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Total Synthesis of the Cyclopeptide Alkaloid Sanjoinine G1 and its C-11 Epimer

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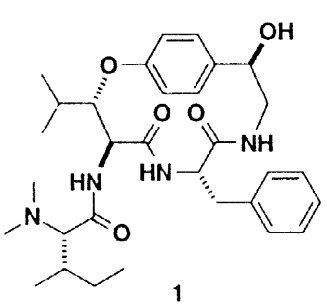
Abstract : The naturally occurring cyclopeptide alkaloid sanjoinine G1 and its C-11 epimer were synthesized in 18 steps from D-serine. The key steps in the synthesis were the formation of the alkyl-aryl ether linkage via an S_NAr reaction with 4-fluorobenzonitrile and the macrocyclization to form the 14-membered ring using a modification of the Schmidt protocol involving an activated pentafluorophenyl ester.

Keywords : Alkaloids; Macrocycles; Strained Compounds

INTRODUCTION

The cyclopeptide alkaloids are a large family of polyamide bases of plant origin.[1-5] In 1966 Pais and co-workers elucidated the structure of pandamine (**1**).[6] Since those pioneering studies, more than 200 cyclopeptide alkaloids containing a 13- (e.g. zizyphine A **2**), 14- (e.g. **1**) or 15-membered macrocycle (e.g. mucronine B **3**) have been isolated and characterized. They are particularly common to plants in the Rhamnaceae family but have been found in more than 25 other species.



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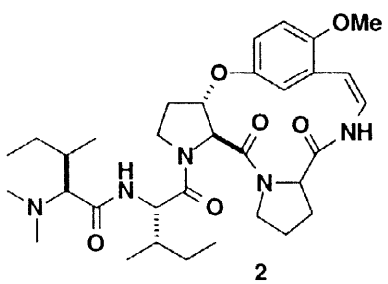

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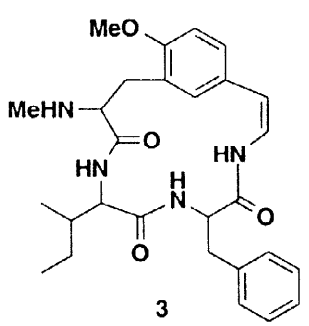

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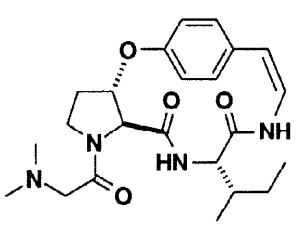
Although the occurrence of cyclopeptide alkaloids is widespread in nature, they are usually present in plants as mixtures and in minor quantities; yields from the dried plants typically range from 0.01 to 1%. Due to the lack of availability from natural sources, the biological activity of these compounds has not been examined thoroughly . Consequently, there has been a steady stream of investigations on the synthesis of members of the cyclopeptide alkaloid family. A successful strategy must address the stereoselective synthesis of the β-hydroxy-α-amino acid, the formation of the alkyl-aryl ether linkage (for 13- and 14-membered systems), the macrocyclization and in some cases the installation of the enamide unit.

Initial synthetic studies were carried out by Pais and co-workers.[7-9] Rapoport later examined possible cyclization methods in model systems.[10,11] Major advances in the field were made by Schmidt and co-workers who developed a novel protocol for cyclization[12,13] and applied this method to the synthesis of representative examples of the 13-,[14,15] 14-[16] and 15-membered macrocycles.[17,18] Lipshutz investigated an ingenious approach to 14-membered macrocycles using oxazolophanes.[19] Most recently, Zhu has utilized a novel method for the preparation of model cyclopeptide systems where macrocyclization occurs with formation of the alkyl-aryl ether bond.[20,21]

For some years, we have focused our attention on the 14-membered macrocycles.[22-26] In addition to being the largest sub-class of cyclopeptide alkaloids, they are perhaps the most synthetically challenging as a result of the strain inherent in this particular ring size. These investigations resulted in the total synthesis of nummularine F (**4**) in 1990[27,28] and we herein describe a new and highly efficient synthesis of the naturally occurring cyclopeptide alkaloid sanjoinine G1 (**5**) and its unnatural C-11 epimer.



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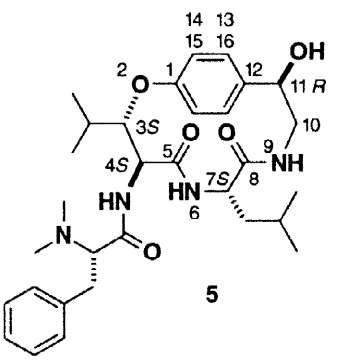


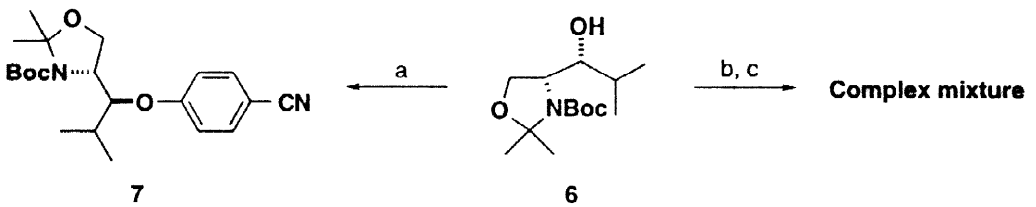
5

Sanjoinine G1 (**5**) was isolated from the seeds of *Zizyphus Vulgaris* var. *spinosus* (Sanjoin) by Han and co-workers.[29] A full stereochemical assignment of **5** was later reported by the same group and in particular the absolute configuration at the C-11 position was established using the circular dichroic exciton chirality method.[30] Additionally, the first total synthesis of this cyclopeptide alkaloid was achieved in 1995 in 1.36% overall yield from D-serine.[31]

RESULTS AND DISCUSSION

Our initial approach towards **5**[32] followed a similar strategy to the one described by Han.[31] We had also aimed to invert the stereochemistry of the hydroxyl group in **6** (prepared from D-serine[33]) with simultaneous alkyl-aryl ether formation. Under Mitsunobu conditions[34] using DEAD, triphenyl phosphine and *p*-cyanophenol, some of the desired product **7** was detected but only in a modest yield (< 25%). Alternatively, activation of the hydroxyl group as a mesylate followed by attempted inversion using methyl 4-hydroxybenzoate and potassium carbonate did not proceed at room temperature and upon warming the reaction a complex mixture of products resulted (**Scheme 1**).

Scheme 1

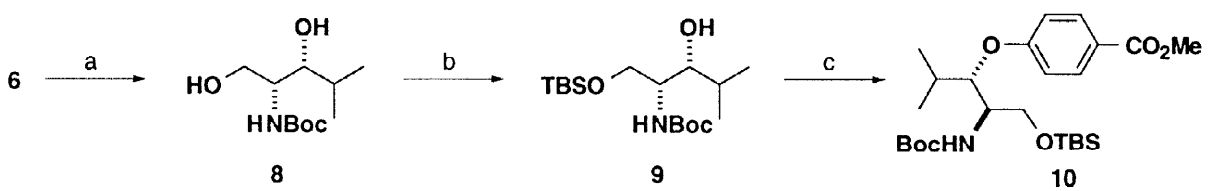


7 **6**

Reagents and conditions : a) PPh_3, DEAD, *p*-cyanophenol, THF, 25%; b) MsCl, pyridine, CH_2Cl_2; c) Methyl 4-hydroxybenzoate, K_2CO_3, DMF.

In agreement with Hans' reasoning,[31] we believed that the poor reactivity of the hydroxyl group in **6** towards inversion was at least partly due to steric restrictions. Consequently, we also opted to improve the conformational mobility of **6** by Lewis acid hydrolysis to give **8**[33] (**Scheme 2**). This step was followed by selective protection of the resulting primary hydroxyl group in **8** as its TBS ether to afford **9** in good yield. Treatment of **9** under Mitsunobu conditions with methyl 4-hydroxybenzoate gave **10**, but the yield of the reaction never exceeded 45% despite the variety of conditions investigated. Attempts to invert the hydroxyl group in **9** by activation as its mesylate and subsequent reaction with methyl 4-hydroxybenzoate and potassium carbonate in DMF did not improve the yield of **10**.

Scheme 2



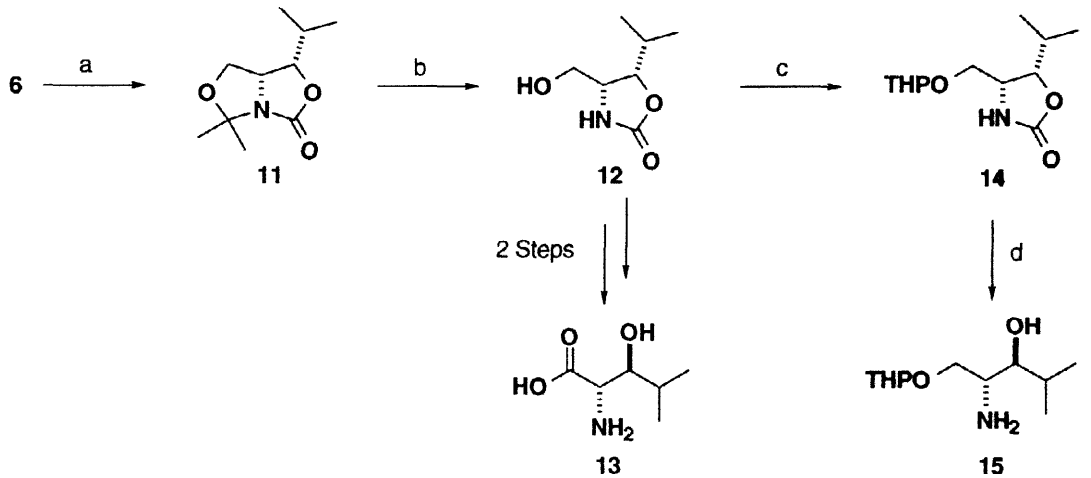
8 **9** **10**

Reagents and conditions : a) BF_3.2AcOH, MeOH, 98%; b) TBSCl, DMAP, Et_3N, CH_2Cl_2, 76%; c) PPh_3, DEAD, methyl 4-hydroxybenzoate, 45%.

The low yield obtained in forming the alkyl-aryl ether linkage via inversion led us to revise our synthetic route, and we investigated alkyl-aryl ether formation with retention of configuration using a simple nucleophilic aromatic substitution strategy. We had observed previously that the hydroxyl group in **6** could be readily inverted by treatment of **6** with trifluoromethanesulfonic anhydride in the presence of a base to give the bicyclic compound **11** (**Scheme 3**).[33] Further, **11** could be hydrolyzed using boron trifluoride-acetic acid to give **12** in

quantitative yield. This oxazolidinone could be readily converted into (2S, 3S)-hydroxyleucine (**13**).[33] Alternatively, **12** could be protected as its THP ether under standard conditions[35] to give **14** and then hydrolyzed using potassium hydroxide[36] to give the amino alcohol **15**.

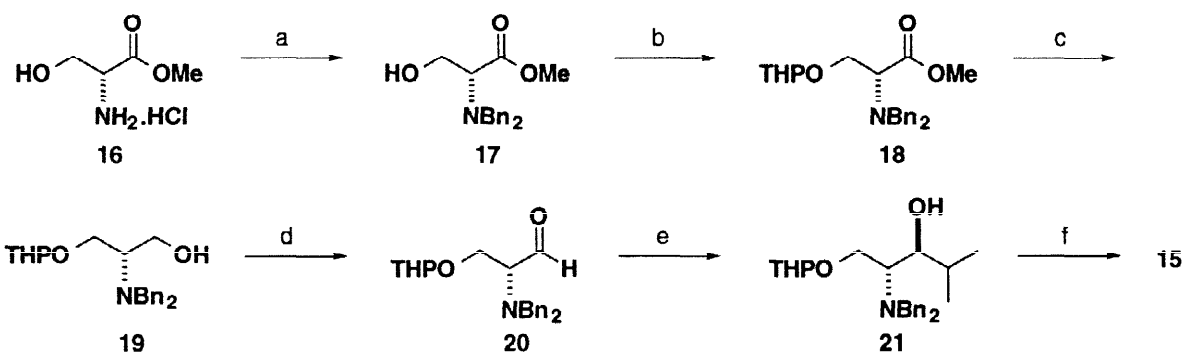
Scheme 3



Reagents and conditions : a) $(CF_3SO_2)_2O$, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 83%; b) $BF_3.2AcOH$, MeOH, quant.; c) 3,4-Dihydro-2*H*-pyran, PPTS, CH_2Cl_2, 75%; d) KOH, MeOH:H_2O (4:1), reflux, quant.

During the course of this work, an alternative synthesis of **15** was investigated utilizing methodology reported by Zhu and co workers.[37,38] Starting form D-serine methyl ester **16**, the amino alcohol **15** could be prepared in six steps as shown in **Scheme 4**.

Scheme 4



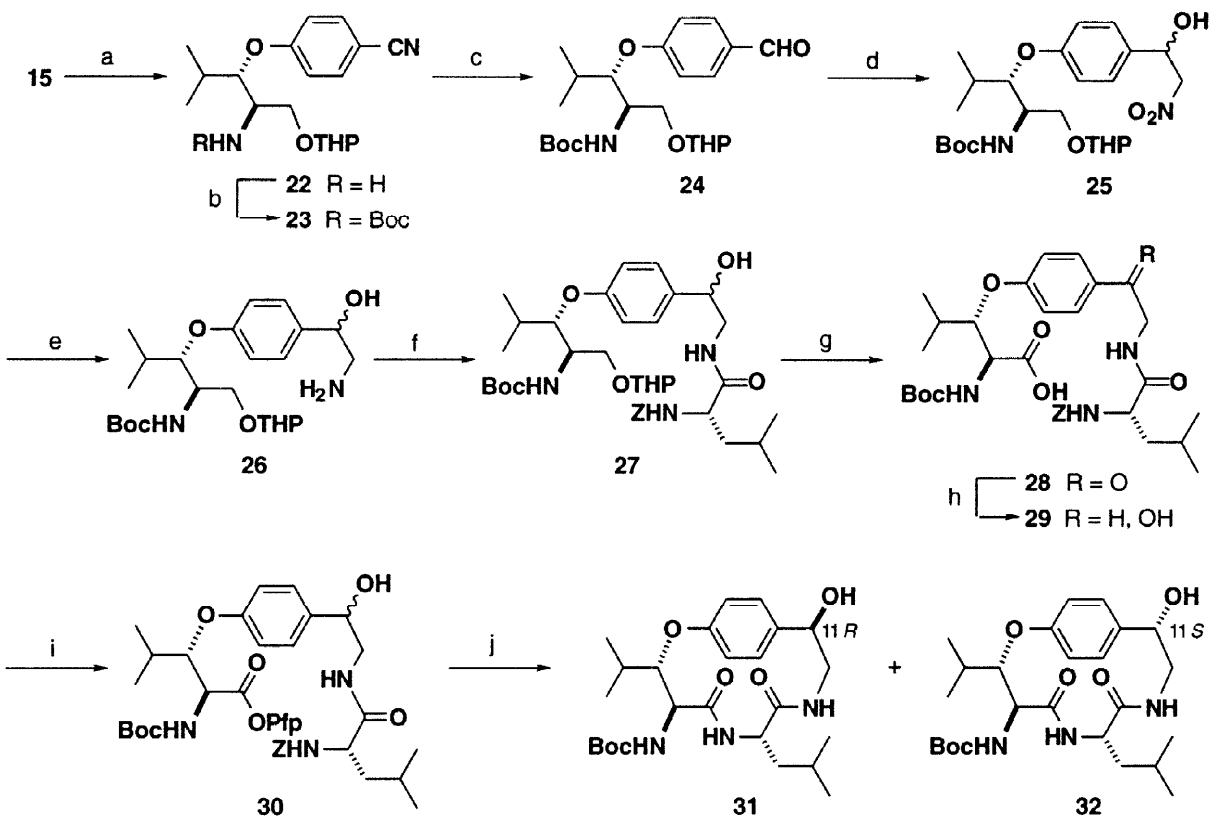
Reagents and conditions : a) BnBr, $NaHCO_3$, NaI, THF:DMSO (4:1), reflux, 92%; b) 3,4-Dihydro-2*H*-pyran, PPTS, CH_2Cl_2, 93%; c) $NaBH_4$, LiCl, THF, EtOH, 91%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 95%; e) *i*-PrMgCl, THF, Et_2O, -78 °C, 82%; f) 10% Pd/C, NH_4CO_2H, MeOH, reflux, quant.

The amino group was protected as its dibenzyl derivative with benzyl bromide.[39] The primary alcohol in **17**[38] was then masked as a THP ether[35] and the ester in **18** was subsequently converted into the aldehyde via a two-step procedure (**Scheme 4**). First, the ester was reduced to the alcohol **19** with sodium borohydride in the presence of lithium chloride. This alcohol was then oxidized to the aldehyde under Swern conditions[40] using oxalyl chloride and DMSO to give **20**. Treatment of **20** with isopropylmagnesium chloride gave the *anti*-isomer

21 with excellent diastereoselectivity (> 95%) in good agreement with Zhu's observations. The benzyl groups were removed by catalytic transfer hydrogenolysis using palladium on charcoal and ammonium formate as the hydrogen source.[41] This route provided large quantities of **15**, and this material was identical in every respect to that prepared by the route shown in **Scheme 3**.

The next step of the synthesis involved the formation of the alkyl-aryl ether linkage. We,[33] and others[42,43] had reported previously the use of 4-fluorobenzonitrile as an effective reagent for the arylation of alcohols. Using this reagent, reaction occurred exclusively at the hydroxyl position of **15**, even in the presence of excess sodium hydride, to give **22** in excellent yield. The reaction proceeded at room temperature and, after several solvents were examined (toluene, THF, DMF), the optimum solvent was found to be DMSO. The amino group in **22** was then protected as its Boc-derivative to provide **23** (**Scheme 5**).

Scheme 5



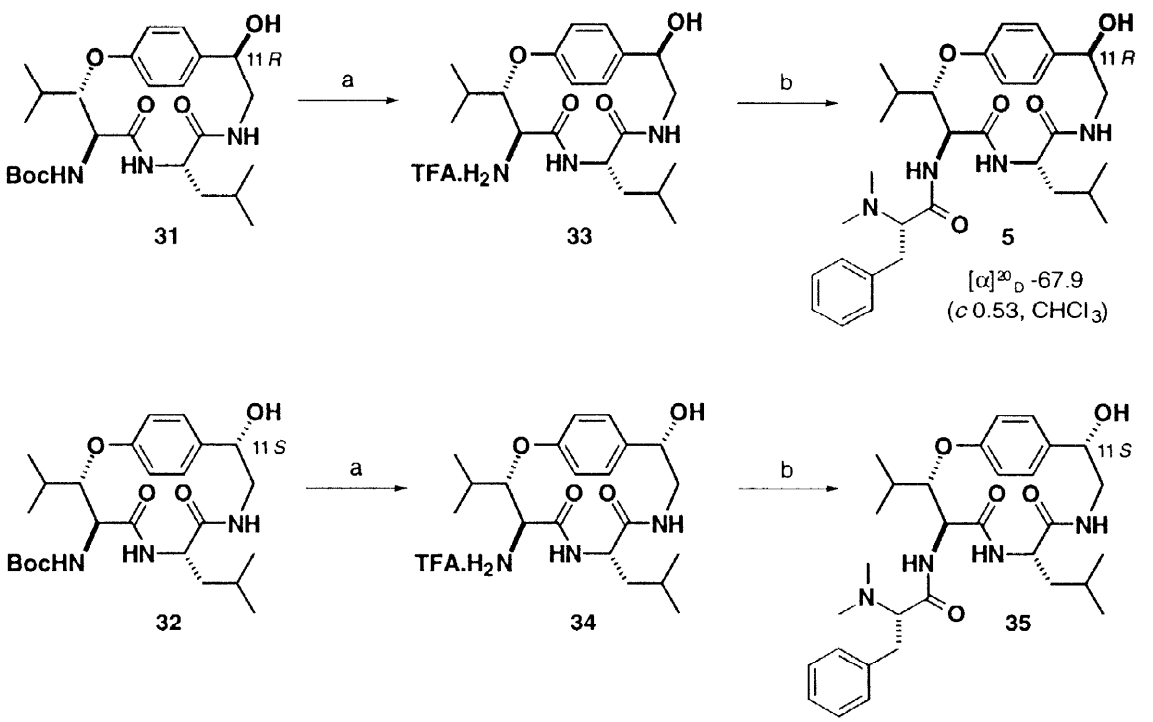
Reagents and Conditions : a) 4-Fluorobenzonitrile, NaH, DMSO, 85%; b) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 92%; c) Raney Ni, $NaH_2PO_2.H_2O$, pyridine:AcOH:H_2O (2:1:1), 93%; d) CH_3NO_2, NaOMe, 0 °C, 96% (based on recovered starting material); e) 10% Pd/C, NH_4CO_2H, MeOH, 94%; f) *N*-Z-Leucine, BOP, DIPEA, CH_2Cl_2, 0 °C to rt, 81%; g) Jones reagent, acetone, 83%; h) $NaBH_4$, LiCl, THF, EtOH, 97%; i) Pentafluorophenol, EDAC, DMAP (cat.), 97%; j) Pd black, γ-terpinene, 1,4-dioxane, *t*-BuOH, 4-pyrrolidinopyridine, reflux, 49%.

The cyano group in **23** was reduced to the aldehyde using Raney nickel and sodium hypophosphite hydrate in a buffered pyridine, water and acetic acid mixture to give **24**.[44] The aldehyde was then treated with the anion of nitromethane under Henry conditions[45] to provide **25** in excellent yield after recovery of starting material. In contrast with our previous studies on the synthesis of nummularine F, we found that protection of the secondary alcohol resulting from the Henry reaction was not necessary for the subsequent steps. The nitro

group was reduced using palladium on charcoal and ammonium formate[46] and the resulting amine **26** was coupled with *N*-Z-leucine using benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and diisopropylethylamine (DIPEA) to give **27**. Treatment of **27** with Jones reagent removed the THP group and oxidized the resulting primary alcohol to the acid **28**. The benzylic alcohol was also oxidized to the ketone in this reaction and so it was reduced back to the alcohol selectively using sodium borohydride and lithium chloride to provide **29**. The acid was activated as a pentafluorophenyl ester **30** by treament of **29** with pentafluorophenol, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of 4-dimethylaminopyridine (DMAP). The ester **30** was not purified for the cyclization because it was found to decompose on silica.

The cyclization was effected using a modification of the macrolactamization protocol developed by Schmidt.[12] The pentafluorophenyl ester **30** was added slowly via a syringe pump to a refluxing suspension of palladium black in 1,4-dioxane containing *t*-BuOH, γ-terpinene (as the hydrogen source) and 4-pyrrolidinopyridine. These conditions gave a reproducible yield (40-50%) of the cyclized product as a mixture of diastereomers **31** and **32** in a 1.2:1—1.3:1 ratio. The isomers could be separated by chromatography on silica.[47]

Scheme 6



Reagents and Conditions : a) 25% TFA/CH_2Cl_2, 0 °C to rt, 83% for **33**, 87% for **34**; b) *N,N*-Dimethylphenylalanine, BOP, DIPEA, CH_2Cl_2, 0 °C to rt, 64% for **5**, 53% for **35**.

The configuration of the hydroxyl groups in **31** and **32** was determined by installation of the basic amino acid side chain and comparing the two products with the reported data for **5**. Deprotection of the Boc-group was achieved using 25% trifluoroacetic acid (TFA) in dichloromethane at 0 °C to room temperature to give **33** and **34** (**Scheme 6**). The *N,N*-dimethylphenylalanine side chain was subsequently introduced using the BOP

reagent and DIPEA as the base. Isomer **33** gave **5**, which was identical to the natural sample reported by Han.[30] Isomer **34** gave the C-11 epimer of the natural product.

CONCLUSION

We have demonstrated an efficient new synthesis (18 steps, overall yield = 6.6%) of the naturally-occurring cyclopeptide alkaloid sanjoinine G1 (**5**). In addition, we have also prepared its C-11 epimer **35**. The key steps in this synthesis were the formation of the alkyl-aryl ether linkage via an S_NAr reaction of the amino-alcohol **15** with 4-fluorobenzonitrile and the macrolactamization of the acyclic precursor **30** using a modification of Schmidt's procedure.

ACKNOWLEDGMENTS

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EXPERIMENTAL PROCEDURES

General Procedures All solvents were reagent grade and were distilled before use. Petroleum ether refers to the boiling point fraction 40-60 °C. Melting points (in degrees centigrade) were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic reasonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AMX-500 spectrometer operating at 500 MHz for ^{1}H; 125 MHz for ^{13}C. Chemical shifts are in parts per million (ppm) relative to the residual solvent as the internal reference. Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281-B spectrometer. Absorptions are reported as strong (s), medium (m) or weak (w) bands in wavenumbers (cm^{-1}). Optical rotations (in degrees) were measured with a Perkin-Elmer Model 241 polarimeter. High-resolution mass spectra (HRMS) were obtained on the following mass spectrometers: a VG ZAB-E for chemical ionization (CI) or a micromass AutoSpec for electrospray ionization (ESI). Elemental Analyses were performed on a Perkin Elmer 2400 Series II CHNS/O Analyzer at the University of Pennsylvania. Analytical thin-layer chromatography (TLC) was performed on Merck silicagel 60 F_{254} plates (0.25 mm) precoated with a fluorescent indicator. Preparative TLC was performed on Merck silicagel 60 F_{254} plates (0.5 mm) precoated with a fluorescent indicator. Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in absolute ethanol containing 2% acetic acid or phosphomolybdic acid hydrate (7% w/v) in 95% ethanol. Flash column chromatography was carried out on E. Merck silicagel 60 (240-400 mesh) using the solvent systems listed under individual experiments.

The preparation of compounds **6**, **11**, **12**, **13** and **16** has been reported previously.[33]

[2*R*, 1*R*]-[2-(Hydroxy-1-hydroxymethyl-3-methylbutyl]carbamic acid *tert*-butyl ester (8). Boron trifluoride-acetic acid (17.0 mL, 122 mmol) was added to a solution of **6** (2.23 g, 8.16 mmol) in methanol (71 mL) at 0 °C under argon. The reaction was stirred for 2.5 h at 0 °C and then quenched by the slow addition of $NaHCO_3$. The resulting suspension was stirred for 20 min at rt and then filtered through Celite. The solids were washed with additional methanol (2 x 20 mL) and then chloroform (3 x 10 mL). The solvent was removed under reduced pressure and the crude residue was purified by chromatography on silica to give **8** as a colorless oil (1.87 g, 98%): R_f 0.42 (ethyl acetate:petroleum ether 50:50); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6, 3H), 0.97 (d, J = 6.6, 3H), 1.41 (s, 9H), 1.71 (m, 1H), 2.87-3.05 (br s, 2H), 3.46 (m, 1H), 3.75 (br s, 2H), 5.23 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 19.0, 28.3, 31.0, 52.1, 65.6, 78.0, 79.9, 156.9; IR (film) 3396 (m), 2963 (m), 1686 (s), 1508 (m) cm^{-1}; HRMS (CI) calcd for $C_{11}H_{24}NO_4$ (M + H): *m/z* 234.1705, found 234.1701; $[\alpha]^{20}_D$ -8.1 (*c* 1.30, $CHCl_3$).

[1*R*, 2*R*]-[1-(*tert*-Butyldimethylsilanyloxymethyl)-2-hydroxy-3-methylbutyl]carbamic acid *tert*-butyl ester (9). To a solution of compound **8** (2.30 g, 9.86 mmol) in dichloromethane (25 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (1.52 g, 10.0 mmol), 4-dimethylaminopyridine (48 mg, 0.394 mmol) and triethylamine (3.80 mL, 21.7 mmol). This solution was stirred for 2.5 h at 0 °C and then warmed to rt where it was stirred for an additional 1 h. After this time, the reaction was diluted with ethyl acetate (25 mL) and quenched with sat. NH_4Cl (25 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with sat. NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide a crude oil. This oil was purified by column chromatography, eluting with an ethyl acetate:petroleum ether gradient (10:90 - 30:70) to afford **9** (2.64 g, 77%) as a colorless oil: R_f 0.42 (ethyl acetate:petroleum ether 50:50); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.86 (d, J = 6.6, 3H), 0.97 (d, J = 6.6, 3H), 1.41 (s, 9H), 1.69 (m, 1H), 3.40 (br s, 1H), 3.49 (m, 1H), 3.68 (m, 1H), 3.75 (dd, J = 10.2 3.2, 1H), 3.90 (dd, J = 10.2 2.2, 1H), 5.16 (d, J = 8.4, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.7, 18.1, 18.8, 18.9, 25.7, 28.3, 30.7, 51.2, 66.6, 78.8, 79.9, 155.8; IR ($CHCl_3$) 3444 (m), 2956 (s), 1716 (s), 1693 (s), 1502 (m) cm^{-1}; HRMS (CI) calcd for $C_{17}H_{38}O_4NSi$ (M + H): *m/z* 348.2570, found 348.2581; $[\alpha]^{20}_D$ -23.6 (*c* 1.50, $CHCl_3$).

4-[[1*S*, 2*R*]-2-*tert*-Butoxycarbonylamino-3-(*tert*-butyldimethylsilanyloxy)-1-isopropylpropoxy]benzoic acid methyl ester (10). To a solution of compound **9** (0.670 g, 1.93 mmol), triphenylphosphine (1.01 g, 3.86 mmol) and methyl 4-hydroxybenzoate (0.730 g, 4.83 mmol) in THF (3 mL) at 0 °C , was added a solution of the diethyl azodicarboxylate (0.61 mL, 3.86 mmol) in THF (3 mL) over 3 h. After the addition was complete, the reaction was allowed to warm to 25 °C and was stirred for 20 h. The mixture was then concentrated under reduced pressure to give a crude residue which was purified by column chromatography, eluting with a diethyl ether:hexanes gradient (2:98 - 10:90). Pure **10** was obtained as a colorless oil (0.420 g, 45%) which crystallized upon cooling: mp 76-78 °C; R_f 0.25 (diethyl ether:hexanes 30:70); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.10 (s, 3H), -0.04 (s, 3H), 0.84 (s, 9H), 0.94 (d, J = 6.7, 3H), 1.00 (d, J = 6.7, 3H), 1.42 (s, 9H), 2.05 (m, 1H), 3.48 (m, 2H), 3.86 (s, 1H), 3.91 (m, 1H), 4.38 (m, 1H), 4.76 (d, J = 8.9, 1H), 6.95 (d, J = 8.6, 2H), 7.91 (d, J = 8.6, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.7, -5.4, 16.2, 18.5, 20.4, 25.9 and 25.8 (rotamers), 28.4, 29.9, 51.8, 52.8, 61.5, 79.5, 80.8, 115.2, 122.5, 136.1,

155.4, 164.0, 166.8; IR (film) 3375 (w), 2956 (m), 2856 (m), 1720 (s), 1603 (m), 1507 (m) cm^{-1}; HRMS (CI) calcd for $C_{25}H_{44}NO_6$ (M + H): *m/z* 482.2937, found 482.2930; $[\alpha]^{20}_D$ +1.0 (*c* 1.01, $CHCl_3$).

[4*R*, 5*S*]-5-Isopropyl-4-(tetrahydropyran-2-yloxymethyl)oxazolidin-2-one (14). PPTS (0.133 g, 0.53 mmol) was added to a solution of **12** (0.830 g, 5.28 mmol) in dichloromethane (25 mL) containing 3,4-dihydro-2*H*-pyran (1.33 g, 15.8 mmol) at rt under argon. The mixture was stirred for 4 h and then diluted with ethyl acetate (50 mL) and washed with sat. NaCl (10 mL). After the organic layer was separated, dried over Na_2SO_4, and filtered, the solvent was removed under reduced pressure to yield a white solid. This solid was purified by chromatography on silica eluting with an ethyl acetate/petroleum ether gradient (20:80 - 100) to give **14** (white solid) as a mixture of inseparable diastereomers (0.968 g, 75%): mp 118-121 °C; R_f 0.43 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.6), 1.07 (d, *J* = 6.4), 1.50-1.60 (m), 1.67-1.80 (m), 1.85-1.94 (m), 3.35 (m), 3.48-3.52 (m), 3.56 (m), 3.72 (m), 3.77-3.86 (m), 3.88 (m), 4.15-4.18 (m), 4.53-4.55 (m), 4.56-4.58 (m), 5.31 (br s), 5.44 (br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.71, 19.16, 19.33, 19.57, 19.61, 25.10, 25.15, 27.42, 27.46, 30.31, 54.83, 54.87, 62.31, 62.55, 65.91, 65.96, 84.15, 99.21, 99.69, 159.42, 159.50; IR (film) 3296 (s), 2951 (s), 2922 (s), 2869 (s), 2854 (m), 1742 (s), 1708 (s) cm^{-1}; HRMS (CI) calcd for $C_{12}H_{25}N_2O_4$ (M + NH_4): *m/z* 261.1814, found 261.1817; $[\alpha]^{20}_D$ + 71.5 (*c* 1.01, $CHCl_3$); Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.96; H, 8.55; N, 5.41.

[2*R*]-Dibenzylamino-3-hydroxypropionic acid methyl ester (17).[38] Sodium bicarbonate (14.0 g, 0.17 mol) and sodium iodide (3.66 g, 0.024 mol) were added to a suspension of **16** (7.60 g, 0.049 mol) in a mixture of DMSO (40 mL) and THF (160 mL). Benzyl bromide (13.9 mL, 0.12 mol) was introduced slowly and the mixture was warmed to reflux where it was maintained for 2 h. The suspension was cooled to rt and diluted with ethyl acetate (200 mL) and H_2O (50 mL). The aqueous phase was removed and the organic layer was washed with additional H_2O (3 x 50 mL), sat. NaCl (50 mL), then dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to reveal a pale yellow oil which was purified by chromatography on silica eluting with an acetone:hexanes gradient (2:98 - 20:80). The title compound **17** was isolated as a colorless oil (13.5 g, 92%): R_f 0.32 (acetone:hexanes 20:80); ^1H NMR (500 MHz, $CDCl_3$) δ 2.49 (br s, 1H), 3.56 (t, *J* = 7.5, 1H), 3.67, 3.90 (AB q, *J* = 13.5, 4H), 3.74-3.76 (m, 2H), 3.78 (s, 3H), 7.23-7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.4, 54.8, 59.4, 61.8, 127.4, 128.5, 129.0, 138.7, 171.7; IR (film) 3447 (s), 3084 (w), 3062 (m), 3029 (m), 2951 (m), 2871 (m), 2846 (m), 1732 (s), 1603 (w), 1494 (m), 1453 (m) cm^{-1}; HRMS (CI) calcd for $C_{18}H_{22}NO_3$ (M + H): *m/z* 300.1599, found 300.1615; $[\alpha]^{20}_D$ + 109.6 (*c* 1.13, MeOH); lit[38] $[\alpha]_D$ + 138 (c 1.2, $CHCl_3$).

[2*R*]-Dibenzylamino-3-(tetrahydropyran-2-yloxy)propionic acid methyl ester (18). PPTS (2.27 g, 9.03 mmol) was added to a solution of **17** (13.5 g, 0.045 mol) and 3,4-dihydro-2*H*-pyran (7.02 g, 83.5 mmol) in dichloromethane (40 mL) at rt under argon and the reaction was stirred for 24 h. The solution was then diluted with diethyl ether (150 mL), washed with sat. NaCl (25 mL), separated, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resulting pale yellow oil was adsorbed onto silica and purified by flash chromatography, eluting with an ethyl acetate:petroleum ether gradient (5:95 - 20:80) to provide **18** (colorless oil) as a mixture of inseparable diastereomers (16.1 g, 93%): R_f 0.45 (ethyl

acetate:petroleum ether 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43-1.69 (br m), 1.71-1.80 (m), 3.41-3.47 (m), 3.63-3.70 (m), 3.71-3.78 (m), 3.74 (s) 3.75 (s), 3.79 (m), 3.88-3.94 (m), 4.11 (m), 4.51 (m), 4.57 (m), 7.19-7.22 (m), 7.26-7.29 (m), 7.36-7.39 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.86, 19.22, 25.38, 25.40, 30.43, 51.19, 55.31, 60.70, 61.09, 61.52, 62.01, 66.37, 66.60, 98.55, 98.94, 126.92, 126.97, 128.20, 128.68, 128.72, 139.58, 139.69, 171.88; IR (film) 3085 (w), 3062 (w), 3028 (m), 2946 (s), 2872 (m), 2846 (m), 1734 (s), 1602 (w), 1494 (m), 1453 (m) cm^{-1}; HRMS (CI) calcd for $C_{23}H_{30}NO_4$ (M + H): *m/z* 384.2174, found 384.2162; $[\alpha]^{20}_D$ + 57.0 (*c* 1.31, $CHCl_3$); Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.77; H, 7.76; N, 3.53.

[2*S*]-Dibenzylamino-3-(tetrahydropyran-2-yloxy)propan-1-ol (19). Lithium chloride (10.4 g, 0.245 mol) and sodium borohydride (9.30 g, 0.246 mol) were added to a solution of **18** (11.8 g, 30.8 mmol) in a mixture of THF (400 mL) and EtOH (400 mL) at rt under argon and the resulting suspension was stirred for 20 h. The mixture was subsequently filtered and the collected solid was washed with additional EtOH (3 x 50 mL). After removing the solvent from the filtrate under reduced pressure, the white residue that remained was partitioned between ethyl acetate (200 mL) and sat. NaCl (50 mL). The organic layer was separated and the aqueous phase was extracted with additional ethyl acetate (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed to give a pale yellow oil. This oil was purified by flash chromatography on silica, eluting with an ethyl acetate:petroleum ether gradient (2:98 - 30:70) to give **19** as a colorless oil (13.7 g, 91%): R_f 0.28 (ethyl acetate:petroleum ether 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54-1.64 (br m), 1.71-1.75 (m), 1.78-1.92 (m), 2.89 (br s), 3.08-3.13 (m), 3.42 (m), 3.51-3.64 (m), 3.81-3.90 (m), 4.05 (m), 4.58 (m), 7.20-7.25 (m), 7.29-7.45 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.37, 25.39, 25.43, 30.66, 54.07, 54.12, 58.07, 58.23, 59.68, 59.73, 62.22, 62.29, 64.81, 65.10, 98.94, 99.33, 127.14, 128.42, 128.97, 139.50; IR (film) 3454 (m), 3088 (w), 3061 (m), 3027 (m), 2941 (s), 2870 (s), 2845 (m), 1602 (w), 1494 (m), 1453 (m) cm^{-1}; HRMS (CI) calcd for $C_{22}H_{30}NO_3$ (M + H): *m/z* 356.2225, found 356.2223; $[\alpha]^{20}_D$ -71.0 (*c* 0.96, $CHCl_3$).

[2*R*]-Dibenzylamino-3-(tetrahydropyran-2-yloxy)propionaldehyde (20). DMSO (1.54 mL, 21.7 mmol) in dichloromethane (5 mL) was added dropwise to a solution of oxalyl chloride (0.94 mL, 10.8 mmol) in dichloromethane (25 mL) at -78 °C under argon. The mixture was stirred for 5 min before **19** (3.50 g, 9.85 mmol) in dichloromethane (10 mL) was introduced over 5 min. After stirring this mixture for 30 min, triethylamine (6.86 mL, 49.2 mmol) was added and the resulting cloudy suspension was left for a further 15 min at -78 °C. The reaction was then warmed to rt and washed with 0.1N HCl (5 mL), sat. Na_2CO_3 (5 mL) and sat. NaCl (5 mL). The organic layer was separated, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford **20** as a pale yellow oil (3.31 g, 95%), which was used crude for the next step: R_f 0.22 (ethyl acetate:petroleum ether 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52-1.63 (m), 1.68-1.76 (m), 1.77-1.84 (m), 3.49-3.57 (m), 3.75-3.90 (m), 4.16-4.23 (m), 4.61 (m), 4.64 (m), 7.22-7.25 (m), 7.29-7.32 (m), 7.39-7.41 (m), 9.71 (s), 9.72 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.18, 19.29, 25.37, 25.40, 30.54, 55.63, 55.67, 61.98, 62.18, 63.57, 66.31, 66.34, 99.10, 99.28, 127.22, 127.25, 128.35, 128.81, 128.84, 139.24, 139.30, 202.30, 202.51; IR (film) 3089 (w), 3062 (m), 3028 (m), 2867 (s), 2850 (s), 2806 (s), 2942 (s), 1729

(s), 1602 (w), 1494 (m), 1453 (s) cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{28}NO_3$ (M + H): *m/z* 354.2069, found 354.2069; $[\alpha]^{20}_D$ + 12.8 (*c* 1.00, $CHCl_3$).

[2*R*, 3*S*]-2-Dibenzylamino-4-methyl-1-(tetrahydropyran-2-yloxy)pentan-3-ol (21). Aldehyde **20** (3.31 g, 9.36 mmol) in diethyl ether (28 mL) was added dropwise to isopropylmagnesium chloride (23.4 mL of a 2M solution in THF, 46.8 mmol) in diethyl ether (28 ml) at -78 °C under argon. The mixture was stirred for 1 h at -78 °C and then warmed to 0 °C where it was quenched by the slow addition of sat. NH_4Cl (10 mL). The two phase mixture was diluted with diethyl ether (50 mL) and the organic phase was separated. The aqueous layer was extracted with additional diethyl ether (3 x 20 mL) and the combined organic extracts were washed with sat. NaCl (10 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to afford a pale yellow oil. The oil was purified by flash chromatography on silica, eluting with an acetone:hexanes gradient (5:95 - 30:70) to give **21** as a colorless oil which partially crystallized on cooling (3.04 g, 82%): R_f 0.34 (acetone:hexanes 20:80); ^1H NMR (500 MHz, $CDCl_3$) δ 0.44 (d, *J* = 6.7), 0.52 (d, *J* = 6.7), 0.87 (d, *J* = 7.0), 0.91 (d, *J* = 7.0), 1.54-1.60 (br m), 1.71-1.81 (m), 2.04-2.10 (m), 2.12-2.18 (m), 2.46 (br s), 2.76-2.79 (m), 2.82-2.86 (m), 3.52-3.90 (m), 4.12-4.18 (m), 4.57-4.59 (m), 4.61-4.62 (m), 7.19-7.45 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.47, 15.17, 19.50, 20.00, 20.38, 20.64, 25.27, 25.33, 28.98, 29.79, 30.65, 30.89, 55.11, 55.26, 57.66, 58.03, 62.55, 63.25, 65.22, 65.39, 75.41, 99.35, 100.01, 126.88, 128.15, 128.17, 128.99, 129.09, 140.11; IR (film) 3472 (m), 3085 (w), 3062 (w), 3027 (m), 2950 (s), 2870 (s), 2846 (m), 1602 (w), 1494 (m), 1454 (m) cm^{-1}; HRMS (CI) calcd for $C_{25}H_{36}NO_3$ (M + H): *m/z* 398.2695, found 398.2699; $[\alpha]^{20}_D$ -64.8 (*c* 1.05, $CHCl_3$).

[2*R*, 3*S*]-2-Amino-4-methyl-1-(tetrahydropyran-2-yloxy)pentan-3-ol (15). Method 1: Potassium hydroxide (0.750 g, 13.4 mmol) was added to a suspension of **14** (0.542 g, 2.23 mmol) in methanol (3.60 mL) and H_2O (0.90 mL) causing complete dissolution. The mixture was then warmed to reflux where it was maintained for 20 h. The solution was cooled to rt and the solvent was removed under reduced pressure. Chloroform (10 mL) was added and the resulting suspension was filtered through a bed of Celite. The solids were washed with additional chloroform (4 x 10 mL) and the solvent was removed from the filtrate under reduced pressure to yield a colorless oil (0.484 g, 100%). Method 2: Ammonium formate (5.23 g, 0.083 mol) was added to a suspension of 10% palladium on charcoal (1.00 g) and **21** (3.30 g, 8.30 mmol) in methanol (60 mL) at rt under argon. The mixture was heated to reflux where it was maintained for 1 h. The suspension was then cooled back to rt, filtered through Celite and the solids were washed with additional methanol (3 x 25 mL) and chloroform (3 x 25 mL). The solvent was removed from the filtrate under reduced pressure and dissolved in a solution of methanol:dichloromethane (10:90). This solution was filtered through a short silica column eluting with additional methanol:dichloromethane containing 1% NH_4OH. The solvent was then removed under reduced pressure to give **15** as a oil which was used without further purification (1.80 g, 100%): R_f 0.17 (methanol:dichloromethane 10:90 containing 1% NH_4OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.6), 0.90 (d, *J* = 6.6), 0.96 (d, *J* = 6.6), 0.97 (d, *J* = 6.6), 1.48-1.58 (m), 1.68-1.79 (m), 1.98 (br s), 3.03-3.06 (m), 3.09-3.12 (m), 3.16-3.20 (m), 3.38 (m), 3.46-3.51 (m), 3.54 (m), 3.80-3.85 (m), 3.81 (m), 3.88 (m), 4.53-4.55 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.07, 18.48, 19.00, 19.21, 19.61, 19.78, 25.22, 25.26, 30.12, 30.15, 30.55, 30.60, 51.98, 52.05, 62.54, 62.81, 68.95, 69.04, 78.72, 78.79, 99.37, 99.63; IR (film)

3364 (s), 2954 (s), 2870 (s) 1585 (m), 1467 (m) cm^{-1}; HRMS (CI) calcd for $C_{11}H_{24}NO_3$ (M + H): *m/z* 218.1756, found 218.1755; $[\alpha]^{20}_D$ +2.5 (*c* 1.45, $CHCl_3$).

4-[[1*S*, 2*R*]-2-Amino-1-isopropyl-3-(tetrahydropyran-2-yloxy)propoxy]benzonitrile (22). Sodium hydride (0.380 g, 9.45 mmol as a 60% suspension in oil) was added to a solution of **15** (1.03 g, 4.74 mmol) and 4-fluorobenzonitrile (0.860 g, 7.11 mmol) in DMSO (15 mL) at rt under argon. The resulting yellow suspension was stirred for 5 h at rt and then diluted with ethyl acetate (50 mL). The organic layer was washed with water (3 x 20 mL), sat. NaCl (20 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give a pale yellow oil which was purified by chromatography on silica eluting with a methanol:dichloromethane gradient (5:95 - 10:90) to give **22** as a colorless oil (1.28 g, 85%): R_f 0.29 (methanol:dichloromethane 5:95); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.9), 0.94 (d, *J* = 6.7), 0.95 (d, *J* = 6.8), 1.38 (br s), 1.41-1.79 (br m), 2.12-2.20 (m), 3.18 (m), 3.28 (m), 3.34-3.38 (m), 3.41-3.47 (m), 3.46 (m), 3.51 (m), 3.64 (m), 3.80 (m), 3.85 (m), 4.25 (m), 4.31 (m), 4.55 (m), 6.98-7.02 (m), 7.49-7.52 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.63, 16.75, 19.32, 19.65, 19.90, 19.97, 25.23, 29.62, 29.68, 30.43, 30.54, 52.41, 52.53, 61.98, 62.60, 69.20, 69.24, 83.93, 84.07, 99.04, 99.44, 103.50, 116.11, 116.22, 119.20, 133.92, 133.95, 163.46, 163.50; IR (film) 3384 (w), 3310 (w), 2952 (m), 2940 (m), 2874 (m), 2223 (m), 1654 (w), 1603 (s), 1570 (w), 1506 (s), 1466 (w) cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{27}N_2O_3$ (M + H): *m/z* 319.2022, found 319.2021; $[\alpha]^{20}_D$ -0.5 (*c* 1.00, $CHCl_3$).

[[1*R*, 2*S*]-2-(4-Cyanophenoxy)-3-methyl-1-(tetrahydropyran-2-yloxymethyl)butyl]carbamic acid *tert*-butyl ester (23). Triethylamine (0.93 mL, 6.71 mmol) followed by di-*tert*-butyl dicarbonate (0.730 g, 3.35 mmol) was added to a solution of **22** (0.890 g, 2.80 mmol) in dichloromethane (35 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then warmed to rt where it was maintained for 16 h. After this time, the solution was diluted with diethyl ether (100 mL) and washed with 5% $KHSO_4$ (20 mL), 5% $NaHCO_3$ (20 mL), 10% citric acid (20 mL) and sat. NaCl (20 mL). The organic layer was separated, dried over $NaSO_4$, filtered, and the solvent removed under reduced pressure to give a crude oil. This oil was purified by chromatography on silica eluting with ethyl acetate:petroleum ether (20:80) to give **23** as a colorless sticky foam (1.08 g, 92%): R_f 0.23 (ethyl acetate:petroleum ether 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 7.1), 0.95 (d, *J* = 7.0), 0.97 (d, *J* = 6.8), 0.98 (d, *J* = 6.8) 1.34-1.55 (br m), 1.40 (s), 1.41 (s), 1.63-1.66 (br m), 1.73-1.76 (br m), 2.00-2.06 (m), 3.31-3.33 (br m), 3.38-3.40 (br m), 3.42-3.53 (br m), 3.78-3.82 (br m), 4.02-4.10 (br m), 4.19 (br m), 4.41-4.47 (m), 4.54 (br m), 4.84 (d, *J* = 8.4), 4.99 (d, *J* = 8.8), 6.95-7.00 (m), 7.50-7.52 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.85, 17.72, 19.07, 19.66, 19.83, 20.03, 25.16, 25.21, 28.33, 29.70, 30.06, 30.28, 30.53, 51.25, 51.48, 61.74, 62.98, 65.62, 66.62, 79.56, 79.63, 81.60, 82.07, 98.83, 99.71, 103.59, 103.63, 116.09, 116.18, 119.18, 133.89, 133.92, 155.37, 163.37, 163.41; IR (film) 3348 (w), 3354 (w), 2964 (m), 2937 (m), 2876 (w), 2224 (m), 1712 (s), 1604 (s), 1572 (w), 1505 (s) cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{34}N_2O_5Na$ (M + Na): *m/z* 441.2365, found 441.2371; $[\alpha]^{20}_D$ +14.0 (*c* 0.25, $CHCl_3$).

[[1*R*, 2*S*]-2-(4-Formylphenoxy)-3-methyl-1-(tetrahydropyran-2-yloxymethyl)butyl]carbamic acid *tert*-butyl ester (24). Raney nickel W-2 activity (~2 g) as a suspension in H_2O (2 mL) was added to a

solution of **23** (2.00 g, 4.78 mmol) in a mixture of pyridine:acetic acid:H_2O (36 mL:18 mL:18 mL) containing sodium hypophosphite hydrate (4.05 g, 38.2 mmol) at 0 °C under argon. The suspension was stirred for 15 min at 0 °C and then warmed to 40 °C where it was maintained for 2 h. The reaction mixture was then cooled to rt and filtered through a bed of Celite. The solids were washed with methanol (4 x 50 mL) and the solvent was removed from the filtrate under reduced pressure. The resulting residue was partitioned between ethyl acetate (50 mL) and sat. $NaHCO_3$ and the organic layer was removed. The aqueous phase was extracted with additional ethyl acetate (2 x 50 mL) and then the combined organic layers were washed with 10% citric acid (25 mL), 5% $NaHCO_3$ (25 mL) and sat. NaCl (25 mL), dried over Na_2SO_4, and filtered. After removal of the solvent under reduced pressure, the resulting oil was purified by chromatography on silica, eluting with an ethyl acetate:petroleum ether gradient (30:70 - 50:50). This gave **24** as a colorless sticky foam (1.88 g, 93%): R_f 0.38 (ethyl acetate:petroleum ether 50:50); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, J = 6.9), 0.97 (d, J = 6.9), 0.98 (d, J = 6.9), 1.00 (d, J = 6.8), 1.39 (s), 1.40 (s), 1.43-1.61 (br m), 1.63-1.76 (br m), 2.02-2.06 (m), 3.28-3.30 (br m), 3.37-3.44 (br m), 3.48-3.54 (br m), 3.76-3.83 (br m), 4.03-4.10 (br m), 4.19 (br s), 4.47-4.52 (br m), 4.55-4.56 (br m), 4.86 (d, J = 8.3), 4.99 (d, J = 8.8), 7.01-7.05 (m), 7.74-7.76 (m), 9.82 (s), 9.83 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.85, 17.75, 18.93, 19.64, 19.76, 20.02, 25.18, 25.21, 28.33, 29.76, 30.13, 30.25, 30.49, 51.28, 51.54, 61.54, 62.85, 65.64, 66.61, 79.48, 79.54, 81.52, 82.03, 98.69, 99.64, 115.64, 115.72, 129.79, 131.87, 131.91, 155.37, 165.14, 190.53; IR (film) 3364 (br m), 2962 (m), 2876 (w), 2735 (w), 1712 (s), 1703 (s), 1693 (s), 1682 (s), 1599 (s), 1574 (w), 1504 (s) cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{36}NO_6$: m/z 422.2543, found 422.2522; $[\alpha]^{20}_D$ +18.7 (c 0.79, $CHCl_3$).

[[1*R*, 2*S*]-2-[4-(1-Hydroxy-2-nitroethyl)-phenoxy)-3-methyl-1-(tetrahydropyran-2-yloxy-methyl)butyl]carbamic acid *tert*-butyl ester (25). Nitromethane (8.9 mL) was added over 10 min to a solution of sodium methoxide (generated from 0.308 g of sodium) in methanol (3.6 mL) at 0 °C under argon. The resulting white suspension was maintained at 0 °C for 15 min before a solution of **24** (1.88 g, 4.46 mmol) in nitromethane (5 mL) was introduced over 10 min. The pale yellow reaction mixture was stirred at 0 °C for 5 h and then quenched by the dropwise addition of sat. NH_4Cl (10 mL). After warming the reaction to rt, the two phase mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic extracts were washed with sat. NaCl (15 mL), separated, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to reveal a yellow foam. This foam was purified by chromatography on silica, eluting with an ethyl acetate:petroleum ether gradient (20:80 - 50:50) to give **25** (colorless sticky foam) as a mixture of four diastereomers (1.86 g, 86%; 96% based on recovered starting material) and unreacted **24** (0.19 g, 10%): R_f 0.28 (ethyl acetate:petroleum ether 30:70); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94-0.99 (m), 1.40 (s), 1.32-1.59 (m), 1.61-1.77 (m), 1.99-2.03 (m), 3.06-3.09 (m), 3.30-3.32 (br m), 3.41-3.54 (m), 3.79-3.81 (m), 3.99-4.01 (m), 4.03-4.04 (m), 4.19 (br m), 4.27-4.34 (m), 4.41-4.45 (m), 4.52-4.59 (m), 4.84 (d, J = 8.4), 4.97 (d, J = 9.0), 5.33-5.36 (m), 6.92-6.96 (m), 7.22-7.23 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.96, 17.97, 18.94, 19.65, 20.09, 25.21, 25.28, 25.30, 28.34, 29.83, 30.28, 30.46, 51.42, 51.70, 61.58, 62.64, 65.74, 66.68, 70.57, 79.41, 81.27, 81.30, 81.43, 81.48, 82.15, 98.58, 99.47, 116.00, 116.02, 116.05, 127.13, 127.18, 127.24, 130.27, 155.41, 155.46, 160.56; IR (film) 3402 (m), 2964 (m), 2942 (m), 2877 (w), 1700 (s), 1609 (m), 1584 (w), 1556 (s), 1509 (s) cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{39}N_2O_8$ (M + H): m/z 483.2706, found 483.2716; $[\alpha]^{20}_D$ +17.7 (c 0.87, $CHCl_3$).

[[1*R*, 2*S*]-2-[4-(2-Amino-1-hydroxyethyl)-phenoxy)-3-methyl-1-(tetrahydropyran-2-yloxy-methyl)-butyl]carbamic acid *tert*-butyl ester (26). Ammonium formate (0.743 g, 11.8 mmol) was added to a suspension of **25** (1.06 g, 2.20 mmol) in methanol (15 mL) containing 10% palladium on charcoal (0.280 g) at 0 °C under argon. The mixture was held at 0 °C for 15 min and then warmed to rt where it was maintained for 4 h. The suspension was filtered through a bed of Celite and the solids were washed with additional methanol (5 x 15 mL). After the solvent was removed from the filtrate under reduced pressure the resulting residue was partitioned between 50% NaCl (10 mL) and ethyl acetate (20 mL). The organic phase was separated, the solvent was removed under reduced pressure and the product was purified by chromatography on silica eluting with methanol:dichloromethane (10:90) containing 1% NH_4OH to give **26** as a colorless foam (0.940 g, 94%): mp 63-66 °C; R_f 0.10 (methanol:dichloromethane 10:90 containing 1% NH_4OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.95-1.00 (m), 1.41 (s), 1.45-1.52 (m), 1.56-1.72 (m), 2.00-2.02 (m), 2.90-2.92 (br m), 3.02-3.04 (br m), 3.30 (br m), 3.39-3.43 (m), 3.50-3.54 (m), 3.79-3.82 (m), 3.86-4.05 (br m), 4.17 (br s), 4.29-4.31 (m), 4.57 (br s), 4.72-4.74 (m), 4.85 (d, J = 8.7), 4.96 (d, J = 9.3), 6.87-6.91 (m), 7.19-7.21 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.92, 17.91, 18.88, 19.65, 19.71, 20.15, 25.22, 25.28, 28.35, 29.79, 30.27, 30.44, 48.23, 51.41, 51.72, 61.43, 62.58, 65.80, 66.74, 72.44, 79.25, 81.38, 81.42, 82.03, 98.44, 98.85, 99.43, 115.62, 127.00, 133.73, 155.35, 155.41, 159.65, 159.75; IR (film) 3344 (m), 2962 (s), 2928 (s), 2877 (m), 1708 (s), 1608 (w), 1584 (w), 1509 (s) cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{41}N_2O_6$ (M + H): m/z 453.2965, found 453.2948; $[\alpha]^{20}_D$ -0.6 (c 0.63, $CHCl_3$).

[[1*R*, 2*S*]-2-{4-[2-(2*S*-Benzyloxycarbonylamino-4-methylpentanoylamino)-1-hydroxyethyl]-phenoxy}-3-methyl-1-(tetrahydropyran-2-yloxymethyl)butyl]carbamic acid *tert*-butyl ester (27). To a solution of **26** (0.821 g, 1.81 mmol) and *N*-Z-leucine (0.577 g, 2.18 mmol) in dichloromethane (20 mL) at 0 °C under argon was added BOP (0.963 g, 2.18 mmol), followed by the dropwise addition of diisopropylethylamine (0.63 mL, 3.63 mmol). The mixture was stirred for 30 min at 0 °C and then warmed to rt where it was left for 4 h. The solution was diluted with ethyl acetate (50 mL) and washed with sat. NaCl (25 mL). The organic layer was separated and the aqueous phase was extracted with additional ethyl acetate (2 x 25 mL). The organic layers were then combined and washed with 10% citric acid (15 mL), 5% $NaHCO_3$ (15 mL), sat. NaCl (15 mL), dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the oil that remained was adsorbed onto silica and purified by chromatography eluting with an ethyl acetate:petroleum ether gradient (30:70 - 50:50). This operation gave **27** (colorless foam) as an inseparable mixture of eight diastereomers (1.03 g, 81%): mp 71-75 °C; R_f 0.16 (ethyl acetate:petroleum ether 50:50); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91-1.01 (m), 1.42 (s), 1.45-1.59 (br m), 1.64-1.73 (br m), 1.98-2.05 (m), 2.79 (br s), 3.15-3.32 (br m), 3.41-3.45 (br m), 3.50-3.55 (br m), 3.63 (br m), 3.77-3.83 (m), 4.01-4.19 (m), 4.31 (m), 4.58 (m), 4.71 (br s), 4.81 (d, J = 9.1), 4.94 (d, J = 9.2), 5.06-5.11 (m), 5.09 (s), 6.40 (br s), 6.89-6.92 (m), 7.18-7.20 (m), 7.29-7.34 (m); ^{13}C NMR (125 MHz, CD_3OD) δ 16.88, 17.07, 19.86, 20.32, 20.52, 21.90, 23.44, 25.86, 26.52, 28.79, 31.03, 31.19, 31.39, 31.58, 42.18, 42.22, 47.95, 47.97, 53.23, 53.69, 55.05, 62.40, 63.17, 67.72, 67.85, 67.92, 72.90, 73.04, 80.20, 81.59, 81.65, 81.87, 99.78, 100.49, 116.55, 128.40, 128.45, 128.84, 129.03, 129.48, 135.90, 135.95, 138.14, 157.83, 158.44, 160.90, 161.01, 175.58, 175.65; IR (film) 3414 (m), 3321 (m), 3064 (w), 3034 (w), 2959 (s), 2873 (m), 1707 (s), 1702 (s), 1697 (s), 1609

(w), 1538 (m), 1522 (m), 1509 (s) cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{57}N_3O_9Na$ (M + Na): *m/z* 722.3993, found 722.3993; $[\alpha]^{20}_D$ -10.2 (*c* 0.53, $CHCl_3$); Anal. Calcd for $C_{28}H_{57}N_3O_9$: C, 65.21; H, 8.21; N, 6.00. Found: C, 65.21; H, 8.32; N, 5.83.

[2*R*, 3*S*]-3-{4-[(2*S*-Benzyloxycarbonylamino-4-methyl-pentanoylamino)acetyl]phenoxy}-2-*tert*-butoxycarbonylamino-4-methylpentanoic acid (28). Jones reagent (2.0 mL) was added dropwise to a solution of **27** (0.300 g, 0.429 mmol) in acetone (20 mL) at 0 °C under argon. The mixture was stirred for 15 min at 0 °C and then warmed to rt where it was left for 2 h. After this time, the suspension was cooled back to 0 °C and excess Jones reagent was quenched by the addition of isopropanol (2.0 mL). The mixture was warmed to rt, diluted with 50% NaCl (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure to yield a white solid. This product was purified by chromatography on silica eluting with methanol:dichloromethane (10:90) to give **28** (white foam) as a single diastereomer (0.224 g, 83%): mp 101-103 °C; R_f 0.15 (methanol:dichloromethane 10:90); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93-0.94 (br m, 12H), 1.10 (br m, 2H), 1.42 (br s, 9H), 1.55 (br m, 1H), 1.65 (br m, 2H), 2.32 (br m, 1H), 4.50 (br m, 2H), 4.58 (br m, 3H), 4.74 (br m, 1H), 5.12 (br s, 2H), 5.45 (br s, 1H), 5.78 (br s, 1H,), 6.90 (br m, 2H), 7.24-7.33 (br m, 5H), 7.76 (br m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.97, 19.52, 21.85, 22.90, 24.66, 28.31, 30.48, 41.85, 46.02, 53.40, 55.33 and 55.40 (rotamers), 67.11, 79.95, 84.51 and 84.97 (rotamers), 115.38, 127.17, 127.94, 128.09, 128.44, 130.29, 136.09, 155.10, 156.45, 163.97 and 164.48 (rotamers), 172.22, 173.16, 191.70; IR (film) 3334 (m), 3066 (w), 3032 (w), 2960 (m), 2932 (w), 2872 (w), 1704 (s), 1698 (s), 1660 (s), 1599(s), 1573 (m), 1510 (s) cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{45}N_3O_9Na$ (M + Na): *m/z* 650.3054, found 650.3057; $[\alpha]^{20}_D$ -32.5 (*c* 1.01, $CHCl_3$).

[2*R*, 3*S*]-3-{4-[2-(2*S*-Benzyloxycarbonyl-4-methylpentanoylamino)-1-hydroxyethyl]phenoxy}-2-*tert*-butoxycarbonylamino-4-methylpentanoic acid (29). To a solution of **28** (0.370 g, 0.589 mmol) in a mixture of THF (10 mL) and ethanol (10 mL) was added lithium chloride (0.050 g, 1.18 mmol) followed by sodium borohydride (0.045 g, 1.18 mmol) at rt under argon. The suspension was stirred for 4 h at rt and then filtered. The solids were collected and washed with ethyl acetate (4 x 10 mL) and the solvent was removed under reduced pressure to afford a white solid. The solid was partitioned between 50% NaCl (5 mL) and ethyl acetate (25 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure to give **29** (white solid) as a mixture of inseparable diastereomers (0.360 g, 97%), which were used without further purification: mp 152-156 °C; R_f 0.11 (methanol:dichloromethane 10:90); ^1H NMR (500 MHz, CD_3OD) δ 0.89, 0.91 (d, *J* = 6.7, 2 x 3H, diastereomers), 0.99 (d, *J* = 6.6, 2 x 3H, diastereomers), 1.01 (d, *J* = 6.6, 2 x 3H, diastereomers), 1.21-1.28 (br m, 2 x 2H, diastereomers), 1.40 (s, 2 x 9H, diastereomers), 1.42-1.49 (br m, 2 x 1H, diastereomers), 1.57-1.66 (m, 2 x 1H, diastereomers), 2.17-2.21 (m, 2 x 1H, diastereomers), 3.34-3.45 (m, 2 x 2H, diastereomers), 4.10-4.13 (2 x 1H, m, diastereomers), 4.43-4.46 (m, 2 x 1H, diastereomers), 4.65-4.67 (m, 2 x 1H, diastereomers), 5.05-5.12 (m, 2 x 2H, diastereomers), 6.97-6.99 (m, 2 x 2H, diastereomers), 7.22-7.24 (m, 2 x 2H, diastereomers), 7.27-7.30 (m, 2 x 1H, diastereomers), 7.31-7.36 (m, 2 x 4H, diastereomers); ^{13}C NMR (125 MHz, CD_3OD) δ 19.55, 20.07, 21.89, 23.43, 25.86, 28.76, 31.35, 42.20, 47.87, 55.12, 58.09, 67.73,

73.02, 73.12, 80.16, 85.34, 117.00, 128.34, 128.84, 129.01, 129.47, 135.68, 138.13, 157.32, 158.45, 160.68, 175.69, 176.35; IR (film) 3306 (s), 3094 (w), 3062 (w), 3032 (w), 2960 (s), 2928 (m), 2877 (m), 1694 (s), 1650 (s), 1608 (s), 1535 (s), 1510 (s) cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{47}N_3O_9Na$ (M + Na): *m/z* 652.3210, found 652.3204; $[\alpha]^{20}_D$ -20.4 (*c* 1.17, MeOH).

[2*R*, 3*S*]-3-{4-[2-(2*S*-Benzyloxycarbonyl-4-methyl-pentanoylamino)-1-hydroxyethyl]phenoxy}-2-*tert*-butoxycarbonylamino-4-methyl-pentanoic acid pentafluorophenyl ester (30). To a solution of **29** (0.350 g, 0.556 mmol) and EDAC (0.117 g, 0.610 mmol) in dichloromethane (15 mL) at 0 °C under argon was added pentafluorophenol (0.113 g, 0.610 mmol) followed by DMAP (13.5 mg, 0.111 mmol). The mixture was stirred for 30 min at 0 °C and then warmed to rt where it was maintained for 3 h. The solution was then diluted with ethyl acetate (30 mL) and washed with 10% citric acid (5 mL), 5% $NaHCO_3$ (5 mL) and sat. NaCl (5 mL). The organic layer was separated, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to yield **30** as a pale yellow foam, which was used crude for the next step (0.439 g, 99%): R_f 0.46 (ethyl acetate:petroleum ether 50:50); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 5.8, 2 x 6H, diastereomers), 1.02, 1.11 (d, *J* = 6.3, 2 x 3H, diastereomers), 1.41, 1.42 (s, 2 x 9H, diastereomers), 1.60-1.80 (m, 2 x 3H, diastereomers), 2.21-2.28 (m, 2 x 1H, diastereomers), 3.15-3.25 (br m, 2 x 2H, diastereomers), 3.63 (br m, 2 x 1H, diastereomers), 4.09-4.13 (br m, 1H, diastereomers), 4.42 (br m, 2 x 1H, diastereomers), 4.74 (br s, 2 x 1H, diastereomers), 5.02-5.15 (m, 2 x 3H, diastereomers), 5.23-5.25 (m, 2 x 2H, diastereomers), 6.46 (br s, 2 x 1H, diastereomers), 6.90-6.92 (m, 2 x 2H, diastereomers), 7.23-7.24 (m, 2 x 2H, diastereomers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.04, 19.35, 19.40, 21.96, 22.85, 24.67, 24.71, 28.21, 30.77, 41.30, 47.29, 53.76, 55.78, 67.18, 72.56, 2.89, 80.83, 84.09, 84.20, 115.83, 127.26, 128.05, 128.10, 128.26, 128.54, 134.74, 136.07, 136.87 (m), 138.89, 140.05 (m), 141.98 (m), 142.05, 154.86, 156.34, 158.71, 166.39, 173.16, 173.25; IR (film) 3419 (m), 3338 (m), 2961 (w), 2931 (w), 2878 (w), 1789 (w), 1709 (m), 1659 (m), 1652 (m), 1520 (s) cm^{-1}; HRMS (ESI) calcd for $C_{39}H_{46}N_3O_9F_5Na$ (M + Na): *m/z* 818.3052, found 818.3039; $[\alpha]^{20}_D$ -44.8 (*c* 0.31, $CHCl_3$). A small sample was purified by chromatography on silica to obtain a melting point and analysis: mp 81-84 °C; Anal. Calcd for $C_{39}H_{46}N_3O_9F_5$: C, 58.86; H, 5.83; N, 5.28. Found: C, 58.48; H, 5.95; N, 5.06.

[3*S*, 4*S*, 7*S*, 11*R*]-(11-Hydroxy-7-isobutyl-3-isopropyl-5,8-dioxo-2-oxa-6,9-diazabicyclo-[10.2.2]hexadeca-1(15), 12(16), 13-trien-4-yl)-carbamic acid *tert*-butyl ester (31) and [3*S*, 4*S*, 7*S*, 11*S*]-(11-Hydroxy-7-isobutyl-3-isopropyl-5,8-dioxo-2-oxa-6,9-diazabicyclo-[10.2.2]-hexadeca-1(15), 12(16), 13-trien-4-yl)-carbamic acid *tert*-butyl ester (32). To a suspension of palladium black (0.350 g) in 1,4-dioxane (540 mL) containing γ-terpinene (54 mL), *tert*-butanol (11.2 mL) and 4-pyrrolidinopyridine (0.048 g, 0.323 mmol) at reflux under argon was added a solution of **30** (0.175 g, 0.219 mmol) in 1,4-dioxane (48 mL) and γ-terpinene (24 mL) via a syringe pump over 3 h. The resulting mixture was held at reflux for a further 3.5 h, cooled to rt and then filtered through Celite. The solids were washed with ethanol (5 x 50 mL) and the solvent was removed from the filtrate under reduced pressure. Excess γ-terpinene was removed by azeotroping the mixture with toluene. The oil that remained was adsorbed onto silica and purified by chromatography eluting with an ethyl acetate:petroleum ether gradient (30:70 - 100:0) to give **31** (0.028 g, 27%) as a white solid: mp 248-249 °C (decomp.); R_f 0.26 (ethyl acetate:petroleum ether

70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.7, 3H), 0.81 (d, *J* = 6.6, 3H), 1.00 (d, *J* = 6.7, 3H), 1.08 (d, *J* = 6.8, 3H), 1.22-1.35 (m, 2H), 1.38 (s, 9H), 1.41-1.45 (m, 1H), 2.08-2.11 (m, 1H), 3.07 (d, *J* = 14.0, 1H), 3.15 (br s, 1H), 3.98-4.02 (m, 2H), 4.23-4.29 (m, 1H), 4.67 (d, *J* = 8.3, 1H), 5.13 (d, *J* = 10.5, 1H), 5.17 (br s, 1H), 5.97 (d, *J* = 10.5, 1H), 6.13 (d, *J* = 9.3, 1H), 6.81 (dd, *J* = 8.3 2.3, 1H), 6.93 (dd, *J* = 8.5 2.1, 1H), 6.99 (dd, *J* = 8.5 2.1, 1H), 7.35 (dd, *J* = 8.6 2.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.42, 20.08, 22.39, 22.79, 24.50, 28.25, 28.67, 42.28, 47.52, 51.92, 57.31, 72.10, 79.73, 80.24, 114.50, 119.42, 125.97, 127.15, 133.54, 154.99, 156.80, 170.70, 171.07; IR (film) 3298 (s), 2960 (m), 2930 (m), 2869 (w), 1700 (m), 1646 (s),1540 (m), 1508 (s) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{39}N_3O_6Na$ (M + Na): *m/z* 500.2737, found 500.2731; $[\alpha]^{20}_D$ -54.4 (*c* 0.16, MeOH); lit.[31] $[\alpha]_D^{25}$ -33.3 (*c* 0.19, $CHCl_3$); and **32** (0.023 g, 22%) as a white solid: mp 260-262 °C (decomp.); R_f 0.15 (ethyl acetate:petroleum ether 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.3, 3H), 0.80 (d, *J* = 6.4, 3H), 0.99 (d, *J* = 6.7, 3H), 1.16 (d, *J* = 6.9, 3H), 1.26-1.46 (m, 3H), 1.39 (s, 9H), 2.05-2.09 (m, 1H), 3.24-3.29 (m, 1H), 3.66 (d, *J* = 7.1, 1H), 3.87-3.94 (m, 2H), 4.00-4.03 (m, 1H), 4.60 (dd, *J* = 8.5 1.7, 1H), 4.84 (dd, *J* = 12.2 6.0, 1H), 4.92 (d, *J* = 10.5, 1H), 5.60 (br m, 1H), 5.75 (d, *J* = 8.2, 1H), 6.86 (dd, *J* = 8.4 1.9, 1H), 6.89 (dd, *J* = 8.2 2.1, 1H), 6.93 (dd, *J* = 8.4 2.2, 1H), 7.39 (dd, *J* = 8.4 1.8, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.36, 20.14, 22.00, 22.79, 24.18, 28.20, 28.82, 40.22, 47.99, 51.18, 57.26, 73.07, 80.44, 81.55, 117.90, 121.61, 126.57, 127.55, 135.53, 154.94, 156.63, 171.15, 171.58; IR (film) 3344 (m), 3273 (s), 2961 (w), 2931 (w), 2869 (w), 1674 (m), 1638 (s), 1542 (m), 1510 (w) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{39}N_3O_6Na$ (M + Na): *m/z* 500.2737, found 500.2739; $[\alpha]^{20}_D$ -51.4 (*c* 0.14, MeOH).

[3*S*, 4*S*, 7*S*, 11*R*]-4-Amino-11-hydroxy-7-isobutyl-3-isopropyl-2-oxa-6,9-diazabicyclo-[10.2.2]hexadeca-1(15), 12(16), 13-triene-5,8-dione trifluoroacetic acid salt (33). Isomer **31** (14 mg, 0.0293 mmol) was partially dissolved in dichloromethane (0.75 mL) and cooled to 0 °C under argon. Trifluoroacetic acid (0.25 mL) was introduced and the mixture was stirred for 15 min at 0 °C and then warmed to rt where it was left for 1 h. The solvent was removed under reduced pressure and the resulting off-white solid was washed with diethyl ether (2 x 5 mL) to give **33** as a white solid (12 mg, 83%): mp 180-183 °C (decomp.); ^{1}H NMR (500 MHz, CD_3OD) δ 0.85 (d, *J* = 6.4, 3H), 0.86 (d, *J* = 6.4, 3H), 1.09 (d, *J* = 6.7, 3H), 1.16 (d, *J* = 6.6, 3H), 1.20-1.25 (m, 1H), 1.27-1.43 (m, 2H), 1.98-2.03 (m, 1H), 2.97 (d, *J* = 13.9, 1H), 3.83 (d, *J* = 9.3, 1H), 4.07-4.17 (m, 2H), 4.79 (d, *J* = 9.3, 1H), 5.05 (d, *J* = 3.7, 1H), 6.71 (dd, *J* = 8.4 2.5, 1H), 6.87 (dd, *J* = 8.7 2.5, 1H), 6.98 (dd, *J* = 8.4 1.9, 1H), 7.36 (dd, *J* = 8.6 1.8, 1H), 7.63 (d, *J* = 10.5, 1H), 7.79 (d, *J* = 9.2, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.47, 20.27, 22.84, 23.16, 25.57, 29.38, 44.05, 49.05, 53.18, 55.83, 72.84, 77.60, 112.21, 118.97, 127.97, 128.81, 135.72, 157.56, 168.07, 172.17; IR (film) 3288 (m), 2961 (m), 2929 (m), 1653 (s), 1610 (m), 1539 (m), 1511 (m) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{31}N_3O_4Na$ (M + Na): *m/z* 400.2212, found 400.2225; $[\alpha]^{20}_D$ + 62.3 (*c* 0.31, MeOH).

[3*S*, 4*S*, 7*S*, 11*S*]-4-Amino-11-hydroxy-7-isobutyl-3-isopropyl-2-oxa-6,9-diazabicyclo-[10.2.2]hexadeca-1(15), 12(16), 13-triene-5,8-dione trifluoroacetic acid salt (34). The C-11 epimer **34** was prepared in the same way from isomer **32** (10 mg, 0.0209 mmol) to give **34** as an off-white solid (9 mg, 87%): mp 183-185 °C (decomp.); ^{1}H NMR (500 MHz, CD_3OD) δ 0.84 (d, *J* = 6.3, 3H), 0.86 (d, *J* = 6.4, 3H), 1.09 (d, *J* = 6.7, 3H), 1.16 (d, *J* = 6.6, 3H), 1.19-1.24 (m, 1H), 1.31-1.41 (m, 2H), 1.97-2.02

(m, 1H), 3.06-3.10 (m, 1H), 3.75-3.81 (m, 1H), 3.84 (d, J = 9.3, 1H), 4.02-4.11 (m, 1H), 4.59 (m, 1H), 4.78 (d, J 9.2, 1H), 6.78 (dd, J = 8.5 2.5, 1H), 6.82 (dd, J = 8.5 2.5, 1H), 6.91 (dd, J = 8.4 1.8, 1H), 7.39 (dd, J = 8.5 1.9, 1H), 7.63 (d, J = 10.5, 1H), 7.89 (d, J = 9.0, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.46, 20.25, 22.63, 23.21, 25.59, 29.35, 43.96, 46.86 and 46.96 (rotamers), 53.27 and 53.32 (rotamers), 55.67 and 55.70 (rotamers), 73.91, 77.77, 111.85, 120.09, 128.96, 130.41, 136.21, 158.15, 168.02, 171.81; IR (film) 3313 (m), 2962 (m), 2925 (m), 2873(m), 1661 (s), 1647 (s), 1611 (m), 1554 (m), 1533 (m), 1512 (m) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{31}N_3O_4Na$ (M + Na): m/z 400.2212, found 400.2207; $[\alpha]^{20}_D$ + 54.4 (c 0.36, MeOH).

Sanjoinine G1 (5). DIPEA (8.3 μL, 0.0479 mmol), followed by BOP (10.6 mg, 0.0239 mmol) was added to a suspension of **33** (10.7 mg, 0.0218 mmol) and *N,N*-dimethylphenylalanine (4.2 mg, 0.0218 mmol) in dichloromethane at 0 °C under argon. The mixture was stirred for 30 min at 0 °C and then warmed to rt where it was left for 4 h. The solution was diluted with diethyl ether and extracted with 10% citric acid (3 x 1 mL). After combining the aqueous fractions, the pH was adjusted to 9 using NH_4OH and then extracted with ethyl acetate (5 x 5 mL). The organic layers were combined, washed with water (10 x 10 mL), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave the crude product which was purified by preparative TLC to give **5** as a white solid (7.7 mg, 64%): mp 235-236 °C (decomp.), lit.[30] 236-238 °C; R_f 0.38 (methanol:dichloromethane 10:90); ^{1}H NMR (500 MHz, CD_3OD) δ 0.77 (d, J = 6.5, 3H), 0.79 (d, J = 6.6, 3H), 0.93 (d, J = 6.8, 3H), 1.09 (d, J = 6.8, 3H), 1.12-1.17 (m, 1H), 1.20-1.33 (m, 2H), 2.03-2.09 (m, 1H), 2.35 (s, 6H), 2.90 (ABX, J_{AB} = 16.1 J_{AX} = 5.5, 1H), 2.96 (d, J = 14.0, 1H), 3.02 (ABX, J_{AB} = 14.1 J_{BX} = 8.4, 1H), 3.32 (ABX, J_{BX} = 8.6 J_{AX} = 5.5, 1H), 3.98-4.02 (m, 1H), 4.11-4.17 (m, 1H), 4.35 (d, J = 9.1, 1H), 4.76 (dd, J = 9.1 1.9, 1H), 5.03 (d, J = 4.1, 1H), 6.71 (dd, J = 8.4 2.6, 1H), 6.87 (dd, J = 8.7 2.6, 1H), 6.91 (dd, J = 8.4 2.1, 1H), 7.13-7.24 (m, 5H), 7.31 (dd, J = 8.6 2.0, 1H), 7.47-7.51 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 15.06, 20.50, 22.95, 22.96, 25.65, 29.77, 36.00, 42.56, 43.32, 48.70, 52.57, 56.81, 71.32, 72.78, 80.13, 114.83, 119.92, 127.38, 127.52, 128.20, 129.48, 130.04, 135.56, 139.80, 157.79, 171.31, 172.51, 172.58; IR (film) 3304 (s), 2957 (m), 2931 (s), 2868 (s), 1638 (s), 1508 (m) cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{44}N_4O_5Na$ (M + Na): m/z 575.3209, found 575.3215; $[\alpha]^{20}_D$ -67.9 (c 0.53, $CHCl_3$); lit.[30] $[\alpha]^{20}_D$ -68.6 (c 0.175, $CHCl_3$).

[2*S*]-2-Dimethylamino-3-phenyl-*N*-[[3*S*, 4*S*, 7*S*, 11*S*]-11-hydroxy-7-isobutyl-3-isopropyl-5,8-dioxo-2-oxa-6,9-diazabicyclo[10.2.2]hexadeca-1(15), 12(16), 13-trien-4-yl]-propanamide (35). The C-11 epimer was prepared in a similar way from **34** (10.8 mg, 0.0220 mmol) to give **35** as a white solid (6.4 mg, 53%): mp 246-249 °C (decomp.); R_f 0.36 (methanol:dichloromethane 10:90); ^{1}H NMR (500 MHz, CD_3OD) δ 0.76 (d, J = 6.3, 3H), 0.78 (d, J = 6.4, 3H), 0.93 (d, J = 6.8, 3H), 1.09 (d, J = 6.8, 3H), 1.09-1.13 (m, 1H), 1.21-1.30 (m, 2H), 2.03-2.07 (m, 1H), 2.33 (s, 6H), 2.89 (ABX, J_{AB} = 14.0 J_{AX} = 5.4, 1H), 3.01 (ABX, J_{AB} = 14.0 J_{BX} = 8.5, 1H), 3.08 (AMX, J_{AM} = 12.8 J_{AX} = 6.3, 1H), 3.28 (ABX, J_{BX} = 8.5 J_{AX} = 5.4, 1H), 3.82 (AMX, J_{AM} = 12.8 J_{MX} = 10.1, 1H), 3.90 (t, J = 7.5, 1H), 4.35 (d, J = 9.1, 1H), 4.57 (AMX, J_{MX} = 10.1 J_{AX} = 6.4, 1H), 4.74 (dd, J = 9.1 1.9, 1H) , 6.78 (dd, J = 8.4 2.5, 1H), 6.81 (dd, J = 8.5 2.5, 1H), 6.87 (dd, J = 8.4 2.1, 1H), 7.12-7.23 (m, 5H), 7.32 (dd, J = 8.4 2.0, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 15.05, 20.47, 22.81, 22.96, 25.64, 29.74, 36.01, 42.54, 43.32, 46.56, 52.69, 56.68,

71.34, 74.05, 80.28, 114.47, 120.99, 127.33, 128.36, 129.44, 130.03, 130.37, 135.91, 139.91, 158.46, 171.40, 172.22, 172.69; IR (film) 3284 (m), 2958 (m), 2927 (m), 2877 (m), 1636 (s), 1627 (s), 1561 (w), 1541 (w), 1510 (m) cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{44}N_4O_5Na$ (M + Na): *m/z* 575.3209, found 575.3213; $[\alpha]^{20}_D$ -9.5 (*c* 0.19, MeOH).

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