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Synthesis of 1-Aza-cryptophycin 1, an Unstable Cryptophycin. An Unusual Skeletal Rearrangement

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Abstract—A total synthesis of cryptophycin 337 (1-aza-cryptophycin 1, **2**), an analogue of the potent antitumor antibiotic cryptophycin 1 (**1**), is described. Cryptophycin 337 was unstable and underwent an unexpected skeletal rearrangement. (*R*)-Mandelic acid was used as the sole source of asymmetry for the synthesis of unit A.

The cryptophycins are highly potent, tumor-selective cytotoxins which have been isolated from the terrestrial blue-green algae *Nostoc* sp. GSV 224[1] and sp. ATCC 53789.[2] Arenastatin A, (cryptophycin 24) which is a structurally related cytotoxin, has been isolated from an Okinawan sponge.[3] Following the first synthesis of cryptophycin 1,[4] Sih[5] and Leahy[6] independently disclosed total syntheses, while Kitagawa has described a synthesis of arenastatin A.[7] Other synthetic work directed toward the cryptophycin skeleton has appeared since then.[8] The importance of this class of compounds as potential chemotherapeutic agents against refractory cancers has provided the impetus for this synthetic work, and has also motivated the present research. As a part of our systematic structure–activity exploration we required the preparation of the cryptophycin analogue (**2**) in which the unit A to unit D ester link had been substituted by an amide link. Our early work had provided strong evidence that the 'northwestern' region of the molecule played an important role in determining the potency of the cytotoxicity. For example, the cytotoxicities (IC_{50}'s, KB cell line) of cryptophycin 1 and cryptophycin 3 were 0.0092 and 3.13 nM, respectively.[9] Therefore structural modifications in this region have demanded our attention. In this paper the preparation of cryptophycin 337 (**2**) and its remarkable reactivity are described (Fig. 1).

One of the difficulties which has bedeviled each of the published cryptophycin syntheses to date is the control of the epoxide stereochemistry in unit A. The lability of this functional group suggested that the styrene oxide be introduced at the end of the total synthesis, however, the obvious approach of epoxidising the styrene double bond suffers from rather low stereoselectivity, the ratio of β:α epoxides being approximately 2:1 at best. Furthermore, the chromatographic mobilities of the two epoxide diastereomers are similar enough that the separation is not trivial. This problem has now been solved by addressing the issue of C7–C8 stereochemistry during the preparation of unit A.

Commercially available and cheap (*R*)-mandelic acid **3** (Scheme 1) was an attractive starting material. Leahy had also used **3** as the starting point for his synthesis of unit A,[6] however, whereas Leahy combined the Evans chiral auxiliary[10] with a protected mandelaldehyde derivative to control absolute stereochemistry, our goal was to use **3** as the sole source of asymmetry for the synthesis of unit A. Mandelic acid was first converted to methyl mandelate **4** in quantitative yield, which was transformed to the Weinreb amide **5**,[11] and silylated (TBS=*tert*-butyldimethylsilyl) to produce **6**. Exposure of **6** to freshly prepared ethylmagnesium bromide in THF led to ethyl ketone **7** in high yield following distillation. Removal of the TBS group from **7** and subsequent Mosher analysis indicated that the material was >95% enantiomerically pure. If the amide displacement was attempted on the free alcohol, or if the trimethylsilyl ether was used in place of TBS, the yield of ketone suffered. Furthermore, if the TMS protecting group was used, desilylation took place to a significant extent, and a mixture of protected and unprotected ketones was obtained.

Aldehyde **8** was prepared in two steps from ethyl vinyl ether according to the published procedures.[12] Aldol condensation between the enolate derived from reaction of ketone **7** with LDA and aldehyde **8** proceeded in good yield to give a ca. 10:1 ratio of *syn* and *anti* diastereoisomers. Lewis acid catalyzed enolization with di-*n*-butylboryl triflate and Hünig's base produced the *syn* isomer as the exclusive product.[13] Hydrolytic removal of the diethyl acetal group took place uneventfully in 87% yield. Selective homologation of the aldehyde in the presence of the ketone was

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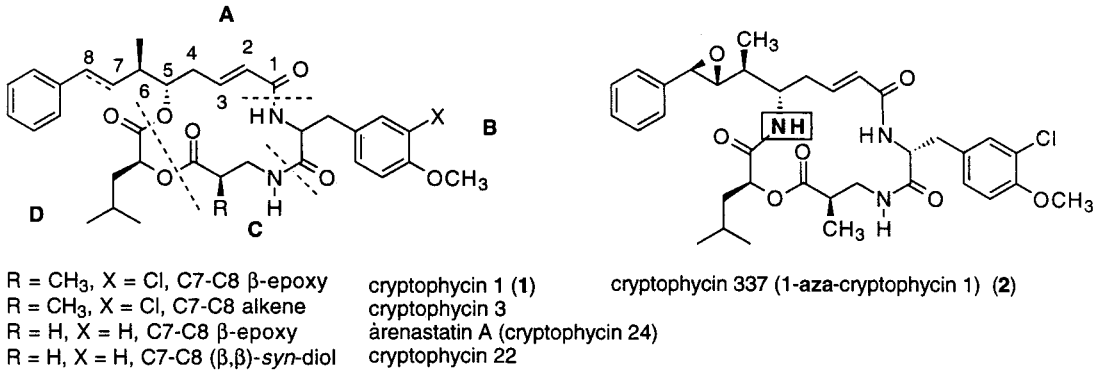
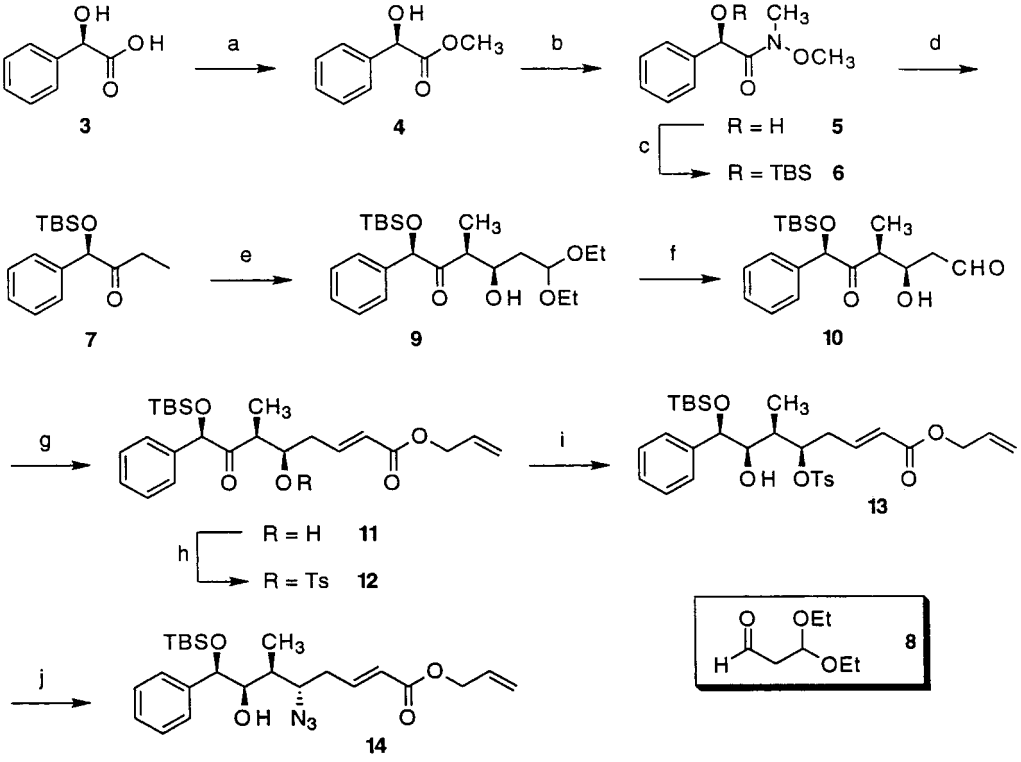


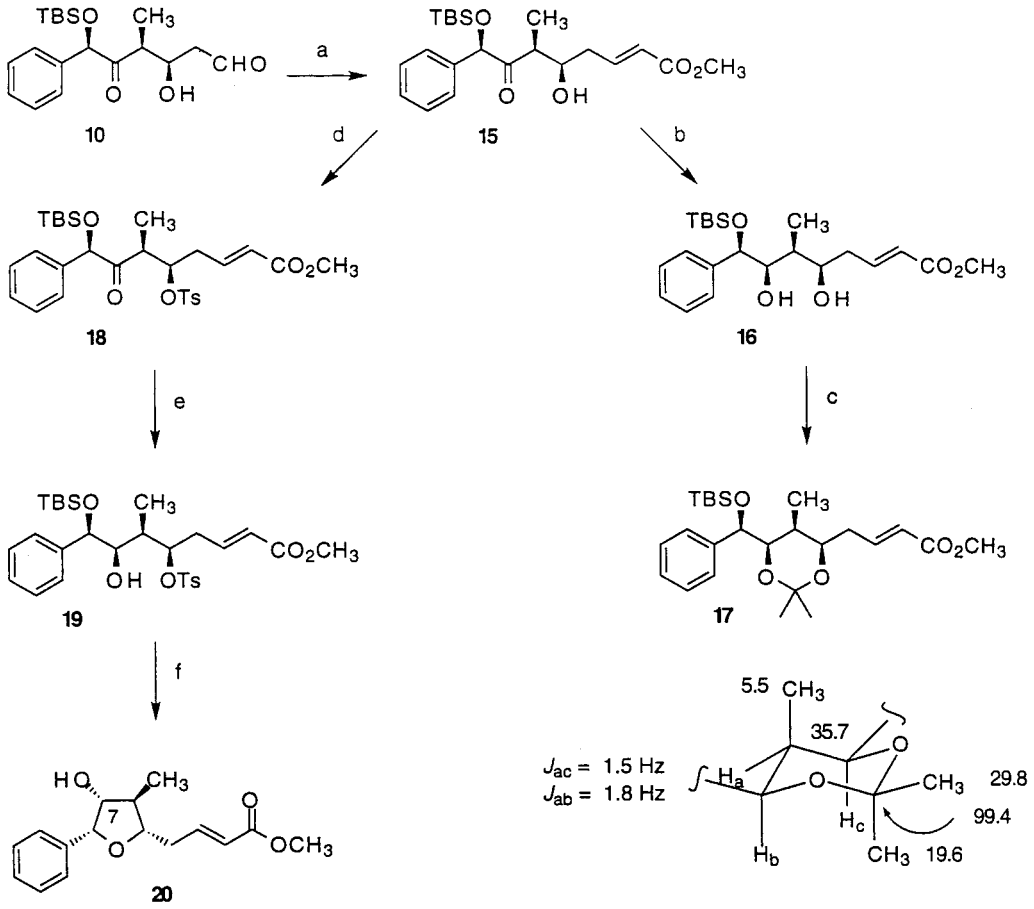
Figure 1.

accomplished with allyldiethylphosphonoacetate under Masamune–Roush conditions.[14] Tosylation of the free hydroxyl group in **11** gave keto tosylate **12** in 86% yield. Luche reduction[15] of the ketone took place with high stereoselectivity (20:1) to furnish alcohol **13** in 96% yield. Reduction of the carbonyl group with lithium borohydride also produced a mixture of diastereoisomers, but in a ratio of approximately 6:1, whereas sodium triacetoxyborohydride and tetramethylammonium triacetoxyborohydride gave very low stereoselectivity. Displacement of the tosyloxy group in **13** with tetramethylguanidinium azide[16] furnished the key intermediate **14** in 69% yield.

It was important to determine the stereochemistry at C5, C6 and C7 in an unambiguous way. The stereochemical relationships were established using the methyl ester **15**, obtained by exposure of **10** to trimethylphosphonoacetate (Scheme 2). The secondary alcohol group in **15** was subjected to the advanced Mosher method.[17] The results of these experiments are summarized in Fig. 2, and clearly demonstrate that the stereochemistry at C5 must be *R*. Subsequent reduction of the keto group in **15** produced the diol **16** which was converted to acetonide **17**, in preparation for ^{13}C NMR analysis (see Scheme 2) according to Rychnovsky's method.[18] The chemical shifts of the geminal methyl carbon atoms were 29.8 and 19.6 ppm whereas the quaternary acetal carbon atom appeared at 99.4 ppm, which is consistent with the 1,3-*syn* acetonide existing in a chair conformation. The nOe enhancements which are observed between H_b and H_c lend further support for the 1,3-*syn*



Scheme 1. (a) CH_2N_2, Et_2O, 10 min, 0°C, 100%; (b) $HNCH_3(OCH_3)\cdot HCl$, Me_3Al, PhH, 0° to 5°C, 2 h; add **4**; 12 h, rt, 93%; (c) TBSOTf, Et_3N, CH_2Cl_2, 3 h, 0°C, 93%; (d) EtMgBr, THF, 5 h, 94%; (e) Bu_2BOTf, iPr_2NEt, CH_2Cl_2, −78°C; 15 min; 0°C, 2 h; add **8**, −78°C, 1 h; 0°C, 2 h; MeOH, H_2O_2, 0°C, 2 h, 65%; (f) Cl_3CCO_2H, CH_2Cl_2/H_2O (20:1), rt, 1 h, 87%; (g) allyldiethylphosphonoacetate, LiCl, iPr_2NEt, CH_3CN, rt, ca. 4 h, 63%; (h) TsCl, KOH (s), THF, 0°C to rt, 86%; (i) $NaBH_4$, $CeCl_3\cdot 7H_2O$, EtOH, 0°, 96%; (j) tetramethylguanidiniumazide, CH_3NO_2, 70–80°C, 5 h, 69%.



Scheme 2. (a) $(H_3CO)_2P(O)CH_2CO_2CH_3$, LiCl, iPr$_2$NEt, CH_3CN, rt, 3 h, 77%; (b) $LiBH_4$, THF, −78 to −30°C, 70%; (c) $(H_3CO)_2C(CH_3)_2$, PPTS, CH_2Cl_2, rt, 1 h. 95%; (d) TsCl, KOH (s), THF, 0°C to rt, 83%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 0°C, 2.5 h, 96%; (f) CsOAc, DMF, rt; aq HF, CH_3CN, 86%.

relationship of the diol. From the known stereochemistry at C5 it then follows that the stereochemistry at C7 is *R*. The small coupling constants between H_a and H_c (J_{ac}=1.5 Hz) and between H_a and H_b (J_{ab}=1.8 Hz) indicate that the C6 methyl group is axial in the acetonide ring, that the stereochemistry at C6 is *S*, and that the aldol reaction of **7** produced **9** with *syn* stereochemistry.

In order to show that the stereochemical outcome of the reduction is the same whether C5 is substituted by a hydroxyl or by a tosyloxy group, hydroxyketone **15** was converted to tosylate **18** and reduced to hydroxytosylate **19** (Scheme 2). This material was not stable, and upon standing at room temperature silyl group migration from the benzylic (C8) position to the homobenzylic position took place, followed by intramolecular displacement of the tosyloxy group to form the tetrahydrofuran derivative (**20**). The same transformation could also be accomplished very easily by exposure of **19** to cesium acetate in DMF at room temperature. Brief treatment of the product with aq HF

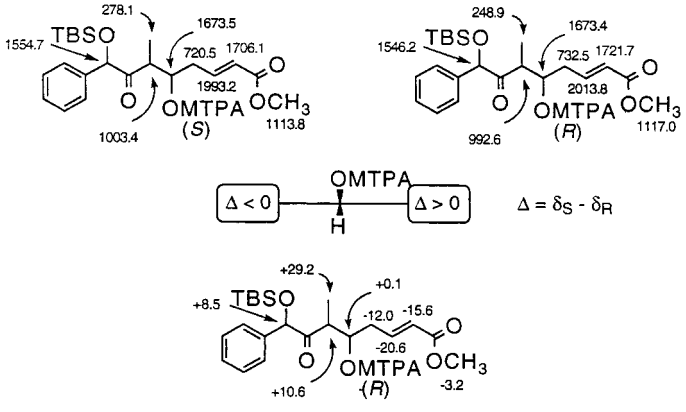
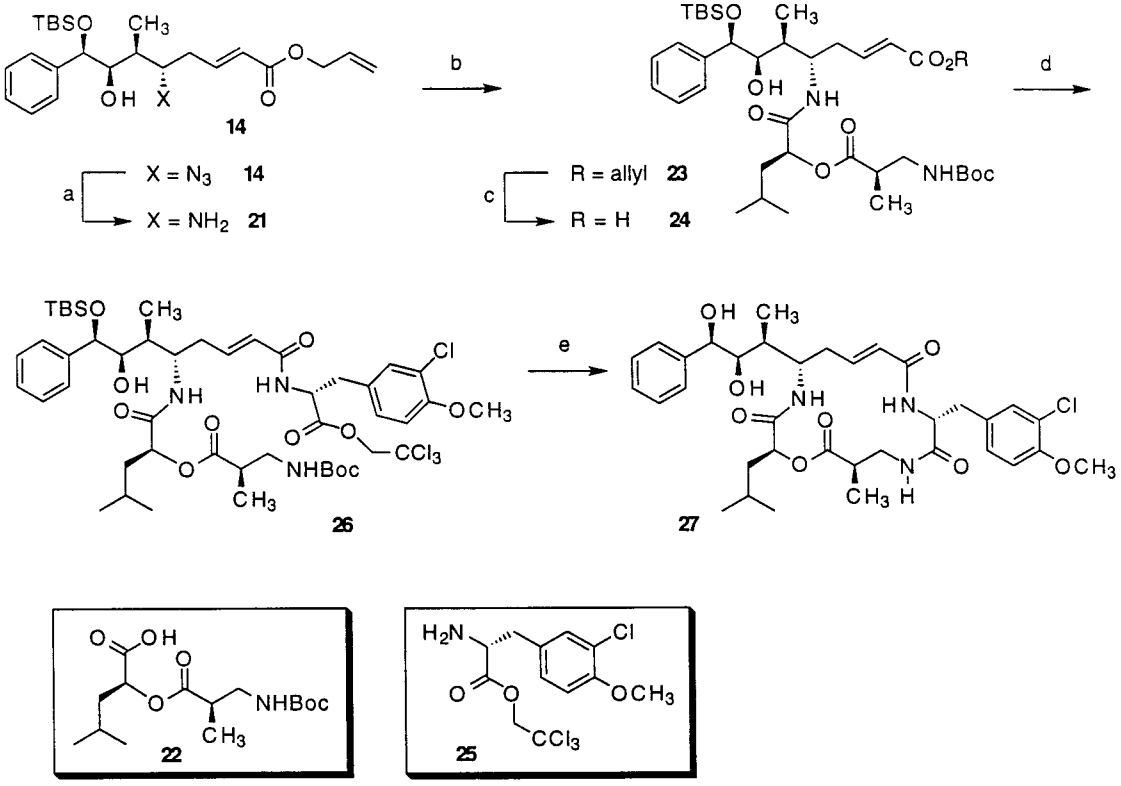


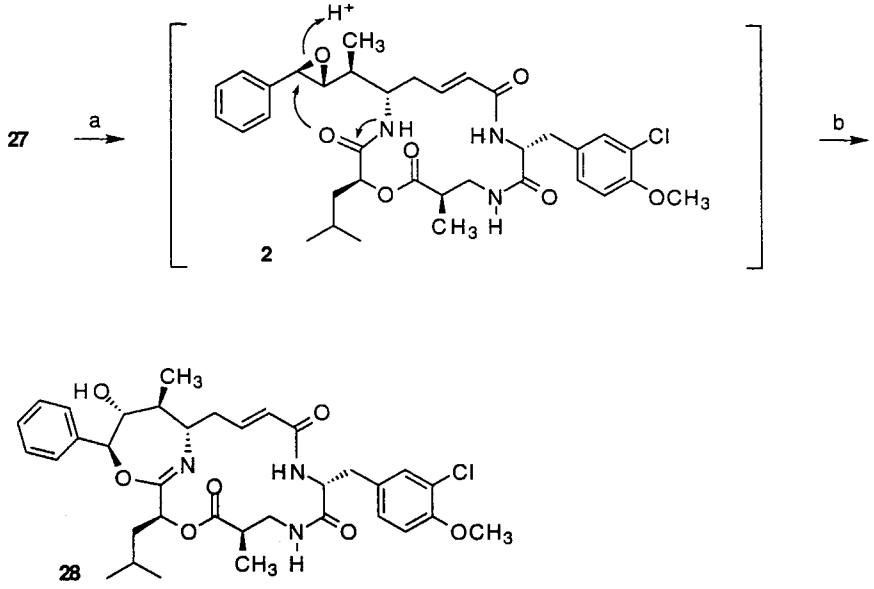
Figure 2. Absolute stereochemical determination of **15** by the advanced Mosher method.[17] The absolute stereochemistry of the secondary alcohol was shown to be *R*. Chemical shifts are shown in Hertz downfield from TMS, 0.00 Hz.



Scheme 3. (a) PPh_3, THF, H_2O, 50–60°C, 12 h; (b) **22**, DMF, FDPP, $i Pr_2NEt$, rt, 5 min; add **21**, 4 h, rt; 74% for two steps from **14**; (c) $Pd(PPh_3)_4$, THF, morpholine, rt, 4 h, 91%; (d) FDPP, DMF; add **25**, Et_3N, rt, 5 h, 69%; (e) TFA, 0°C to rt, 1 h; evaporate to dryness; 2-hydroxypyridine, PhMe, rt, 20 h, 50%.

in DMF gave a high yield of **20**. Mosher analysis showed that the stereochemistry at C7 in **20** was also *R*, and therefore reduction of hydroxyketone **15** or tosyloxy ketone **18** gives the *syn*-1,3 stereochemistry.

Having secured the critical stereochemistry in unit A, attention was focussed on the assembly of unit A through D, and the closure of the macrocycle. The azido group in **14** was reduced to the corresponding amine by treatment with triphenylphosphine (Scheme 3) to afford **21** which was then coupled with **22**, the protected C-D unit, in 74% overall yield from **14**. Removal of the allyl group of **23** took place with palladium(0) catalysis. As the intention was to close the macrocycle by allowing the primary amine group of unit C to attack an activated ester group of unit B, **24** was coupled with *O*-methylchlorotyrosine derivative **25**,[4]



Scheme 4. (a) (i) PPTS, $(MeO)_3CH$, CH_2Cl_2, rt, 2 h; (ii) MeCOBr, CH_2Cl_2, 6 h, rt; (iii) aq $NaHCO_3$; DME, EtOH, MeOH, $KHCO_3$, 40°C, 15 h; (b) column chromatography on SiO_2; 62% from **27**.

leading to seco compound **26**. Macrocyclization of **26** was accomplished in 50% yield in a single operation, without isolating any intermediates. Exposure of **26** to TFA at 0°C, followed by warming to room temperature and evaporation to dryness, served to cleave the Boc group and produced the trifluoroacetate salt of the primary amine group of unit C. Simply exposing this amine salt to 2-hydroxypyridine for 20 h at room temperature in toluene solution led to the 1-*aza*-cryptophycin 22 analogue, cryptophycin 226 (**27**).[8e] The trichloroethyl group in unit B served to both mask the carboxy group of **25** during the coupling step which led to **26**, and also provided the carbonyl activation for the ring closure step. This concludes a description of a brief synthesis of cryptophycin 226 (**27**) (1-aza-cryptophycin 22).

All the cryptophycin SAR work indicated that compounds with the C7–C8 epoxide were the most potent cytotoxins. Consequently, our goal had been to convert the *syn*-diol group in **27** to the epoxide. This was accomplished through the intermediacy of the cyclic orthoester, which was prepared from **27** and trimethyl orthoformate. Exposure of the orthoformate to acetyl bromide in dichloromethane led to an intermediate formyloxy bromide which was immediately exposed to potassium bicarbonate.[19] The crude product was a mixture of two compounds, one of which appeared to be the desired epoxide **2** (cryptophycin 337), and another, which turned out to be **28** (cryptophycin 338; Scheme 4). The characteristic epoxide signals could be clearly seen at 3.0 (H-7) and 3.7 (H-8) ppm in the ^{1}H NMR spectrum of the mixture. Approximately equal amounts of **2** and **28** were present in the crude product mixture. The conversion of **2** to **28** took place spontaneously, even at −5°C in the freezer. The isomerization reaction also took place during our attempts to separate the product mixture by chromatography. Flash column chromatography on basic alumina, HPLC on cyanopropyl, or reverse phase HPLC on C18 stationary phases failed to produce pure **2**, leading instead to mixtures which were enriched in **28**. Chromatography on silica gel led to **28** as the exclusive product. We were unable to secure a pure sample of **2**, since it rearranged spontaneously and all of the conditions for the chromatography evidently catalyzed its conversion to **28**. As a result, cryptophycin 337 was not considered any further as a candidate for in vivo SAR studies.

The structural assignment of **28** was made on the basis of COSY, HMQC and HMBC experiments. Further evidence to support the structural assignment came from an isotope exchange experiment. The following isotope-induced chemical shifts were observed when the ^{13}C NMR spectra were recorded in CD_3OD, or a 1:1 mixture of CD_3OD/CD_3OH: unit A, C1 ($\Delta\delta$ 0.100), C7 ($\Delta\delta$ 0.110); unit B, C1 ($\Delta\delta$ 0.066), C2 ($\Delta\delta$ 0.100); unit C, C3 ($\Delta\delta$ 0.122). These data indicate that in **28** C7 in unit A is substituted by a hydroxyl group, whereas the oxygen atom at C8 is not present as a free hydroxyl. It also indicates that the nitrogen atom at C5 of unit A lacks a hydrogen substituent. All other spectroscopic evidence supports the structural assignment as **28**.

The mechanism for the conversion of **2** to **28** is indicated in Scheme 4. Proton transfer to the epoxide group in **2** provides the activation which is necessary for nucleophilic attack by the amide carbonyl oxygen atom of unit D at the benzylic carbon atom. Loss of a proton from the amide nitrogen completes the process, leading to the seven-membered ring imino ether group of **28**. The mechanism which has been proposed is supported by the stereospecificity of the formation of **28**. Alternative mechanisms involving a discreet benzylic carbocation would have been expected to lead to diastereomeric products, and perhaps also to products resulting from carbocation rearrangement. For example, treatment of cryptophycin 1 with ferric chloride leads to the C7 ketone, presumably through the intermediacy of a benzylic carbocation. No such ketone was detected in the rearrangement of **2** to **28**. An alternative reaction pathway leading to a six-membered ring iminoester can also be imagined, however, no evidence for this product was detected. If the six-membered ring iminoester was present, it was below the detection limit of ^{1}H NMR. The striking difference in reactivity that substitution of oxygen by nitrogen in unit D of the cryptophycins engenders may reflect a lowering of the kinetic barrier for nucleophilic attack at C8, this being a consequence of higher electron density on the amide carbonyl oxygen atom as compared to the ester. Release of strain upon cleavage of the epoxide ring provides the thermodynamic driving force for the rearrangement.

In conclusion, a synthesis of cryptophycin 226 has led to the discovery of an unanticipated reaction pathway in this series. The exceptional reactivity of the styrene oxide function in **2** precludes the consideration of this compound as a candidate for clinical development, while underscoring the critical role which the epoxide plays in cryptophycin SAR. The aldol method for the control of stereochemistry in unit A, has been demonstrated successfully. This method has provided a practical solution to a problem which was not addressed in a satisfactory way in our original synthesis,[4] and has general utility for cryptophycin synthesis.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz ^{1}H (75 MHz ^{13}C) or 500 MHz ^{1}H (125 MHz ^{13}C) in deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference. Chemical shifts are given in δ; multiplicities are indicated as br (broadened), s (singlet), t (triplet), q (quartet), sext (sextet), sept (septet), m (multiplet); coupling constants (*J*) are reported in hertz (Hz). Infrared spectra were recorded on a Perkin–Elmer IR 1430 spectrometer. Electron impact (EI) and FAB mass spectra were performed on a VG-70SE mass spectrometer. Mass spectral data are reported in the form of *m*/*z*. Thin layer chromatography (TLC) was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash column chromatography was performed on Brinkmann silica gel (0.040–0.063 mm). Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone ketyl, dichloromethane (CH_2Cl_2) from phosphorus pentoxide and hexane from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions were performed under a static argon atmosphere in flame-dried glassware. Organic phases were dried with $MgSO_4$ during

workup, unless otherwise specified. The purity and homogeneity of the products on which the high resolution mass spectral data are reported were determined on the basis of 300 MHz ^{1}H NMR and multiple elution TLC analysis or HPLC analysis.

(*R*)-(−)-Methyl (2-hydroxy-2-phenyl) acetate. [(R)-(−)-Methyl mandelate] 4. Diazomethane generated by an adaptation of the method described in Fieser and Fieser[20] was used to methylate a solution of 8.0 g (53 mmol) (*R*)-(−)-mandelic acid in 50 mL ether. After TLC indicated the complete consumption of starting material, the solvent was evaporated to produce methyl mandelate as a fluffy colorless solid, 8.7 g (100% yield): mp 56–57°C [lit. 55.5°C[21]]; $[\alpha]_D$=−140.7° (*c*=1.4, $CHCl_3$), $[\alpha]_D$=−143.9° (*c*=2.7, CH_3OH). IR (neat) 3390, 2954, 1740, 1434, 1211, 1067, 982, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.5 (Ph_5, m), 5.20 (2-H, d, 5.8), 3.78 (OCH_3, s), 3.48 (2-OH, d, 5.8).

(*R*)-(−)-*N*-Methyl-*N*-methoxyl(2-hydroxy-2-phenyl) acetamide 5. *N*-methyl-*O*-methyl hydroxylamine hydrochloride (4.6 g, 47.4 mmol) was placed in a dry flask equipped with a stir bar and attached to a mercury bubbler. Anhydrous benzene (50 mL) was added and the suspension cooled to ca. 0°C. Trimethylaluminum (2 M solution in hexanes, 23.7 mL, 47.4 mmol) was then added slowly [rapid generation of methane occurs] between 0–5°C. The mixture was allowed to warm to rt and was stirred for 2 h. The aluminum amide thus prepared (ca. 0.7 M) was used immediately in the next step.

A solution of 4.0 g (24 mmol) methyl mandelate in 30 mL dry benzene was added with stirring to the aluminum amide solution at rt over 20 min. The solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by the addition of dilute HCl (5% aq, 50 mL). The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried and concentrated to produce 4.35 g of **5** as a colorless waxy solid (93% yield). This material was essentially pure and was used as obtained after workup in the next reaction. $[\alpha]_D$=−86.7° (*c*=5.6, $CHCl_3$); IR (neat) 3431, 2938, 1650, 1454, 1372, 1190, 1059, 989, 702 cm^{-1}; EIMS (70 eV) *m/z* 195 (M^+, 1), 107 (37), 106 (37), 105 (100), 79 (23), 77 (80); HREIMS *m/z* 195.0922 (M^+, $C_{10}H_{13}NO_3$, Δ −2.7 mmu); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.5 (Ph_5, m), 5.37 (2-H, bs), 4.30 (2-OH, bs), 3.23 (NCH_3 and OCH_3, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (2), 139.7 (1″), 128.5 (3″/5″), 128.1 (4″), 127.4 (2″/6″), 71.5 (1), 60.6 (OCH_3), 32.7 (NCH_3).

(*R*)-(−)-*N*-Methyl-*N*-methoxyl(2-*tert*-butyldimethylsilyloxy-2-phenyl) acetamide 6. To a solution of amide **5** (4.0 g, 20.5 mmol) at 0°C in 60 mL dry CH_2Cl_2, was added triethylamine (5.4 mL, 4.1 g, 40.6 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf, 6.9 mL, 7.9 g, 30.0 mmol). The sample was stirred at 0°C for 3 h, diluted with 100 mL Et_2O and washed with 100 mL sat. aq. NH_4Cl. The organic layer was collected, washed with water and brine, then dried and concentrated to produce a pale yellow oil. Short path distillation produced 5.9 g of **6** as a colorless mobile oil (93% yield): bp 111–114°C @ 0.4 mmHg; $[\alpha]_D$=−9.4° (*c*=6.8, $CHCl_3$); IR (neat) 2955, 2930, 2856, 1660, 1462, 1384, 1254, 1070, 994, 873, 778 cm^{-1}; EIMS (70 eV) *m/z* 309 (M^+, <1), 294 (M^+-CH_3, 5), 252 (75), 221 (87), 192 (15), 163 (21), 149 (31), 106 (10), 105 (20), 89 (42), 77 (19), 75 (41), 73 (100); HREIMS *m/z* 294.1532 (M^+-CH_3, $C_{15}H_{24}NO_3Si$, Δ −0.6 mmu); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (2″/6″-H, d, 7.0), 7.25–7.35 (3″/4″/5″-H, m), 5.59 (2-H, s), 3.49 (OCH_3, bs), 3.13 (NCH_3, s), 0.91 ($SiCMe_3$, s), 0.12 (SiMe, s), 0.04 (SiMe, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (2), 139.5 (1″), 128.2 (3″/5″), 127.7 (4″), 126.7 (2″/6″), 73.7 (1), 60.7 (OCH_3), 33.2 (NCH_3), 25.9 ($SiCMe_3$), 18.4 ($SiCMe_3$), −4.7 (SiMe), −4.9 (SiMe).

(*R*)-(+)-(1-*tert*-Butyldimethylsilyloxy-1-phenyl)butan-2-one 7. To a stirred solution of 5.5 g (18 mmol) of Weinreb amide **6** in 100 mL THF at 0°C was added freshly prepared ethylmagnesium bromide (1.8 M in Et_2O, 30 mL, 54 mmol). After the addition was complete (ca. 30 min, during which time a precipitate may develop) the mixture was stirred at 0°C for 5 h, after which time TLC indicated that the reaction was complete. The mixture was diluted with 200 mL Et_2O and washed with 200 mL 10% w/w aq $KHSO_4$ solution, then brine. The ethereal layer was dried and concentrated to give a pale yellow oil. Short path distillation produced 4.6 g of the desired compound as a mobile colorless oil (94% yield): bp 103–105°C @ 0.8 mmHg; $[\alpha]_D$+28.0° (*c*=17.5, $CHCl_3$); IR (neat) 2955, 2930, 2858, 1720, 1462, 1346, 1254, 1099, 1071, 871, 837, 780 cm^{-1}; EIMS (70 eV) *m/z* 263 (M^+-CH_3, 3), 221 (71), 192 (4), 163 (5), 149 (6), 115 (5), 91 (6), 75 (19), 73 (100); HREIMS *m/z* 263.1457 (M^+-CH_3, $C_{15}H_{23}O_2Si$, Δ 1.0 mmu); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (2″/6″-H, d, 7.3), 7.27–7.35 (3″/4″/5″-H, m), 5.08 (1-H, s), 2.62 (3-H_b, dq, 18.6, 7.3), 2.46 (3-H_a, dq, 18.6, 7.3), 0.95 ($SiCMe_3$, s), 0.94 (4-H_3, t, 7.3), 0.08 (SiMe, s), −0.02 (SiMe, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7 (2), 139.0 (1″), 128.3 (3″/5″), 127.8 (4″), 125.9 (2″/6″), 81.1 (1), 29.3 (3), 25.8 ($SiCMe_3$), 18.2 ($SiCMe_3$), 7.5 (4), −4.9 (SiMe), −5.1 (SiMe).

(3*R*, 4*S*, 6*R*)-1,1-Diethoxy-3-hydroxy-4-methyl-5-oxo-6-[(*tert*-butyl-dimethylsilyl)oxy]-6-phenylhexane 9. To a stirred solution of ketone **7** (1.87 g, 6.7 mmol) in 35 mL anhydrous CH_2Cl_2 was added diisopropylethylamine (1.04 g, 1.4 mL, 8.1 mmol) followed by dibutylboron triflate[22] (7.4 mL of a 1 M solution in CH_2Cl_2) at −78°C. The mixture was stirred at −78°C for 15 min then warmed to 0°C and stirred for 2 h. The clear orange solution was cooled to −78°C and 1,1-diethoxy-3-propanal **8** (1.50 g, 10.1 mmol) was added dropwise in 5 mL of anhydrous CH_2Cl_2. The mixture was stirred at −78°C for 1 h then allowed to warm to 0°C and stirred for an additional 2 h at this temperature. The mixture was cooled to −78°C, 20 mL of sat. aq. NH_4Cl was added, and the mixture stirred vigorously while warming to rt. The reaction mixture was diluted with 50 mL CH_2Cl_2, the organic layer was separated, then mixed with MeOH/H_2O_2 (3:1, 20 mL) at 0°C. This mixture was allowed to warm to rt and vigorously stirred for 2 h before the organic layer was separated, washed with 40 mL sat. aq. $NaHCO_3$ followed by brine. The organic layer was collected, dried and concentrated to give a pale yellow oil that consisted of the desired product and excess aldehyde **8**. Removal of the excess aldehyde at high vacuum

provided a product that could be used in the following reaction. The crude product was purified by column chromatography (silica, 15% EtOAc/hexane) to provide 1.85 g of **9** as a colorless mobile oil, (65% yield): $[\alpha]_D=-8.6°$ (c=1.2, $CHCl_3$); IR (neat) 3507, 2966, 2919, 2872, 1713, 1448, 1255, 1120, 1061, 861, 832, 773 cm^{-1}; EIMS (70 eV) *m/z* 379 (M^+-OEt, <1), 361 ($M^+-OEt-H_2O$, 1), 321 ($M^+-OEt-{}^tBu-H$, 1), 263 (3), 249 (3), 222 (18), 221 (100), 103 (12), 75 (49), 73 (90), HREIMS *m/z* 379.2247 (M^+-OEt, $C_{21}H_{35}O_4Si$, Δ 5.8 mmu), 361.2200 ($M^+-OEt-H_2O$, $C_{21}H_{33}O_3Si$, Δ −0.1 mmu), 321.1495 ($M^+-OEt-{}^tBuH$, $C_{17}H_{25}O_4Si$, Δ 2.7 mmu); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (8/12-H, bd, 7.4), 7.33 (9/11-H, bdd, 7.4, 2.2), 7.28 (10-H, bt, 7.2), 5.12 (6-H, s), 4.60 (1-H, dd, 5.8, 5.3), 3.95 (3-H, ddd, 9.9, 5.2, 2.5), 3.67 (1″-H_b, dq, 9.4, 7.2), 3.58 (1″-H_b, dq, 9.4, 7.2), 3.47 (1″-H_a, dq, 9.4, 7.2), 3.46 (1″-H_a, dq, 9.4, 7.2), 3.32 (3-OH, s, $W_{1/2}$=10), 3.07 (4-H, dq, 5.2, 6.9), 1.62 (2-H_b, ddd, 14.1, 9.9, 5.3), 1.51 (2-H_a, ddd, 14.1, 5.8, 2.5), 1.19 (2″-H_3, t, 7.2), 1.16 (2″-H_3, t, 7.2), 0.93 (4-Me, d, 6.9), 0.93 ($SiCMe_3$), 0.09 (SiMe, s), −0.04 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7 (5), 138.4 (7), 128.5 (9/11), 128.2 (10), 126.4 (8/12), 101.8 (1), 80.7 (6), 68.4 (3), 62.3 (1″), 61.6 (1″), 45.1 (4), 38.3 (2), 25.8 ($SiCMe_3$), 18.2 ($SiCMe_3$), 15.3 (2″), 15.2 (2″), 12.4 (4-Me), −4.9 (SiMe), −5.0 (SiMe).

(3*R*, 4*S*, 6*R*)-3-Hydroxy-4-methyl-5-oxo-6-[(*tert*-butyldimethylsilyl)oxy]-6-phenylhexanal 10. Trichloroacetic acid (300 mg) was added to a solution of 500 mg of acetal **9** (1.18 mmol) in a mixture of 20 mL CH_2Cl_2 and 1 mL water. The solution was stirred vigorously at rt for 1 h, then diluted with 20 mL water, the phases separated, and the organic layer washed with 20 mL sat. aq $NaHCO_3$ and brine. The organic layer was dried and the solvent evaporated to produce 363 mg of **10** as a colorless oil (87% yield following chromatographic purification on silica, 25% EtOAc/hexane): $[\alpha]_D=-12.2°$ (c=1.0, $CHCl_3$); IR (neat) 3492, 2955, 2930, 2858, 1722, 1712, 1453, 1256, 1118, 1068, 867, 837, 779 cm^{-1}; EIMS (70 eV) *m/z* 349 (M^+-H, <1), 314 (M^+-2H_2O, 1), 293 ($M^+-{}^tBu$, 3), 275 ($M^+-{}^tBu-H_2O$, 2), 249 (6), 222 (19), 221 (100), 163 (6), 105 (13), 75 (63), 73 (90); HREIMS *m/z* 314.1702 (M^+-2H_2O, $C_{19}H_{26}O_2Si$, Δ 0.0 mmu), 293.1191 ($M^+-{}^tBu$, $C_{15}H_{21}O_4Si$, Δ 1.8 mmu), 275.1135 ($M^+-{}^tBu-H_2O$, $C_{15}H_{19}O_3Si$, Δ −3.2 mmu); ^1H NMR (500 MHz, $CDCl_3$) δ 9.70 (1-H, dd, 1.9, 1.6), 7.40 (8/12-H, bd, 7.3), 7.35 (9/11-H, bdd, 7.3, 6.9), 7.30 (10-H, bt, 6.9), 5.14 (6-H, s), 4.32 (3-H, ddd, 8.8, 4.4, 3.8), 3.14 (4-H, dq, 4.4, 7.1), 3.07 (3-OH, s, $W_{1/2}$=10), 2.48 (2-H_b, ddd, 17.0, 8.8, 1.9), 2.35 (2-H_a, ddd, 17.0, 3.8, 1.6), 0.94 (4-Me, d, 7.1), 0.93 ($SiCMe_3$, s), 0.10 (SiMe, s), −0.02 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6 (5), 201.4 (1), 138.1 (7), 128.5 (9/11), 128.4 (10), 126.3 (8/12), 80.6 (6), 67.0 (3), 47.6 (2), 44.2 (4), 25.7 ($SiCMe_3$), 18.2 ($SiCMe_3$), 12.0 (4-Me), −4.9 (SiMe), −5.0 (SiMe).

Allyl (5*R*, 6*S*, 8*R*)-5-hydroxy-6-methyl-7-oxo-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyl-oct-2(*E*)-enoate 11. To a flame dried flask at rt was added 190 mg LiCl (4.5 mmol) and 20 mL acetonitrile. To this suspension was added allyl diethylphosphonoacetate (1.05 g, 4.4 mmol) followed by diisopropylethylamine (500 mg, 675 μL, 3.9 mmol). After 5 min 1.28 g (3.7 mmol) of aldehyde **10** in 5 mL acetonitrile was added, and the colorless suspension became orange. The mixture was stirred at rt for ca. 4 h until TLC (silica, 15% EtOAc/hexane) indicated consumption of starting material, then 80 mL water was added and the suspension stirred for 10 min. The mixture was diluted with 100 mL Et_2O, the phases separated and the organic layer washed with water, brine, dried, and the solvent evaporated to give a pale yellow oil. Chromatographic purification (silica, 15% EtOAc/hexane) produced 1.15 g of **11** as a colorless oil (63% yield): $[\alpha]_D=-11.3°$ (c=4.6, $CHCl_3$); IR (neat) 3518, 2931, 2858, 1722, 1715, 1657, 1453, 1257, 863, 837, 780 cm^{-1}; EIMS (70 eV) *m/z* 375 ($M^+-OCH_2CH{=}CH_2$, <1), 357 ($M^+-{}^tBu-H_2O$, <1), 309 (7), 263 (7), 222 (48), 221 (100), 163 (14), 149 (24), 105 (19), 91 (26), 75 (99), 73 (99); HREIMS *m/z* 375.2021 ($M^+-OCH_2CH{=}CH_2$, $C_{21}H_{31}O_4Si$, Δ −3.0 mmu), 357.1551 ($M^+-{}^tBu-H_2O$, $C_{20}H_{25}O_4Si$, Δ −2.9 mmu); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (10/14-H, bd, 7.2), 7.35 (11/13-H, dd, 7.2, 6.9), 7.29 (12-H, m), 6.89 (3-H, ddd, 15.6, 8.1, 7.4), 5.94 (2″-H, ddt, 17.1, 10.4, 5.7), 5.88 (2-H, d, 15.6), 5.33 (3″-H_t, ddt, 17.1, 1.2, 1.2), 5.24 (3″-H_c, ddt, 10.4, 1.2, 1.2), 5.11 (8-H, s), 4.63 (1″-H_2, d, 5.7), 3.90 (5-H, m), 3.13 (6-H, dq, 3.0, 7.2), 2.91 (5-OH, s), 2.34 (4-H_b, dddd, 14.6, 8.1, 6.7, 1.5), 2.12 (4-H_a, dddd, 14.6, 7.4, 6.2, 1.1), 0.92 ($SiCMe_3$, s), 0.90 (6-Me, d, 7.2), 0.07 (SiMe, s), −0.03 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6 (7), 165.7 (1), 145.2 (3), 138.1 (9), 132.3 (2″), 128.6 (11/13), 128.3 (12), 126.2 (10/14), 123.4 (2), 118.2 (3″), 80.6 (8), 70.0 (5), 65.0 (1″), 43.3 (6), 36.7 (4), 25.7 ($SiCMe_3$), 18.2 ($SiCMe_3$), 10.7 (6-Me), 4.9 (SiMe), −5.1 (SiMe).

Allyl (5*R*, 6*S*, 8*R*)-5-tosyloxy-6-methyl-7-oxo-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyl-oct-2(*E*)-enoate 12. Ketoalcohol **11** (380 mg, 0.88 mmol) was dissolved in 40 mL reagent grade THF[23] and cooled to 0°C. Tosyl chloride (850 mg, 4.5 mmol) was added followed by the slow addition (five portions over 30 min) of freshly powdered KOH (500 mg, 8.9 mmol). After addition was complete the reaction mixture was warmed to rt and allowed to stir until TLC indicated that no starting material remained. The reaction mixture was then diluted with 100 mL Et_2O and washed with 80 mL sat. aq. $NaHCO_3$, water and brine. The organic layer was dried and the solvent evaporated to give a waxy solid that was purified by flash chromatography (silica, 15% EtOAc/hexane). Tosylate **12** was obtained as a colorless viscous oil (442 mg 86% yield): $[\alpha]_D=-37.8°$ (c=4.0, $CHCl_3$); IR (neat) 2954, 2858, 1724, 1658, 1454, 1365, 1258, 1177, 1097, 908, 839, 781 cm^{-1}; EIMS (70 eV) *m/z* 529 ($M^+-{}^tBu$, 4), 357 (9), 222 (25), 221 (100), 165 (12), 105 (18), 91 (24), 73 (98); HREIMS *m/z* 529.1680 ($M^+-{}^tBu$, $C_{27}H_{33}O_7SSi$, Δ 3.6 mmu); FABMS, nitrobenzylalcohol, *m/z* 609 (M+Na, 4), 587 (M+H, 10), 529 (5), 455 (4), 415 (8), 357 (10), 283 (20), 243 (15), 221 (100); ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (2″/6″-H, d, 8.3), 7.27–7.32 (3″/5″/10/11/12/13/14, m), 6.58 (3-H, ddd, 15.5, 7.5, 7.0), 5.94 (2′-H, ddt, 17.1, 10.6, 5.7), 5.55 (2-H, d, 15.5), 5.33 (3′-H_t, bd, 17.1), 5.26 (3′-H_c, bd, 10.6), 5.10 (8-H, s), 4.93 (5-H, ddd, 8.4, 5.4, 5.4), 4.60 (1′-H_2, d, 5.7), 3.31 (6-H, dq, 8.4, 7.2), 2.42 (4″-CH_3, s), 2.40 (4-Hb, m), 2.28 (4-H_a, bddd, 15.3, 7.5, 5.4), 0.94 (6-Me, d, 7.2), 0.89 ($SiCMe_3$, s), 0.06 (SiMe, s), −0.10 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3 (7), 165.1 (1) 144.9 (4″), 142.0 (3), 138.2 (9), 133.8 (1″), 132.2 (2′), 129.8

(3″/5″), 128.6 (11/13), 128.5 (12), 127.8 (2″/6″), 126.7 (10/14), 124.7 (2), 118.2 (3′), 81.1 (5), 80.5 (8), 65.0 (1′), 44.2 (6), 35.6 (4), 25.7 ($SiCMe_3$), 21.6 (4″-Me), 18.2 ($SiCMe_3$), 14.2 (6-Me), −4.9 (SiMe), −5.1 (SiMe).

Allyl (5*R*, 6*R*, 7*R*, 8*R*)-5-tosyloxy-6-methyl-7-hydroxy-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyl-oct-2(*E*)-enoate 13. Ketotosylate **12** (900 mg, 1.54 mmol) and cerium trichloride heptahydrate (570 mg, 1.54 mmol) were dissolved in 50 mL ethanol and cooled to 0°C. Sodium borohydride (150 mg, 3.94 mmol) was added in seven portions over 90 min between 0–5°C. The mixture was allowed to stir for 30 min, then diluted with 100 mL Et_2O. Excess borohydride was destroyed by washing with 20 mL 0.1N HCl, then the mixture warmed to rt. The phases were separated and the organic layer washed with water, brine, dried and concentrated to give 869 mg of **13** as a viscous colorless oil in 20:1 diastereomeric ratio (96% yield):[24] $[\alpha]_D=-40.6°$ (c=3.7, $CHCl_3$); IR (neat) 3563, 2953, 2857, 1723, 1658, 1462, 1365, 1258, 1176, 1096, 901, 837, 779, 677 cm^{-1}; EIMS (70 eV) m/z 531 ($M^+-{}^t$Bu, 2), 359 (14), 309 (20), 222 (34), 221 (89), 165 (22), 105 (36), 91 (72), 73 (100); HREIMS m/z 531.1879 ($M^+-{}^t$Bu, $C_{27}H_{35}O_7SSi$, Δ −0.6 mmu); ^{1}H nmr (500 MHz, $CDCl_3$) δ 7.67 (2″/6″-H, d, 8.1), 7.23–7.35 (3″/5″/11/12/13-H, m), 7.20 (10/14-H, bd, 6.5), 6.56 (3-H, ddd, 15.6, 8.3, 7.6), 5.92 (2′-H, ddt, 17.0, 10.8, 5.4), 5.67 (2-H, d, 15.6), 5.31 (3′-H_t, bd, 17.0), 5.25 (3′-H_c, bd, 10.8), 4.61 (5-H, m), 4.57 (1′-H_2, d, 5.4), 4.45 (8-H, d, 8.1), 3.68 (7-H, bd, 8.1) 2.75 (7-OH, s), 2.58 (4-H_2, bm, $W_{1/2}$=25), 2.41 (4″-CH_3, s), 1.52 (6-H, bdq, 7.0, 6.7), 0.89 (6-Me, d, 6.7), 0.85 ($SiCMe_3$, s), 0.00 (SiMe, s), −0.28 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (1), 144.6 (4″), 142.6 (3), 140.2 (9), 134.0 (1″), 132.3 (2′), 129.7 (3″/5″), 128.5 (11/13), 128.2 (12), 127.7 (2″/6″), 127.0 (10/14), 124.4 (2), 118.1 (3′), 84.0 (5), 77.4 (8), 74.6 (7), 64.9 (1′), 36.2 (6), 34.2 (4), 25.7 ($SiCMe_3$), 21.6 (4″-Me), 18.1 ($SiCMe_3$), 9.5 (6-Me), −4.5 (SiMe), −5.1 (SiMe).

Allyl (5*S*, 6*S*, 7*R*, 8*R*)-5-azido-6-methyl-7-hydroxy-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-2(*E*)-enoate 14. A solution of hydroxytosylate **13** (870 mg, 1.48 mmol) in 70 mL anhydrous nitromethane was stirred at 70–80°C while 490 mg (3.10 mmol) tetramethylguanidinium azide was added. The mixture was stirred for 5 h, cooled to rt, diluted with 100 mL Et_2O and the suspension was treated with 30 mL 0.5 N HCl. The phases were separated and the organic phase was washed with water, then brine, dried and concentrated to produce a pale yellow oil that was purified by flash chromatography (silica, hexane to 5% EtOAc/hexane) to yield 466 mg of **14** as a colorless mobile oil (69% yield) and 97 mg of the conjugated diene resulting from elimination of the tosylate as a colorless oil (16% yield).

Data for **14**: $[\alpha]_D=-31.1°$ (c=6.3, $CHCl_3$); IR (neat) 3574, 2954, 2857, 2100, 1723, 1658, 1453, 1256, 1169, 1080, 836, 779, 702 cm^{-1}; EIMS (70 eV) m/z 374 ($M^+-{}^t$Bu–N_2, 1), 309 (6), 222 (13), 221 (46), 193 (31), 105 (11), 91 (23), 77 (17), 75 (100), 73 (73); HREIMS m/z 374.1765 ($M^+-{}^t$Bu–N_2, $C_{20}H_{28}NO_4Si$, Δ 2.2 mmu); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.35 (11/12/13-H, m), 7.25 (10/14-H, dd, 6.6, 1.5), 6.85 (3-H, ddd, 15.6, 7.6, 7.1), 5.93 (2′-H, ddt, 17.1, 10.7, 5.6), 5.86 (2-H, d, 15.6), 5.31 (3′-H_t, bd, 17.1), 5.23 (3′-H_c, bd, 10.7), 4.62 (1′-H_2, d, 5.6), 4.48 (8-H, d, 8.6), 3.89 (7-H, dd, 8.6, 1.1), 3.43 (5-H, ddd, 8.6, 8.4, 3.6), 2.87 (7-OH, s), 2.54 (4-H_b, dddd, 15.0, 7.1, 3.6, 1.5), 2.24 (4-H_a, ddd, 15.0, 8.6, 7.6), 1.30 (6-H, m), 0.99 (6-Me, d, 6.9), 0.87 ($SiCMe_3$, s), 0.03 (SiMe, s), −0.24 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (1), 144.7 (3), 140.6 (9), 132.2 (2′), 128.5 (11/13), 128.3 (12), 127.1 (10/14), 123.8 (2), 118.1 (3′), 77.7 (8), 75.7 (7), 65.0 (1′), 64.6 (5), 36.9 (6), 34.5 (4), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), 9.7 (6-Me), −4.5 (SiMe), −5.1 (SiMe).

Data for elimination product: $[\alpha]_D=-22.6°$ (c=2.8, $CHCl_3$); IR (neat) 3565, 2955, 2930, 2857, 1716, 1642, 1454, 1255, 1139, 1003, 836, 778, 701 cm^{-1}; EIMS (70 eV) m/z 359 ($M^+-{}^t$Bu, 6), 309 (4), 235 (6), 222 (19), 221 (55), 193 (10), 165 (20), 105 (13), 91 (38), 79 (17), 75 (100), 73 (78); HREIMS m/z 359.1705, ($M^+-{}^t$Bu, $C_{20}H_{27}O_4Si$, Δ −2.7 mmu); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.33 (10/11/12/13/14-H, m), 7.25 (3-H, dd, 15.5, 9.9), 6.12 (4-H, m), 6.09 (5-H, m), 5.94 (2′-H, ddt, 17.3, 10.4, 5.8), 5.81 (2-H, d, 15.5), 5.33 (3′-H_t, ddt, 17.3, 1.5, 1.3), 5.23 (3′-H_c, ddt, 10.4, 1.3, 1.0), 4.64 (1′-H_2, ddd, 5.8, 1.3, 1.3), 4.54 (8-H, d, 6.1), 3.51 (7-H, dd, 6.1, 5.3), 2.75 (7-OH, bs, $W_{1/2}$=50), 2.23 (6-H, ddq, 6.1, 5.3, 6.9), 1.09 (6-Me, d, 6.9), 0.88 ($SiCMe_3$, s), 0.02 (SiMe, s), −0.26 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7 (1), 147.0 (5), 145.2 (3), 141.5 (9), 132.4 (2′), 128.3 (11/13), 128.0 (12), 127.9 (4), 126.9 (10/14), 119.5 (2), 117.9 (3′), 78.9 (7), 76.4 (8), 64.9 (1′), 38.9 (6), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), 14.3 (6-Me), −4.4 (SiMe), −5.1 (SiMe).

Methyl (5*R*, 6*S*, 8*R*)-5-hydroxy-6-methyl-7-oxo-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyl-oct-2(*E*)-enoate 15. To a flame dried flask at rt was added 17 mg (0.41 mmol) LiCl and 5 mL acetonitrile followed by 75 mg trimethyl phosphonoacetate (67 μL, 0.41 mmol) and 44 mg diisopropylethylamine (60 μL, 0.34 mmol). The reaction mixture was stirred for 5 min and 120 mg of aldehyde **10** (0.34 mmol) in 1 mL of acetonitrile was added, whereupon the colorless suspension became orange. The mixture was stirred at rt until TLC (silica, 20% EtOAc/hexane) indicated consumption of starting material (ca. 3 h), then 20 mL water was added and the suspension stirred for 10 min. The mixture was diluted with 20 mL Et_2O, the phases separated and the organic layer washed with water, brine, dried and the solvent evaporated to give a pale yellow oil. Chromatographic purification (silica, 20% EtOAc/hexane) gave 108 mg of **15** as a colorless oil (77% yield): $[\alpha]_D=-11.7°$ (c=6.1, $CHCl_3$); IR (neat) 3500, 2953, 2930, 2857, 1725, 1715, 1660, 1454, 1257, 1097, 863, 838, 780 cm^{-1}; EIMS (70 eV) m/z 349 ($M^+-{}^t$Bu, 1), 263 (3), 222 (13), 221 (79), 163 (6), 105 (5), 86 (36), 84 (57), 75 (26), 73 (100); HREIMS m/z 349.1469 ($M^+-{}^t$Bu, $C_{18}H_{25}O_5Si$, Δ 0.2 mmu); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (10/14-H, bd, 7.3), 7.34 (11/13-H, bdd, 7.3, 7.0), 7.29 (12-H, tt, 7.0, 1.3), 6.86 (3-H, ddd, 15.6, 7.8, 7.0), 5.85 (2-H, ddd, 15.6, 1.5, 1.5), 5.11 (8-H, s), 3.89 (5-H, ddd, 8.3, 5.5, 3.0), 3.72 (OCH_3, s), 3.13 (6-H, dq, 3.0, 7.3), 2.93 (5-OH, s, $W_{1/2}$=15), 2.33 (4-H_b, dddd, 14.6, 8.3, 7.0, 1.5), 2.18 (4-H_a, dddd, 14.6, 7.8, 5.5, 1.5), 0.92 ($SiCMe_3$, s), 0.90 (6-Me, d, 7.3), 0.07 (SiMe, s), −0.04 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6 (7), 166.5 (1), 145.0 (3), 138.1 (9), 128.6 (11/13), 128.3 (12), 126.2 (10/14), 123.3 (2), 80.7 (8), 70.0 (5),

51.4 (OCH_3), 43.3 (6), 36.7 (4), 25.7 ($SiCMe_3$), 18.2 ($SiCMe_3$), 10.8 (6-Me), −4.9 (SiMe), −5.1 (SiMe).

(*S*)-MTPA ester of 15. To a solution of 5 mg (0.01 mmol) of **15** in 1 mL CH_2Cl_2 was added 40 μL triethylamine, 1 mg DMAP and 10 μL (*R*)-methoxy-trifluoromethyl-phenylacetyl chloride and the mixture was stirred for 1 h. The reaction was diluted with 10 mL Et_2O and washed with 10 mL aq. (10% w/w) $KHSO_4$ and brine. The ethereal layer was dried and evaporated to produce the (*S*)-MTPA ester as a viscous, colorless oil as a single diastereomer: $[\alpha]_D$=−19.0° (*c*=0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.5 (2×Ph_5, m), 6.71 (3-H, ddd, 15.6, 7.8, 7.3), 5.74 (2-H, d, 15.6), 5.58 (5-H, ddd, 6.3, 6.3, 5.6), 5.15 (8-H, s), 3.72 (ester-OCH_3, s), 3.50 (MTPA-OCH_3, s), 3.31 (6-H, dq, 6.3, 7.1), 2.44 (4-H_2, m), 0.92 ($SiCMe_3$, s), 0.83 (6-Me, d, 7.1), 0.09 (SiMe, s), −0.07 (SiMe, s).

(*R*)-MTPA ester of 15. The procedure described above was repeated on the same scale with (*S*)-methoxytrifluoromethyl-phenylacetyl chloride to produce the (*R*)-MTPA ester as a viscous, colorless oil as a single diastereomer: $[\alpha]_D$=17.8° (*c*=1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.5 (2×Ph_5, m), 6.64 (3-H ddd, 15.6, 7.8, 7.3), 5.68 (2-H, d, 15.6), 5.57 (5-H, ddd, 6.1, 5.9, 5.4), 5.12 (8-H, s), 3.71 (ester–OCH_3, s), 3.49 (MTPA–OCH_3, s), 3.34 (6-H, m), 2.40 (4-H_2, m), 0.94 ($SiCMe_3$, s), 0.93 (6-Me, obsc.), 0.10 (SiMe, s), −0.06 (SiMe, s).

Methyl (5*R*, 6*S*, 7*R*, 8*R*)-5,7-dihydroxy-6-methyl-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-2(*E*)-enoate 16. A solution of 30 mg (0.07 mmol) of ketone **15** in 3 mL THF was cooled to −78°C and $LiBH_4$ (15 mg, 0.68 mmol) was added. The solution was warmed to −30°C and was stirred for 30 min at this temperature. The solution was diluted with 10 mL Et_2O, 2 mL 0.5 M HCl was added and the mixture was warmed to rt. The organic phase was separated, washed with water, brine, dried and evaporated to a colorless oil. The major product was purified by HPLC (10μ silica, 250×10 mm, 20% EtOAc/hexane, 3 mL min^{-1}, R_t= 21 min) to give 21 mg of **16** as a colorless oil (70% yield): $[\alpha]_D$=−29.3° (*c*=2.9, $CHCl_3$); IR (neat) 3502, 2953, 2930, 2857, 1724, 1655, 1436, 1257, 1081, 837, 778, 702 cm^{-1}; EIMS (70 eV) *m/z* 333 (M^+−^{t}Bu–H_2O, <1), 309 (M^+−$C_5H_7O_2$, 6), 222 (15), 221 (41), 193 (26), 105 (14), 91 (22), 75 (100); HREIMS *m/z* 333.1537 (M^+−^{t}Bu–H_2O, $C_{18}H_{25}O_4Si$, Δ −1.5 mmu), 309.1858 (M^+−$C_5H_7O_2$, $C_{17}H_{29}O_3Si$, Δ 2.8 mmu); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.34 (10/11/12/13/14-H, m), 6.86 (3-H, ddd, 15.6, 7.3, 7.3), 5.85 (2-H, d, 15.6), 4.50 (8-H, d, 8.9), 3.82 (5-H, ddd, 8.6, 4.4, 2.1), 3.80 (7-H, bd, 8.9), 3.68 (OCH_3, s), 3.38 (OH, s), 3.16 (OH, s), 2.36 (4-H_b, dddd, 14.6, 8.6, 7.3, 1.5), 2.09 (4-H_a, dddd, 14.6, 7.3, 4.4, 1.5), 1.76 (6-H, m), 1.00 (6-Me, d, 7.0), 0.87 ($SiCMe_3$, s), 0.02 (SiMe, s), −0.25 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7 (1), 146.2 (3), 140.6 (9), 128.5 (11/13), 128.2 (12), 127.0 (10/14), 122.6 (2), 81.2 (7), 77.0 (8), 75.1 (5), 51.3 (OMe), 37.4 (4), 36.6 (6), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), 5.5 (6-Me), −4.5 (SiMe), −5.1 (SiMe).

Acetonide 17. To a solution of 10 mg (0.025 mmol) of **16** in 2 mL CH_2Cl_2 at rt was added 2,2-dimethoxy propane (42 mg, 50 μL, 0.40 mmol) and PPTS (ca. 1 mg). The mixture was stirred for 1 h then the solvent was evaporated and the residue purified (Sep-Pak, gradient elution, hexane to CH_2Cl_2) to give 10 mg of the desired acetonide **17** as a colorless oil (95% yield): $[\alpha]_D$=−36.8° (*c*=1.3, $CHCl_3$); IR (neat) 2956, 2930, 2856, 1727, 1659, 1436, 1254, 1200, 1093, 836, 778, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3–7.4 (10/11/12/13/14-H, m), 6.83 (3-H, ddd, 15.7, 7.6, 6.4), 5.80 (2-H, ddd, 15.7, 1.8, 1.3), 4.52 (8-H, d, 8.4), 3.89 (7-H, dd, 8.4, 1.5), 3.83 (5-H, ddd, 8.9, 4.6, 1.8), 3.69 (s, OCH_3), 2.33 (4-H_b, dddd, 15.0, 8.9, 6.4, 1.8), 2.02 (4-H_a, dddd, 15.0, 7.6, 4.4, 1.3), 1.45 (1′-CH_{3ax}, s), 1.43 (1′-CH_{3eq}, s), 0.87 (6-Me/6-H, m), 0.80 ($SiCMe_3$, s), 0.04 (SiMe, s), −0.09 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (1), 145.7 (3), 140.9 (9), 128.2 (11/13), 127.7 (12), 127.3 (10/14), 122.5 (2), 99.4 (1″), 78.6/75.9/72.5 (5/7/8), 51.4 (OCH_3), 35.7 (6), 32.3 (4), 29.8 (1′-Me_{eq}), 25.6 ($SiCMe_3$, s), 19.6 (1′Me_{ax}), 5.5 (6-Me), −4.5 (SiMe), −5.0 (SiMe).

Methyl (5*R*, 6*S*, 8*R*)-5-tosyloxy-6-methyl-7-oxo-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyl-oct-2(*E*)-enoate 18. A solution of 500 mg (1.2 mmol) of **15** in 40 mL reagent grade THF[23] was cooled to 0°C. Tosyl chloride (2.3 g, 12.1 mmol) was added, followed by the slow addition (five portions over 30 min) of freshly powdered KOH (340 mg, 6 mmol). After addition was complete the reaction mixture was warmed to rt and allowed to stir until TLC indicated that no starting material remained. The reaction mixture was then diluted with 100 mL Et_2O and washed with 80 mL sat. aq $NaHCO_3$, water and brine. The organic layer was dried and evaporated to give a waxy solid that was purified by flash chromatography (silica, 15% EtOAc/hexane). Tosylate **18** was obtained as a colorless viscous oil (575 mg, 83% yield): $[\alpha]_D$=−24.7° (*c*=2.3, $CHCl_3$); IR (neat) 2953, 2857, 1725, 1660, 1454, 1364, 1258, 1176, 1097, 905, 838, 780 cm^{-1}; EIMS (70 eV) *m/z* 388 (M^+−TsOH, 1), 331 (15), 222 (52), 221 (100), 155 (23), 105 (29), 91 (78), 73 (98) HREIMS *m/z* 221.1332 (benzylic cleavage, $C_{13}H_{21}OSi$, Δ 3.0 mmu); FABMS, magic bullet matrix plus potassium, *m/z* 599 (M+K, 70), 561 (M+H, 9), 503 (3), 429 (18), 389 (18), 331 (27), 257 (60), 221 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (2′/6′-H, d, 8.1), 7.25–7.35 (3′/5′/10/11/12/13/14-H, m), 6.54 (3-H, ddd, 15.7, 7.9, 7.0), 5.52 (2-H, d, 15.7), 5.10 (8-H, s), 4.92 (5-H, ddd, 8.6, 5.2, 5.0), 3.70 (OCH_3, s), 3.31 (6-H, dq, 8.6, 7.3), 2.42 (4′-CH_3, s), 2.39 (4-H_b, dddd, 15.3, 7.0, 5.0, 1.6), 2.27 (4-H_a, dddd, 15.3, 7.9, 5.2, 1.0), 0.93 (6-Me, d, 7.3), 0.89 ($SiCMe_3$, s), 0.06 (SiMe, s), −0.10 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3 (7), 165.9 (1), 144.9 (4′), 141.8 (3), 138.2 (9), 133.8 (1′), 129.8 (3′/5′), 128.6 (11/13), 128.4 (12), 127.8 (2′/6′), 126.7 (10/14), 124.6 (2), 81.2 (5), 80.5 (8), 51.4 (OCH_3), 44.2 (6), 35.6 (4), 25.7 ($SiCMe_3$), 21.6 (4′-Me), 18.2 ($SiCMe_3$), 14.3 (6-Me), −4.9 (SiMe), −5.1 (SiMe).

Methyl (5*R*, 6*R*, 7*R*, 8*R*)-5-tosyloxy-6-methyl-7-hydroxy-8-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-2(*E*)-enoate 19. Ketotosylate **18** (400 mg, 0.71 mmol) and cerium trichloride heptahydrate (265 mg, 0.71 mmol) were dissolved in 25 mL EtOH and cooled to 0°C. Sodium borohydride (120 mg, 3.2 mmol) was added in 10 portions over 2 h, and the mixture was stirred for 30 min. The reaction was diluted with 100 mL Et_2O, the excess borohydride destroyed by washing with 20 mL 0.1 N HCl, and the mixture warmed to rt. The organic layer was collected,

washed with water and brine, dried and concentrated to produce 385 mg of **19** as a viscous colorless oil (ca. 20:1 ratio of diastereoisomers, 96% yield):[25] $[\alpha]_D=-36.8°$ (c=3.8, $CHCl_3$); IR (neat) 3566, 2953, 2857, 1728, 1661, 1456, 1363, 1258, 1176, 1080, 900, 837, 780 cm^{-1}; EIMS (70 eV) m/z 505 ($M^+-{}^tBu$, 1), 487 ($M^+-{}^tBu-H_2O$, 1), 333 (8), 273 (7), 222 (30), 221 (61), 169 (59), 137 (26), 105 (22), 91 (53), 73 (100); HREIMS m/z 505.1819 ($M^+-{}^tBu$, $C_{25}H_{33}O_7SSi$, Δ −10.3 mmu), 505.1819 ($M^+-{}^tBu-H_2O$, $C_{25}H_{31}O_6SSi$, Δ −0.9 mmu); ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (2′/6′-H, d, 8.4), 7.24–7.31 (3′/5′/11/12/13-H, m), 7.20 (10/14-H, bd, 7.3), 6.52 (3-H, ddd, 15.6, 8.4, 6.7), 5.64 (2-H, d, 15.6), 4.61 (5-H, ddd, 7.8, 4.7, 4.7), 4.45 (8-H, d, 8.1), 3.68 (7-H, bd, 8.1), 3.67 (OCH_3, s), 2.74 (7-OH, s), 2.57 (4-H_2, bm, $W_{1/2}$=25), 2.42 (4′-CH_3, s), 1.52 (6-H, m), 0.89 (6-Me, d, 6.8), 0.85 ($SiCMe_3$, s), 0.00 (SiMe, s), −0.27 (SiMe, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9 (1), 144.6 (4′), 142.4 (3), 140.3 (9), 134.0 (1′), 129.7 (3′/5′), 128.4 (11/13), 128.2 (12), 127.7 (2′/6′), 127.0 (10/14), 124.3 (2), 84.1 (5), 77.4 (8), 74.6 (7), 51.3 (OCH_3), 36.2 (6), 34.1 (4), 25.7 ($SiCMe_3$), 21.6 (4′-Me), 18.1 ($SiCMe_3$), 9.5 (6-Me), −4.5 (SiMe), −5.1 (SiMe).

Methyl (2*E*)-4-((2*S*, 3*R*, 4*R*, 5*R*)-4-hydroxy-3-methyl-5-phenyloxolan-2-yl)-but-2-enoate 20. Treatment of a solution of hydroxytosylate **19** in DMF with excess cesium acetate led to the TBS ether of **20** in 86% isolated yield. Treatment of this material at rt with aq HF in acetonitrile gave **20** as a viscous colorless oil: $[\alpha]_D=-28.4°$ (c=4.4, $CHCl_3$); EIMS (70 eV) m/z 276 (M^+, 2), 274 (2), 260 (4), 258 (6), 177 ($M^+-C_5H_7O_2$, 38), 159 (11), 140 (12), 119 (53), 100 (88), 91 (100), 77 (31); HREIMS m/z 276.1367 (M^+, $C_{16}H_{20}O_4$, Δ −0.6 mmu), 177.0920 ($M^+-C_5H_7O_2$, $C_{11}H_{13}O_2$, Δ −0.4 mmu); ^1H NMR (500 MHz $CDCl_3$) δ 7.30–7.40 (10/11/12/13/14-H, m), 7.09 (3-H, ddd, 15.6, 7.4, 7.2), 5.99 (2-H, ddd, 15.6, 1.5, 1.5), 4.98 (8-H, d, 4.5), 3.98 (7-H, bdd, 4.5, 2.7), 3.74 (OCH_3, s), 3.71 (5-H, ddd, 7.2, 6.9, 5.5), 2.71 (4-H_b, dddd, 14.6, 7.4, 7.2, 1.5), 2.65 (4-H_a, dddd, 14.6, 7.2, 5.5, 1.5), 2.06 (6-H, ddq, 6.9, 2.7, 7.2), 1.17 (6-Me, d, 7.2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9 (1), 145.4 (3), 136.4 (9), 128.6 (11/13), 128.0 (12), 126.9 (10/14), 123.2 (2), 83.7 (5), 83.3 (8), 80.6 (7), 51.4 (OCH_3), 46.9 (6), 37.8 (4), 16.7 (6-Me).

(*S*)-Mosher ester of 20. To a solution of 3 mg (0.01 mmol) of **20** in 1 mL CH_2Cl_2 was added triethylamine (30 μL), DMAP (1 mg) and (*R*)-methoxy-trifluoromethyl-phenylacetyl chloride (10 μL) and the mixture stirred for 1 h. The reaction was diluted with 10 mL Et_2O and washed with 10 mL aq. (5% w/w) $KHSO_4$ and brine. The ethereal layer was collected, dried and concentrated to produce the (*S*)-MTPA ester as a viscous, colorless oil as a single diastereomer: $[\alpha]_D=-29.0°$ (c=1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–7.36 (2×Ph_5, m), 7.04 (3-H, ddd, 15.6, 7.3, 7.1), 5.96 (2-H, ddd, 15.6, 1.5, 1.5), 5.32 (7-H, dd, 4.6, 2.9), 5.10 (8-H, d, 4.6), 3.75 (5-H, obs. m), 3.73 (OCH_3, s), 3.03 (MTPA–OCH_3, s), 2.62 (4-H_2, m), 2.19 (6-H, ddq, 6.8, 2.9, 7.1), 1.27 (6-Me, d, 7.1).

(*R*)-Mosher ester of 20. The procedure described above was repeated on the same scale with (*S*)-methoxy-trifluoromethyl-phenylacetyl chloride to produce the (*R*)-MTPA ester as a viscous, colorless oil as a single diastereomer: $[\alpha]_D=-26.5°$ (c=1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.34 (Ph_5/Ph_3 m), 7.06 (Ph_2, bd, 7.8), 6.93 (3-H, ddd, 15.6, 7.6, 7.3), 5.85 (2-H, bd, 15.6), 5.22 (7-H, dd, 4.4, 2.4), 5.11 (8-H, d, 4.4), 3.73 (OCH_3, s), 3.70 (5-H, obs. m), 3.02 (MTPA-OCH_3, s), 2.36 (4-H_2, bm), 2.01 (6-H, m), 1.22 (6-Me, d, 7.3).

Allyl ester A-D-C-Boc Unit 23. Azide **14** (127 mg, 0.28 mmol) was dissolved in a mixture of 5 mL THF and 1 mL water. Triphenylphosphine (75 mg, 0.29 mmol) was added in a single portion and the solution was stirred at 50–60°C for 12 h. After this time TLC (EtOAc) shows a spot which stains with ninhydrin which is the desired amine. Alternatively, the reaction can be monitored by the disappearance of azide **14** (tlc, 20% EtOAc/hexanes). The THF was evaporated, replaced with an equal volume of CH_2Cl_2 and the phases separated. The CH_2Cl_2 was evaporated to produce a mixture of crude amine **21** and triphenylphosphine oxide as a colorless oil. The crude material was used for the next reaction.[26]

Carboxylic acid **22** (120 mg, 0.38 mmol) was dissolved in 10 mL dry DMF and FDPP (130 mg, 0.34 mmol) was added followed by diisopropylethylamine (75 mg, 100 μL, 0.58 mmol). The mixture was stirred at rt for 5 min, then crude amine **21** (120 mg, 0.28 mmol) from the preceding reaction in 1 mL dry DMF was added dropwise over 5 min. After 4 h the reaction was diluted with 80 mL Et_2O and washed with 20 mL 0.5 M HCl, water and brine. The organic layer was dried and concentrated to give a pale yellow oil. Flash chromatography (silica, 25% EtOAc/hexane) produced 149 mg of **23** as a viscous colorless oil (74% yield from **14**): $[\alpha]_D=-48.7°$ (c=1.6, $CHCl_3$); IR (neat) 3381, 2957, 2858, 1740, 1722, 1525, 1462, 1366, 1253, 1171, 1125, 1075, 868, 837, 779, 702 cm^{-1}; EIMS (70 eV) m/z 732 (M^+, <1), 575 (16), 411 (41), 309 (8), 257 (12), 221 (47), 193 (17), 154 (28), 130 (13), 105 (15), 91 (24), 77 (20), 75 (100); HREIMS m/z 732.4364 (M^+, $C_{39}H_{64}N_2O_9Si$, Δ 1.7 mmu); ^1H NMR (500 MHz, $CDCl_3$) δ Unit A 7.44 (5-NH, d, 8.1), 7.21–7.29 (11/12/13-H, m), 7.20 (10/14-H, d, 6.8), 6.52 (3-H, ddd, 15.4, 8.8, 6.1), 5.90 ($CH_2CH=CH_2$, ddt, 17.2, 10.6, 5.8), 5.54 (2-H, d, 15.4), 5.29 ($CH_2CH=CH_cH_t$, bd, 17.2), 5.22 ($CH_2CH=CH_cH_t$, bd, 10.6), 4.54 ($CH_2CH=CH_2$, d, 5.8), 4.43 (8-H, d, 8.8), 3.92 (5-H, m), 3.88 (7-H, bd, 8.8), 3.19 (7-OH s), 2.48 (4-H_b, dddd, 14.1, 6.1, 6.1, 1.3), 2.16 (4-H_a, ddd, 14.1, 8.8, 8.8), 1.31 (6-H, m), 0.93 (6-Me, d, 7.3), 0.86 ($SiCMe_3$, s), −0.03 (SiMe, s), −0.25 (SiMe, s), Unit C 5.10 (3-NH, m), 3.36 (3-H_b, m), 3.20 (3-H_a, m), 2.83 (2-H, m), 1.42 ($NHCO_2CMe_3$, s), 1.21 (2-Me, d, 7.3), Unit D 5.14 (2-H, dd, 8.6, 3.5), 1.67 (3-H_2/4-H, bm), 0.91 (5-H_3/4-Me, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ Unit A 165.3 (1), 144.4 (3), 140.0 (9), 132.3 ($CH_2CH=CH_2$), 128.5 (11/13), 128.4 (12), 126.8 (10/14), 123.2 (2), 118.0 ($CH_2CH=CH_2$), 77.2 (8), 75.3 (7), 64.8 ($CH_2CH=CH_2$), 52.6 (5), 35.8 (4), 32.3 (6), 25.7 ($SiCMe_3$), 18.1 ($SiCMe_3$), 11.3 (6-Me), −4.5 (SiMe), −5.2 (SiMe), Unit C 174.3 (1), 155.9 ($NHCO_2CMe_3$), 79.3 ($NHCO_2CMe_3$), 43.3 (3), 40.2 (2), 28.3 ($NHCO_2CMe_3$), 14.3 (2-Me), Unit D 170.3 (1), 73.0 (2), 41.1 (3), 24.6 (4), 23.1 (4-Me), 21.6 (5).

Acid A-D-C-Boc Unit 24. To a solution of 168 mg (0.23 mmol) of allyl ester **23** in THF[27] was added

tetrakistriphenylphosphine palladium (26 mg, 0.02 mmol). The mixture was stirred at rt and morpholine (200 mg, 200 μL, 2.3 mmol) added dropwise over 10 min. After 4 h the reaction was diluted with 60 mL Et_2O and washed with 50 mL 0.5N HCl. The organic phase was washed with water, brine, dried and concentrated to give a pale yellow oil. Flash chromatography (silica, 10% EtOAc/hexane to 50% EtOAc/hexane) produced 145 mg of acid **24** as a viscous, colorless oil (91% yield): $[\alpha]_D=-68.6°$ (c=2.8, $CHCl_3$); IR (neat) 3372, 2957, 2857, 2400–3400 (br), 1715, 1704, 1660, 1529, 1462, 1367, 1252, 1173, 1125, 1075, 868, 837, 756, 702 cm^{-1}; FABMS (thioglycerol matrix+potassium) m/z 731 ($M+K^+$, 80), 693 ($M+H^+$, 15), 593 (100); ^1H NMR (500 MHz, $CDCl_3$) δ Unit A 7.46 (5-NH, d, 8.4), 7.25–7.34 (11/12/13-H, m), 7.22 (10/14-H, d, 6.9), 6.60 (3-H, ddd, 15.6, 7.3, 7.1), 5.54 (2-H, d, 15.6), 4.45 (8-H, d, 8.9), 3.94 (5-H, m), 3.88 (7-H, d, 8.9), 3.21 (7-OH, s), 2.52 (4-H_b, m), 2.18 (4-H_a, m), 1.32 (6-H, m), 0.95 (6-Me, d, 6.9), 0.87 ($SiCMe_3$, s), −0.01 (SiMe, s), −0.24 (SiMe, s), Unit C 5.11 (3-NH, m), 3.37 (3-H_b, ddd, 11.9, 6.9, 5.1), 3.21 (3-H_a, m), 2.84 (2-H, m), 1.43 ($NHCO_2CMe_3$, s), 1.22 (2-Me, d, 7.1), Unit D 5.15 (2-H, bd, 8.4), 1.67 (3-H_2/4-H, bm), 0.93 (5-H_3, d, 6.3), 0.92 (4-Me, d, 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ Unit A 169.6 (1), 146.5 (3), 139.9 (9), 128.7 (11/12/13), 126.8 (10/14), 122.9 (2), 77.0 (8), 75.4 (7), 52.7 (5), 35.9 (4), 32.5 (6), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), 11.3 (6-Me), −4.4 (SiMe), −5.1 (SiMe), Unit C 174.4 (1), 156.0 ($NHCO_2CMe_3$), 79.6 ($NHCO_2CMe_3$), 43.4 (3), 40.2 (2), 28.4 ($NHCO_2CMe_3$), 14.4 (2-Me), Unit D 170.5 (1), 73.1 (2), 41.1 (3), 24.6 (4), 23.2 (4-Me), 21.7 (5).

Protected Seco Compound 26. To a solution of 100 mg (0.14 mmol) of carboxylic acid **24** in 4 mL dry DMF at rt was added FDPP (70 mg, 0.18 mmol). The mixture was stirred for 5 min before a solution in 1 mL of DMF of 100 mg (0.25 mmol) of the hydrochloride salt of **25** and triethylamine (45 mg, 62 μL, 0.45 mmol) was added. The resulting mixture was stirred at rt for 5 h, diluted with 40 mL EtOAc and washed with 30 mL 0.5N HCl, 30 mL sat. aq. $NaHCO_3$, water and brine. The organic layer was dried and evaporated to give a pale yellow oil. Flash chromatography (silica, 10% EtOAc/hexane to 50% EtOAc/hexane) produced 98 mg of fully protected seco compound **26** as a viscous, colorless oil (69% yield): $[\alpha]_D=-65.6°$ (c=3.9, $CHCl_3$); IR (neat) 3376, 2957, 2858, 1746, 1715, 1673, 1504, 1463, 1367, 1258, 1172, 1067, 837, 781, 702 cm^{-1}; FABMS (magic bullet matrix+potassium) m/z 1078/1076/1074/1072 (M+K), 1062/1060/1058/1056 (M+Na), 1040/1038/1036/1034 (M+H), 940/938/936/934; ^1H NMR (500 MHz, $CDCl_3$) δ Unit A 7.40 (5-NH, bd, 7.9), 7.20–7.26 (10/11/12/13/14-H, m), 6.43 (3-H, ddd, 15.4, 7.6, 7.4), 5.40 (2-H, d, 15.4), 4.44 (8-H, d, 8.7), 3.90 (7-H, bd, 8.7), 3.85 (5-H, m), 3.22 (7-OH, s), 2.39 (4-H_b, ddd, 14.2, 7.4, 6.8), 2.10 (4-H_a, ddd, 14.2, 7.6, 7.1), 1.36 (6-H, m), 0.94 (6-Me, d, 7.1), 0.86 ($SiCMe_3$, s), −0.01 (SiMe, s), −0.25 (SiMe, s), Unit B 7.18 (5-H, d, 2.1), 7.05 (9-H, dd, 8.4, 2.1), 6.86 (8-H, d, 8.4), 5.95 (2-NH, bd, 7.0), 4.94 (2-H, ddd, 7.0, 6.1, 6.1), 4.76/4.70 (CH_2CCl_3, AB-q, 11.8), 3.86 (7-OCH_3, s), 3.15 (3-H_b, dd, 14.2, 6.1), 3.06 (3-H_a, dd, 14.2, 6.1), Unit C 5.12 (3-NH, m), 3.36 (3-H_b, m), 3.21 (3-H_a, m), 2.82 (2-H, m), 1.42 ($NHCO_2CMe_3$, s), 1.21 (2-Me, d, 7.1), Unit D 5.12 (2-H, m), 1.59-1.71 (3-H_2/4-H, bm), 0.91 (5-H_3, d, 5.8), 0.90 (4-Me, d, 5.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ Unit A 165.2 (1), 140.7 (3), 140.3 (9), 128.6 (11/13), 128.4 (12), 127.1 (10/14), 125.2 (2), 77.1 (8), 75.4 (7), 53.0 (5), 35.6 (4), 32.7 (6), 25.7 ($SiCMe_3$), 18.1 ($SiCMe_3$), 11.4 (6-Me), −4.5 (SiMe), −5.2 (SiMe), Unit **B** 170.0 (1), 154.2 (7), 131.1 (5), 128.7 (4), 128.5 (9), 122.5 (6), 112.3 (8), 94.2 (CH_2CCl_3), 74.7 (CH_2CCl_3), 56.1 (7-OCH_3), 53.2 (2), 36.6 (3), Unit C 174.4 (1), 156.0 ($NHCO_2CMe_3$), 79.3 ($NHCO_2CMe_3$), 43.4 (3), 40.2 (2), 28.4 ($NHCO_2CMe_3$), 14.3 (2-Me), Unit D 170.5 (1), 73.0 (2), 41.0 (3), 24.6 (4), 23.2 (4-Me), 21.6 (5).

Cryptophycin 226 (27). Fully protected seco compound **26** (19 mg, 0.018 mmol) was cooled to 0°C, 1 mL trifluoroacetic acid was added, and the solution stirred for 1 h. The solvent was removed in vacuo to produce a colorless foam which was dissolved in 20 mL EtOAc and washed with 10 mL aq. (10% w/w) Na_2CO_3. The phases were separated and the organic phase was washed with 15 mL water and 15 mL brine, dried and evaporated to give the free amine as a colorless oil. This oil (12 mg, 0.015 mmol) was dissolved in 3 mL toluene and 2-hydroxypyridine (7 mg, 0.074 mmol) was added. The clear, colorless solution was allowed to stir, protected from light, for 20 h. A precipitate appeared. The solvent was evaporated and the residue filtered through a silica plug eluting with 10% MeOH in CH_2Cl_2. The residue was purified by HPLC (ODS, 250×10 mm, 10μ, 50% H_2O/MeCN, 3 mL min^{-1}) to give 6 mg, after lyophilization, of **27** (R_t=9 min) as a fluffy colorless solid (50% yield): $[\alpha]_D=29.1°$ (c=1.1, MeOH); IR (neat) 3365, 3270, 2955, 1748, 1722, 1660, 1632, 1504, 1203, 1153, 1067, 1006, 699 cm^{-1}; EIMS (70 eV) m/z 671/673 (M^+, <1), 653/655 (M^+-H_2O, 3/1), 635/637 (M^+-2H_2O, <1), 564/566 (glycol cleavage, 1.5/0.5), 506/508 (3/1), 411/413 (4.5/1.5), 394/396 (5/2), 289/282 (19/7), 217 (74), 211/213 (53/17), 195/197 (31/11), 184 (27), 91 (72), 77 (84), 69 (100); HREIMS m/z 671.2953 (M^+, $C_{35}H_{46}N_3O_8Cl$ Δ 2.0 mmu), 653.2863 (M^+-H_2O, $C_{35}H_{44}N_3O_7Cl$ Δ 0.4 mmu), 635.2753 (M^+-2H_2O, $C_{35}H_{42}N_3O_6Cl$ Δ 0.9 mmu), 564.2493 ($M^+-C_7H_7O$, $C_{28}H_{39}N_3O_7Cl$ Δ −1.7 mmu); ^1H NMR (500 MHz, $CDCl_3$) δ Unit A 7.27–7.37 (10/11/12/13/14-H, m), 7.17 (5-NH, bd, 9.4), 6.63 (3-H, ddd, 15.2, 9.8, 5.4), 5.81 (2-H, d, 15.2), 4.53 (8-H, d, 8.7), 3.99 (7-H, bd, 8.7), 3.90 (5-H, m), 2.29 (4-H_b, m), 1.98 (4-H_a, m), 1.31 (6-H, m), 0.96 (6-Me, d, 6.9), Unit B 7.20 (5-H, d, 1.2), 7.07 (9-H, dd, 8.5, 1.2), 6.79 (2-NH, obs. m), 6.78 (8-H, d, 8.5), 4.77 (2-H, m), 3.81 (7-OCH_3, s), 3.15 (3-H_b, dd, 14.5, 3.8), 2.89 (3-H_a, dd, 14.5, 9.2), Unit C 6.98 (3-NH, m), 3.44 (3-H_b, ddd, 13.4, 6.6, 6.5), 3.37 (3-H_a, dm, 13.4), 2.68 (2-H, m), 1.23 (2-Me, d, 7.4), Unit D 4.82 (2-H, dd, 8.9, 4.7), 1.79 (3-H_b, m), 1.72 (4-H, m), 1.52 (3-H_a, ddd, 13.0, 7.8, 4.7), 0.93 (5-H_3, d, 6.5), 0.89 (4-Me, d, 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ Unit A 166.2 (1), 142.3 (3), 140.3 (9), 128.8 (11/13), 128.2 (12), 127.0 (10/14), 125.0 (2), 76.0 (8), 75.0 (7), 53.6 (5), 37.3 (4), 36.6 (6), 11.4 (6-Me), Unit B 171.8* (1), 153.8 (7), 130.9 (5), 130.5 (4), 128.6 (9), 122.1 (6), 112.2 (8), 56.1 (7-OCH_3), 54.2 (2), 35.3 (3), Unit C 175.7 (1), 41.1 (3), 38.9 (2), 14.3 (2-Me), Unit D 170.2* (1), 73.0 (2), 40.6 (3), 24.5 (4), 22.8 (4-Me), 21.9 (5). (*Assignments may be reversed.)

Conversion of 27 to cryptophycin 338 (28). A sample of 10 mg of **27** was treated at rt for 2 h with 1 mL of a solution

which was prepared from 150 mg of PPTS, and 13 mL of trimethyl orthoformate in 41 mL of CH_2Cl_2. The mixture was filtered through SiO_2 with 80% EtOAc/hexane, and the solvent was evaporated. The residue was evacuated for 3 h, redissolved in 0.5 mL CH_2Cl_2, and treated at rt with 60 μL of a 0.80 M solution of acetyl bromide in CH_2Cl_2. After 6 h the reaction was quenched with 1 mL aq. $NaHCO_3$ and partitioned between water and CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated, and pumped to dryness to provide crude formyloxy bromide. This material was dissolved in a mixture of 300 μL DME, 200 μL EtOH and 50 μL MeOH. To this solution was added 20 mg $KHCO_3$, and the heterogeneous mixture was stirred vigorously at 40°C for 15 h. The mixture was cooled to rt, diluted with 5 mL EtOAc and filtered. Solvent evaporation followed by flash column chromatography on SiO_2 (25% EtOAc/CH_2Cl_2) provided 6 mg (62% yield) of **28** as an amorphous solid: $[\alpha]_D$=120° (c=0.50, MeOH); IR (CCl_4) 3416, 2956, 2875, 1655, 1449, 1314, 944, 881, 712 cm^{-1}; EIMS (70 eV) m/z 655 (M^++2, 1.3), 653 (M^+, 2.9), 551 (0.6), 498 (1.1), 430 (2.2), 315 (3.9), 259 (26.3), 220 (10.3), 155 (25.4), 107 (100); HREIMS m/z 653.2864 (M^+, $C_{35}H_{44}N_3O_7Cl$ Δ 6.0 mmu); ^{1}H NMR (500 MHz, CD_3OD) δ Unit A 7.45–7.35 (10/14-H, m), 7.35–7.27 (11/12/13-H, m), 6.48 (3-H, dt, 16.0, 6.8), 5.96 (2-H, d, 16.0), 4.99 (8-H, d, 7.0), 3.88–3.85 (5-H, m), 3.62–3.54 (4-H+7-H, m), 2.45 (4-H, dd, 15.5, 6.3), 2.15–2.05 (6-H, m), 1.12 (6-Me, d, 6.3), Unit B 7.28 (5-H, d, 1.9), 7.17 (9-H, dd, 8.5, 1.9), 6.99 (8-H, d, 8.5), 4.36 (2-H, dd, 10.4, 4.6), 3.85 (OMe, s), 3.16 (3-H_b, dd, 14.3, 4.6), 2.96 (3-H_a, dd, 14.3, 10.7), Unit C 3.47–3.37 (3-H, m), 2.75–2.65 (2-H, m), 1.14 (2-Me, d, 7.3), Unit D 4.76 (2-H, dd, 10.9, 2.4), 1.56 (3-H_b, ddd, 15.3, 11.1, 4.9), 1.25–1.17 (4-H, m), 0.59 (5-H_3, d, 6.3), 0.50 (3-H_a, ddd, 14.1, 9.0, 2.4), 0.17 (4-Me, d, 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ Unit A 169.9 (1), 140.2 (3), 132.4 (9), 130.5 (11/13), 129.2 (12), 128.0 (2), 127.9 (10/14), 86.0 (7), 71.3 (8), 56.6 (5), 44.2 (6), 32.2 (4), 14.5 (6-Me), Unit B 174.2 (1), 155.4 (7), 144.6 (6), 131.7 (5), 129.5 (9), 123.3 (4), 113.5 (8), 65.7 (7-OMe), 57.9 (2), 35.9 (3), Unit C 176.9 (1), 41.4 (3), 39.9 (2), 14.5 (2-Me), Unit D 171.6 (1), 73.0 (2), 39.3 (3), 24.9 (4), 23.3 (4-Me), 21.3 (5).

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References

1. Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729.
2. Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113.
3. Kobayashi, M.; Aoki, S.; Ohyabu, N.; Kurosu, M.; Wang, W.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 7969.
4. Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479.
5. Salamonczyk, G. M.; Han, K.; Guo, Z.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893.
6. Gardinier, K. M.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 7098.
7. Kobayashi, M.; Kurosu, M.; Wang, W.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2394.
8. (a) Rej, R., Nguyen, D., Go, B., Fortin, S., Lavallée, J.-F. *J. Org. Chem.* **1996**, *61*, 6289. (b) Ali, S. M., George, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703. (c) Dhokte, U. P., Khau, V. V., Hutchison, D. R., Martinelli, M. J. *Tetrahedron Lett.* **1998**, *39*, 8771. (d) White, J. D., Hong, J., Robarge, L. A. *Tetrahedron Lett.* **1998**, *39*, 8779. (e) Fray, A. H. *Tetrahedron: Asymmetry* **1998**, *39*, 2777. (f) Norman, B. H., Hemscheidt, T., Schultz, R. M., Andis, S. L. *J. Org. Chem.* **1998**, *63*, 5288. (g) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206.
9. Golakoti, T.; Ogino, J.; Heltzel, C. E.; Le Husebo, T.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030.
10. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *69*, 83.
11. (a) Nahm, S., Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Levin, J. I., Turos, E., Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. For a review, see: Sibi, M. P. *Org. Prep. Proc. Intern.* **1993**, *25*, 15. Initially, it had appeared to us that this reaction had failed, since the ^{1}H NMR spectrum revealed only a single resonance in the region where both OCH_3 and NCH_3 resonances were expected. Integration showed that this single broad peak accounted for six hydrogen atoms, however, we are aware of no other example in which the OCH_3 and NCH_3 resonances of Weinreb amides are coincident.
12. (a) Makin, S. M., Raifel'd, Y. E., Limanova, O. V., Shavrygina, O. A., Kosheleva, L. M. *J. Org. Chem. USSR* **1979**, 1665. (b) Trost, B. M., Dumas, J., Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836.
13. (a) Masamune, S., Choy, W., Kerdesky, F. A. J., Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Evans, D. A., Nelson, J. V., Vogel, E., Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
14. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, S. *Tetrahedron Lett.* **1984**, *25*, 2183.
15. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
16. Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426.
17. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
18. (a) Rychnovsky, S. D., Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Rychnovsky, S. D., Rogers, B., Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
19. Liang, J.; Moher, E. D.; Moore, R. E.; Hoard, D. W. *J. Org. Chem.* **2000**, *65*.
20. Fieser, L. F., Fieser, M., Eds.; Wiley: New York, 1967; Vol. 1, p 191.
21. Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.
22. Dibutylboron triflate was obtained from Aldrich Chemical Co. as a 1 M solution in CH_2Cl_2.
23. The reaction does not proceed in scrupulously anhydrous THF. It is necessary to add a small amount of water to the solvent in order for the reaction to proceed.
24. This compound is not very stable, being prone to cyclise to a THF compound with a trace of base, and is used immediately. If the compound is to be stored, it must be kept in solution at −10°C.

25. This compound it not very stable, being prone to cyclise to a THF compound with a trace of base, and is used immediately. If the compound is to be stored, it should be kept in solution and kept cold.
26. Although **21** could be isolated in an acid/base extraction, the yield was low, which suggests that partitioning between the two phases was incomplete. The use of crude material results in a good overall yield of **23**.
27. Air must be rigorously excluded from this reaction.