m, 1H), 1.89 (m, 1H), 3.58 (m, 1H), 3.67 (m, 1H), 3.81 (dd, *J*=3.1, 8.8 Hz, 1H), 4.73 (d, *J*=8.7 Hz, 1H), 7.27–7.37 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 138.2, 128.6, 128.3, 127.0, 108.5, 86.2, 80.4, 60.0, 37.3, 29.7, 27.2, 27.1, 13.5. Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.98; H, 8.90.

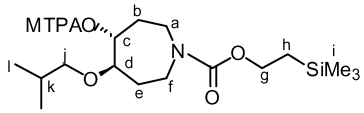
Via the procedure described above for the preparation of iodide (+)-**39**, the reaction of alcohol (212 mg, 0.847 mmol) in benzene (10 mL)–$CH_3CN$ (2.5 mL) with imidazole (215 mg, 3.74 equiv.), $PPh_3$ (220 mg, 1.00 equiv.), $I_2$ (204 mg, 1.02 equiv.), workup, and flash chromatography (hexanes–ether 50:1) gave iodide (−)-**35** as a colorless oil (241 mg, 79% yield): $R_f$ 0.30 (hexanes–EtOAc 10:1); $[\alpha]_D^{20}=-3.1°$ (*c* 1.4, $CHCl_3$); IR (neat) 2982 (s), 2932 (m), 2883 (m), 2359 (w), 1494 (w), 1454 (m), 1378 (s), 1369 (s), 1238 (s), 1164 (m), 1054 (s), 1027 (m), 887 (m), 813 (w) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.00 (d, *J*=6.8 Hz, 3H), 1.46 (s, 3H), 1.53 (s, 3H), 1.68–1.75 (m, 1H), 1.82 (m, 1H), 1.83–1.95 (m, 1H), 3.07–3.19 (m, 2H), 3.75 (dd, *J*=3.6, 8.6 Hz, 1H), 4.71 (d, *J*=8.6 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 138.2, 128.6, 128.3, 126.9, 108.6, 85.4, 80.4, 38.0, 34.1, 27.2, 27.1, 13.2, 4.3. Anal. calcd for $C_{15}H_{21}O_2I$: C, 50.01; H, 5.88. Found: C, 50.00; H, 5.79.

**4.2.25. Alcohol (−)-36.** Jacobsen catalyst (*S*,*S*)-**15** (273 mg, 0.28 equiv.) was added to a solution of epoxide **10** (394 mg, 1.53 mmol) in *iso*-butanol (0.42 mL) at room temperature. After 5 days, the reaction mixture was filtered through a silica gel plug, concentrated in vacuo, and purified by flash chromatography, using hexanes–ether (3:1→1:1) as eluant, to give 316 mg (63% yield) of (−)-**36** as a pale yellow oil: $R_f$ 0.17 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=-6.8°$ (*c* 1.1, $CHCl_3$); IR (neat) 3450 (m, br), 2953 (s), 1674 (s), 1471 (m), 1421 (s), 1350 (w), 1250 (s), 1087 (s), 1002 (w), 859 (s), 837 (s) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.01 (s, 9H), 0.88 (d, *J*=6.6 Hz, 3H), 0.89 (d, *J*=6.6 Hz, 3H), 0.97 (m, 2H), 1.50–1.65 (m, 2H), 1.82 (m, 1H), 2.05 (m, 2H), 2.95 (d, *J*=46.7 Hz, 1H), 3.04–3.11 (m, 2H), 3.19 (m, 1H), 3.29 (m, 1H), 3.35 (dd, *J*=6.5, 8.8 Hz, 1H), 3.49–3.63 (m, 3H), 4.14 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 83.9, 83.5, 76.2, 76.0, 74.2, 73.9, 63.5, 41.2, 41.0, 31.9, 31.5, 30.3, 29.7, 29.0, 28.7, 28.6, 19.4, 17.9, −1.5; HRMS (ESI)

*m/z* 354.2069 [(M+Na)$^+$; calcd for $C_{16}H_{33}NO_4NaSi$: 354.2077].

*Determination of stereochemistry of* (−)-**36**. (*S*)-MTPA ester of (−)-**36**. $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 0.035 (s, 9H), 0.85 (d, *J*=6.9 Hz, 3H), 0.87 (d, *J*=6.7 Hz, 3H), 0.97 (t, *J*=8.3 Hz, 2H), 1.73 (m, 2H), 1.83 (m, 1H), 1.95 (m, 1H), 2.20 (m, 1H), 3.17 (m, 1H), 3.23 (m, 1H), 3.33 (m, 2H), 3.46 (t, *J*=5.5 Hz, 2H), 3.52 (s, 3H), 3.59 (m, 1H), 4.12 (m, 2H), 5.30 (m, 1H), 7.42–7.52 (m, 5H).

(*R*)-MTPA ester of (−)-**36**. $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 0.032 (s, 9H), 0.88 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H), 0.97 (m, 2H), 1.70–1.84 (m, 2H), 1.92 (m, 2H), 2.11 (m, 2H), 3.23–3.64 (m, 7H), 3.52 (s, 3H), 4.13 (m, 2H), 5.26 (m, 1H), 7.41–7.52 (m, 5H).




| | (*S*)-MTPA ester | (*R*)-MTPA ester | (*S*)−(*R*) |
|---|---|---|---|
| b1/b2 | 2.20/1.95 | 2.11/1.83 | +0.09/+0.12 |
| c | 5.30 | 5.26 | +0.04 |
| e | 1.83 | 1.92 | −0.09 |
| g | 4.12 | 4.13 | −0.01 |
| k | 1.73 | 1.80 | −0.07 |
| l | 0.85/0.87 | 0.89/0.90 | −0.04/−0.03 |

**4.2.26. Acetonide (−)-40.** A solution of alcohol (−)-**36** (24.6 mg, 0.0743 mmol) in DMF (0.3 mL) was treated with NaH (95%, 5.0 mg, 2.8 equiv.) and the resulting mixture was stirred at room temperature for 1 h. TBAI (1.2 mg, 0.080 equiv.) and a solution of iodide (−)-**35** (25.4 mg, 0.0705 mmol) in DMF (0.3 mL) were added and the reaction mixture was stirred at room temperature for 12 h. the reaction mixture was diluted with EtOAc (50 mL), washed with water (3×20 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (hexanes–ether 20:1→4:1→1:1) afforded 11.1 mg (26% yield) of acetonide (−)-**40** as a pale yellow oil: $R_f$ 0.47 (hexanes–EtOAc 3:1); $[\alpha]_D^{20}=-19°$ (*c* 0.58, $CHCl_3$); IR (neat) 2954 (s), 1696 (s), 1455 (w), 1420 (m), 1368 (w), 1305 (w), 1237 (m), 1171 (w), 1095 (m), 1049 (m), 860 (m), 837 (m) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.01 (s, 9H), 0.846 (d, *J*=6.7 Hz, 3H), 0.849 (d, *J*=6.7 Hz, 3H), 0.96 (dd, *J*=7.5, 9.3 Hz, 2H), 0.99 (dd, *J*=1.7, 6.8 Hz, 3H), 1.46 (s, 3H), 1.52 (s, 3H), 1.60–1.83 (m, 8H), 3.06–3.45 (m, 10H), 3.76 (m, 1H), 4.12 (m, 2H), 4.70 (d, *J*=8.6 Hz, 1H), 7.26–7.36 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 138.6, 128.5, 128.2, 128.1, 127.0, 108.4, 86.0, 85.9, 80.4, 79.2, 79.1, 79.0, 78.8, 78.7, 78.6, 78.3, 76.5, 76.4, 76.3, 67.2, 67.1, 67.0, 63.1, 40.5, 40.4, 40.2, 34.4, 30.3, 30.0, 29.9, 29.7, 28.8, 28.4, 28.2, 28.1, 28.0, 27.7, 27.5, 27.2, 19.4, 17.9, 14.2, 14.1, −1.5; HRMS (ESI) *m/z* 586.3527 [(M+Na)$^+$; calcd for $C_{31}H_{53}NO_6$ NaSi: 586.3540].

**4.2.27. Amine salt 41.** To a solution of 4-methoxybenzylamine (2.10 mL, 16.1 mmol) in THF (4 mL) at 0°C was added HCl (16.1 mL, 1.00 equiv.) in ether (1.0 M) dropwise. The resulting white suspension was stirred for 20 min and concentrated in vacuo. The residue was diluted in glacial AcOH (30 mL) and sulfuryl chloride (2.6 mL, 2.0 equiv.) was added dropwise. The reaction mixture was heated to 70°C with a gas outlet for 5 h and stirred at room temperature for 12 h. To the white slurry was added ether (70 mL) and the mixture was stirred for 90 min. Filtration and air-drying gave amine salt **41** as a white solid (1.37 g, 44% yield): mp 231–234 °C; IR (KBr) 2998 (m, br), 1609 (m), 1507 (s), 1460 (s), 1385 (m), 1299 (s), 1267 (s), 1221 (w), 1110 (w), 1093 (w), 1068 (s), 1024 (s), 973 (m), 909 (m), 886 (s), 806 (s) cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 3.90 (s, 3H), 4.04 (s, 2H), 7.12 (d, *J*=8.5 Hz, 1H), 7.37 (dd, *J*=2.2, 8.5 Hz, 1H), 7.50 (d, *J*=2.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta$ 157.2, 131.9, 130.2, 127.3, 124.0, 113.8, 56.8, 43.4; HRMS (CI, methane) *m/z* 155.0267 [(M−$NH_3$Cl)+; calcd for $C_8H_8OCl$: 155.0264].

**4.2.28. Urea (−)-42.** Under argon, TBAF (3 equiv.) in THF (0.11 mL, 1.0 M) was added to a solution of (−)-**40** (20.4 mg, 0.0362 mmol) in THF (0.5 mL) at room temperature. The reaction mixture was stirred for 24 h at room temperature and concentrated in vacuo to give a secondary amine, which was used for the next reaction without purification. To a solution of triphosgene (39.8 mg, 3.7 equiv.) in $CH_2Cl_2$ (0.5 mL) was added a mixture of **41** (24.3 mg, 3.5 equiv.) and *i*-$Pr_2NEt$ (0.10 mL, 16 equiv.) in $CH_2Cl_2$ (0.5 mL) dropwise. After 5 min, a solution of the secondary amine in $CH_2Cl_2$ (0.5 mL) was added in one portion. Preparative TLC [0.5 mm×20 cm×20 cm, $CH_2Cl_2$–MeOH (20:1)] afforded 11.9 mg (52% yield) of (−)-**42** as a colorless oil: $R_f$ 0.37 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}=-21.4°$ (*c* 0.238, $CHCl_3$); IR (neat) 3338 (w, br), 2931 (s), 2871 (s), 1626 (s), 1532 (s), 1502 (s), 1462 (m), 1379 (m), 1257 (s), 1169 (w), 1098 (s), 1064 (s), 1027 (m), 888 (w), 812 (w) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.844 (d, *J*=6.7 Hz, 3H), 0.845 (d, *J*=6.7 Hz, 3H), 0.99 (d, *J*=6.9 Hz, 3H), 1.42 (m, 1H), 1.46 (s, 3H), 1.52 (s, 3H), 1.60–1.88 (m, 7H), 3.08 (dd, *J*=6.4, 8.8 Hz, 1H), 3.14 (dd, *J*=6.5, 8.8 Hz, 1H), 3.20 (m, 1H), 3.31–3.44 (m, 7H), 3.75 (dd, *J*=3.4, 8.4 Hz, 1H), 3.86 (s, 3H), 4.30 (m, 2H), 4.69 (d, *J*=8.6 Hz, 1H), 6.84 (d, *J*=8.4 Hz, 1H), 7.14 (dd, *J*=2.2, 8.4 Hz, 1H), 7.24–7.35 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 157.5, 154.1, 138.6, 133.3, 129.5, 128.5, 128.1, 127.1, 126.9, 122.5, 112.1, 108.4, 86.0, 80.4, 78.2, 78.0, 77.8, 76.3, 67.0, 56.2, 44.0, 39.5, 39.2, 34.4, 29.9, 28.8, 28.0, 27.3, 27.2, 19.4, 19.3, 14.1; HRMS (ESI) *m/z* 639.3204 [(M+Na)$^+$; calcd for $C_{34}H_{49}N_2O_6$ NaCl: 639.3177].

**4.2.29. β-Epoxide (+)-34.** A solution of acetonide (−)-**42** (11.1 mg, 0.0180 mmol) in MeOH (0.3 mL) was treated with *p*-toluenesulfonic acid monohydrate (31.5 mg, 9.17 equiv.) and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated to remove MeOH, diluted with EtOAc (40 mL), washed with saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatopraphy ($CH_2Cl_2$–MeOH 45:1) afforded 5.7 mg (55% yield) of diol as a colorless oil: $R_f$ 0.30 ($CH_2Cl_2$–MeOH 10:1); $[\alpha]_D^{20}=-25°$ (*c* 0.24, $CHCl_3$); IR (neat) 3360 (m, br), 2955 (s), 1626 (s), 1532 (s), 1502 (s), 1462 (m), 1399 (m), 1257 (s), 1099 (s), 1064 (s), 1024 (m) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.866 (d, *J*=6.7 Hz, 3H), 0.869 (d, *J*=6.7 Hz, 3H), 0.92 (d,

$J$=6.7 Hz, 3H), 1.49 (m, 1H), 1.55 (br s, 2H), 1.64 (m, 1H), 1.74–1.96 (m, 5H), 3.12–3.21 (m, 2H), 3.27–3.54 (m, 8H), 3.65 (br m, 1H), 3.86 (d, $J$=0.9 Hz, 3H), 4.31 (m, 2H), 4.54 (dt, $J$=5.5, 15.7 Hz, 1H), 4.59 (dd, $J$=5.2, 7.5 Hz, 1H), 6.85 (dd, $J$=2.4, 8.4 Hz, 1H), 7.15 (dd, $J$=2.2, 8.4 Hz, 1H), 7.25–7.35 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 157.6, 157.5, 154.2, 141.4, 133.2, 129.6, 128.5, 127.9, 127.2, 127.0, 126.9, 122.5, 112.2, 78.5, 78.4, 78.2, 78.1, 78.0, 77.9, 77.8, 77.7, 77.6, 77.1, 76.4, 76.3, 75.3, 67.3, 67.2, 56.2, 44.1, 39.8, 39.7, 34.7, 34.6, 31.8, 31.7, 31.6, 28.9, 28.8, 27.8, 27.7, 27.4, 19.4, 13.4, 13.2; HRMS (ESI) $m/z$ found 599.2881 [$(M+Na)^+$; calcd for $C_{31}H_{45}N_2O_6NaCl$: 599.2864].

To a solution of diol (4.1 mg, 0.0035 mmol) in $CH_2Cl_2$ (0.15 mL) was added trimethylorthoacetate (50 μL, 112 equiv.). After 5 min, TMSCl (50 μL, 113 equiv.) was added and the resultant mixture was stirred at room temperature for 3 h then concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and $K_2CO_3$ (1.6 mg, 3.3 equiv.) was added. The reaction mixture was stirred at room temperature for 7 h, diluted with $CH_2Cl_2$ (10 mL), washed with saturated $NH_4Cl$ (5 mL), dried ($MgSO_4$), filtered and concentrated. Preparative TLC [0.5 mm×20 cm×20 cm, benzene–$CH_2Cl_2$–MeOH (10:5:1)] afforded 2.8 mg (70% yield) of epoxide (+)-**34** as a colorless oil: $R_f$ 0.20 (PhH–$CH_2Cl_2$–MeOH 5:5:1); $[\alpha]_D^{20}$=+18° ($c$ 0.25, $CHCl_3$); IR (neat) 3346 (w), 2955 (s), 1627 (s), 1530 (s), 1501 (s), 1462 (m), 1396 (w), 1257 (s), 1102 (s), 1064 (m), 887 (w) $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.86* (dd, $J$=0.7, 6.7 Hz, 3H, rotamers), 0.87* (dd, $J$=0.7, 6.7 Hz, 3H), 1.09 (d, $J$=6.3 Hz, 3H), 1.55–1.69 (m, 3H), 1.74–1.85 (m, 3H), 1.94 (m, 2H), 2.73* (ddd, $J$=2.1, 7.5, 7.5 Hz, 1H), 3.12–3.23 (m, 2H), 3.27–3.58 (m, 8H), 3.64* (dd, $J$=2.1, 5.1 Hz, 1H), 3.85* (d, $J$=1.4 Hz, 3H), 4.31 (m, 2H), 4.51 (dd, $J$=5.5, 13.2 Hz, 1H), 6.84 (d, $J$=8.1 Hz, 1H), 7.15 (dd, $J$=2.1, 8.4 Hz, 1H), 7.22–7.34 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 157.5, 154.2, 137.9, 137.8, 133.3, 129.6, 128.5, 128.0, 127.2, 125.5, 122.5, 112.2, 78.4, 78.3, 78.1, 77.6, 76.9, 76.5, 76.4, 76.3, 67.4, 67.0, 58.3, 58.2, 56.2, 44.0, 39.6, 39.5, 39.3, 34.0, 33.9, 33.3, 28.9, 28.2, 27.8, 27.7, 27.5, 19.4, 17.2, 16.9; HRMS (ESI) $m/z$ 581.2779 [$(M+Na)^+$; calcd for $C_{31}H_{43}N_2O_5NaCl$: 581.2758].

*At 305 K*. $^1$H NMR (500 MHz, DMSO) $\delta$ 0.81* (dd, $J$=0.7, 6.2 Hz, 3H, rotamers), 0.82* (dd, $J$=0.7, 6.7 Hz, 3H), 1.00 (d, $J$=6.3 Hz, 3H), 1.46–1.83 (m, 8H), 2.80* (ddd, $J$=1.9, 6.5, 6.5 Hz, 1H), 3.10–3.51 (m, 10H), 3.72* (dd, $J$=1.9, 6.3 Hz, 1H), 3.79 (s, 3H), 4.12 (d, $J$=5.8 Hz, 2H), 6.67 (m, 1H), 7.02 (d, $J$=8.5 Hz, 1H), 7.15 (dd, $J$=2.1, 8.3 Hz, 1H), 7.23–7.34 (m, 6H).

*At 375 K*. $^1$H NMR (500 MHz, DMSO) $\delta$ 0.84 (d, $J$=6.7 Hz, 3H), 0.85 (d, $J$=6.7 Hz, 3H), 1.03 (d, $J$=6.5 Hz, 3H), 1.50–1.88 (m, 8H), 2.82* (ddd, $J$=2.2, 3.7, 6.0 Hz, 1H), 3.15–3.57 (m, 10H), 3.71* (dd, $J$=2.2, 2.2 Hz, 1H), 3.81 (s, 3H), 4.17 (d, $J$=5.8 Hz, 2H), 6.33 (m, 1H), 7.01 (d, $J$=8.4 Hz, 1H), 7.17 (m, 1H), 7.25–7.34 (m, 6H).

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see: Nogawa, T.; Kamano, Y.; Yamashita, A.; Pettit, G. R. *J. Nat. Prod.* **2001**, *64*, 1148–1152.

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