Synthesis of the C 26 −C 32 Oxazole Fragment of Calyculin C: A Test Case for Oxazole Syntheses

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Synthesis of the C_{26}−C_{32} Oxazole Fragment of Calyculin C: A Test Case for Oxazole Syntheses

Petri M. Pihko and Ari M. P. Koskinen*

Department of Chemistry, University of Oulu, Linnanmaa, FIN-90570 Oulu

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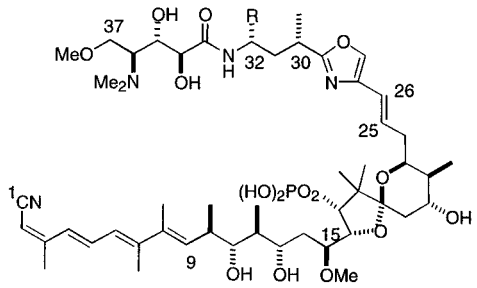
The synthesis of the C_{26}−C_{32} oxazole fragment **4** and its C_{32} epimer **20** of serine/threonine protein phosphatase PP1 and PP2A inhibitor calyculin C is presented. The syn methyl arrangement in **4** was established through cyclic stereocontrol. Several methods for oxidizing the intermediate oxazolines **18** and **19** to the finished oxazole fragments were explored. The best results were obtained with oxidations proceeding through the corresponding ester enolate when the carbamate NH side chain was temporarily protected with a TMS group, or with $CuBr_2$/DBU/HMTA-based oxidations. The finished oxazole fragment **4** was obtained in 21% overall yield, starting from Boc-D-alaninal.

Introduction

The calyculins are a class of highly cytotoxic metabolites isolated from the marine sponge *Discodermia calyx* by Fusetani and co-workers.[1] To date, a total of 13 different calyculins have been described, the most abundant being calyculins A (**1**) and C (**2**) (Figure 1), which differ from each other only by methyl substitution at C_{32}. The remaining calyculins are either geometric isomers of the calyculins A or C, having a different olefin geometry at either the C_2−C_3 or at the C_6−C_7 double bond,[2] or close derivatives of calyculin A (e.g., calyculinamides,[3] dephosphonocalyculin A[4]). The relative stereochemistry of calyculin A was determined by X-ray diffraction, and the structures of the other calyculins have then been deduced from spectroscopic comparisons with calyculin A. The absolute stereochemistry, however, was ascertained only later (1991), by Shioiri et al., who compared the synthetic C_{33}−C_{37} amino acid fragment with the one obtained by hydrolysis of the natural product by Fusetani.[5] Most of the initial synthetic efforts toward the calyculins had therefore been directed at the enantiomer of the natural product.[6] The Evans group reported their synthesis of *ent*-calyculin A[7] in 1992, and later (1994) Masamune et al. published the total synthesis of the natural enantiomer.[8] Shioiri et al. have also reported a formal total synthesis of calyculin A.[9]



R = H Calyculin A (1)
R = Me Calyculin C (2)

Figure 1.

The high cytotoxicity of the calyculins results from their ability to selectively and efficiently inhibit protein phosphatases 1 and 2A (PP1 and PP2A), two of the major enzymes that dephosphorylate serine/threonine residues of proteins in eukaryotic cells.[10] Since a wide variety of cellular events are regulated by reversible protein phosphorylation, protein phosphatase inhibitors have rapidly gained an important position in the study of intracellular processes.[11] Other naturally occurring toxins known to inhibit PP1 or PP2A include okadaic acid, the microcystins, nodularin, motuporin, tautomycin, and cantharidin.[12] Of the commercially available PP1/PP2A inhibitors, calyculin A displays both high activity for the enzymes (the K_i values for PP1 and PP2A are 1.1 and 0.13 nM, respectively) and good cell permeability.[13] X-ray crystal structures are available for the catalytic subunit

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1997.

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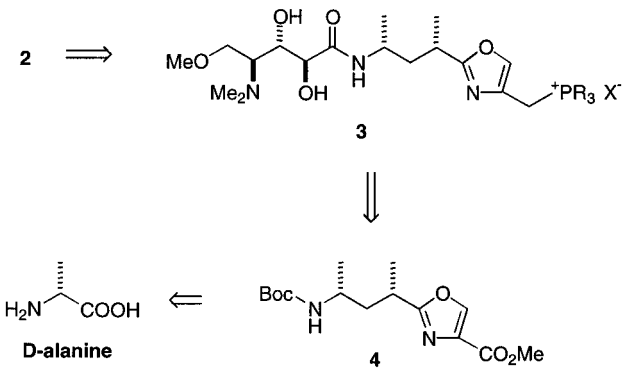
Scheme 1



of rabbit muscle PP1 complexed with microcystin LR,[14] for human PP1, and its complex with tungstate.[15] The structural motifs responsible for the binding of microcystin LR to the enzyme appear to be present in calyculin A, okadaic acid, and tautomycin as well.[16] In our modeling studies, we have developed a spiroketal vector model for the binding of calyculin A to PP1, proposing that calyculin A binds to the enzyme in an extended conformation.[17]

We have selected calyculin C as our prime synthetic target. This decision reflects our strategy to utilize amino acid chemistry for the construction of the northern half (**3**) ($C_{26}-C_{37}$ fragment) of the molecule: the $C_{33}-C_{37}$ amino acid is derived from L-serine,[18] and the $C_{26}-C_{32}$ oxazole fragment **4**, in turn, is derived from D-alanine.[19] The illustrated disconnection at $C_{25}-C_{26}$ parallels the other published approaches to the calyculins[6-9] and conveniently divides the molecule into two comparably complex fragments (Scheme 1). In this paper, we disclose our approach to the $C_{26}-C_{32}$ oxazole fragment of calyculin C.

Results and Discussion

We initially explored the methodology for constructing the correct stereochemistry at C_{30} with L-alanine derived starting materials, leading to chirality opposite to the natural product.[19] Thus, the known amino aldehyde **5**[20] was olefinated with the phosphorane **6** to afford the known (*E*)-enoate **7**[21] in 95% yield with an *E:Z* ratio 18:1 (Scheme 2). Attempts at hydrogenating the double bond with the Pfaltz-type bisoxazoline, semicorrin, or pyridyloxazoline ligands and Co(II)/$NaBH_4$ proved unsuccessful.[22] Direct hydrogenation over Pd/C in EtOH, however, cleanly afforded a 2:1 diastereomeric mixture of the *anti*-

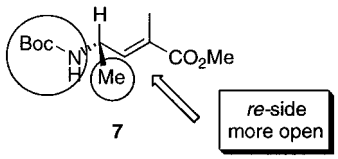
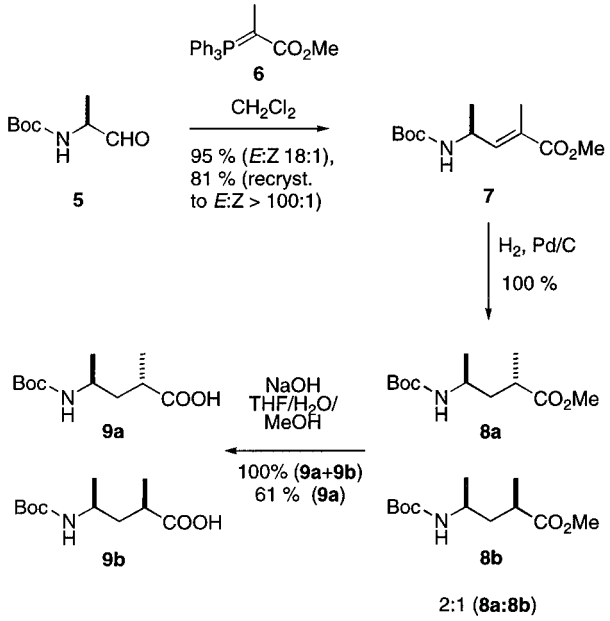


Figure 2.

Scheme 2



and *syn*-isomers **8a** and **8b** in a quantitative yield. The use of Pt/C instead of Pd/C, or changing the solvent, had very little effect on the diastereomer ratio.[23] Hydrolysis with NaOH in aqueous THF/MeOH afforded a mixture of the acids **9a** and **9b**, from which the pure *anti* isomer **9a** was readily obtained by fractional recrystallization in 61% yield. Single-crystal X-ray diffraction of **9a** provided a proof of the relative stereochemistry.[24]

The predominance of the *anti*-isomer could be rationalized on the basis of 1,3-allylic strain:[25] the (*E*)-enoate adopts a conformation where the *si* face is hindered by the Boc group (Figure 2). Since the undesired anti diastereomer was the major product obtained with the (*E*)-enoate, the synthesis was then attempted via the corresponding (*Z*)-enoate *ent*-**12** (see Scheme 3), prepared from Boc-L-alaninal through the Still–Gennari modification[26] of Horner–Emmons–Wadsworth reaction using the phosphonate **11**. To our surprise, hydrogenation of *ent*-**12**[27] over Pd/C gave the esters **8a** and **8b** in *nearly the same diastereomer ratio (5:3), with the undesired anti-isomer predominating*. In this case, a γ-turn type con-

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(24) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(25) (a) Johnson, F. *Chem. Rev. (Washington, D.C.)* **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1841–1860.
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(27) *ent*-**12** was prepared from **5** and **11** as described for **12** (Scheme 3) in 90% yield, see ref 19. In this paper, we report the optimized procedure for the preparation of enantiomeric **12**.

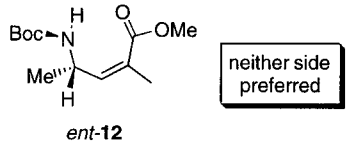
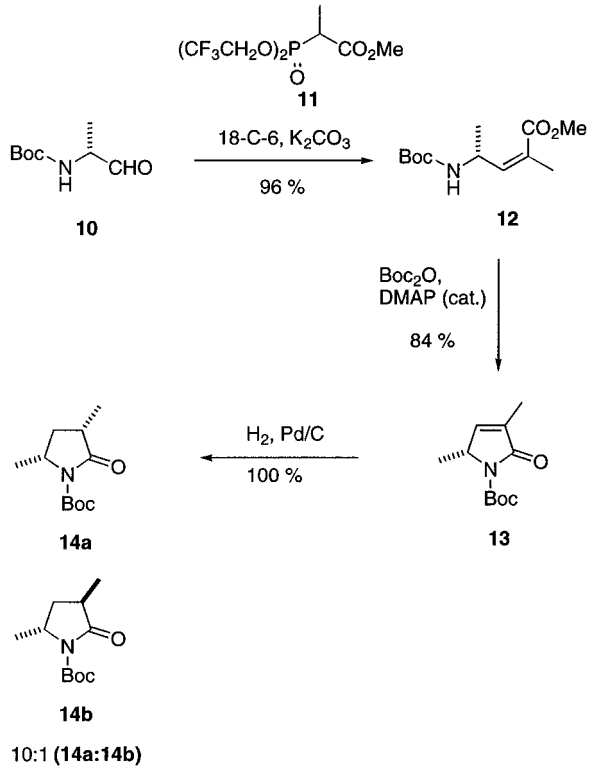


Figure 3.

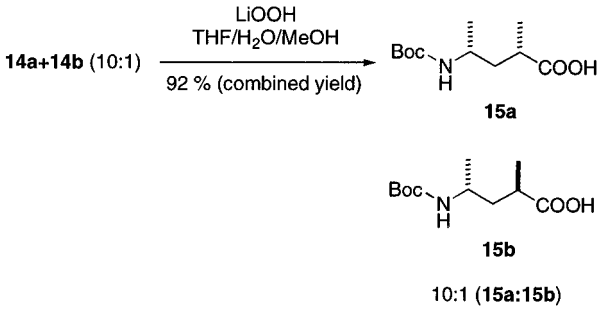
Scheme 3



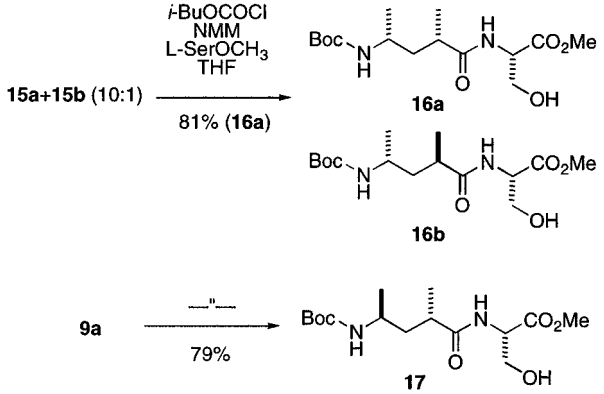
formation (Figure 3), stabilized by the dipolar interaction between the NH and the ester groups, could be invoked to explain the poor selectivity. Allylic isomerization on the surface of the catalyst can also lead to similar results.[28]

A successful route to the desired *syn* isomer was then found which involves *cyclic* stereocontrol, thereby imposing better control over the stereochemistry of the hydrogenation. The synthetic sequence is shown in Scheme 3, starting from the enantiomeric D-alaninal derivative **10**. Cyclization of the (*Z*)-enoate **12** to the corresponding lactam **13** under Ragnarsson−Grehn conditions,[29] followed by hydrogenation over Pd/C, afforded a 10:1 mixture of the *syn* and *anti* pyrrolidones **14a** and **14b**. Subsequent hydrolysis with lithium hydroperoxide[30] gave the open-chain acids **15a** and **15b** (Scheme 4), which were directly carried over to the coupling with L-serine methyl ester under mixed anhydride conditions[31] to afford the dipeptides **16a** and **16b** (Scheme 5). These were readily

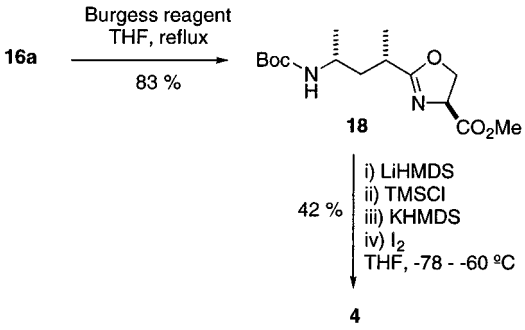
Scheme 4



Scheme 5



Scheme 6



separable by chromatography. The use of LiOH[32] instead of lithium hydroperoxide in the ring opening led to partial epimerization at the C_{30} stereocenter, eroding the ratio of **15a** to **15b** to 4:1.

Conversion of **16a** to the oxazoline **18** was best accomplished with the Burgess reagent[33, 34] (Scheme 6). Thionyl chloride/pyridine also gave the oxazoline, but in slightly lower yields (75%) and with ca. 5% epimerization at the C_{30} stereocenter. The corresponding *epi*-C_{32} oxazoline **19** was similarly synthesized by coupling the acid **9a** with L-serine methyl ester to give the dipeptide **17** in 79% yield after recrystallization (Scheme 5). Dehydration with the Burgess reagent afforded oxazoline **19** in 82% yield (Scheme 7).

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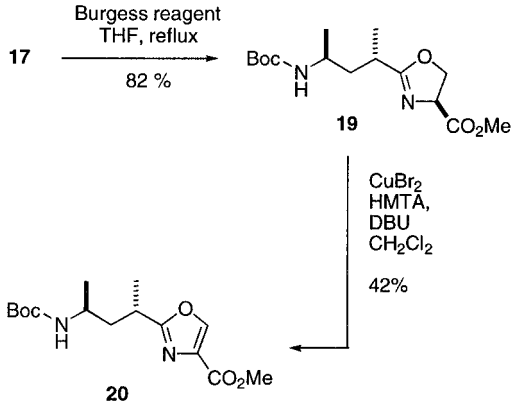
(33) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907−910.
(34) We eventually found that aqueous workup was necessary to obtain a clean product. Direct silica gel chromatography of the reaction mixture, according to the procedure described in ref 33, failed to remove traces of the reagent.

Scheme 7



Several novel methods for oxidizing oxazolines to the oxazoles have been disclosed in recent years. We thus began exploring them with high hopes. Table 1 summarizes our results obtained with different oxidation methods. Heterogeneous oxidants (activated MnO_2,[35] NiO_2[36]) led to poor and irreproducible yields, even in the presence of added base.[37] Copper(II) acetate-mediated oxidation in the presence of *tert*-butyl perbenzoate[38] led to extensive fragmentation and poor yields. The best results were obtained with either the $CuBr_2$/HMTA/DBU oxidation,[39] or with our own method involving temporary TMS protection of the carbamate nitrogen,[40] deprotonation of the oxazoline with KHMDS, and oxidation of the intermediate enolate via the phenyl selenide[7] or, even more cleanly, directly with iodine.[41] The use of TMS as a temporary protecting group for the carbamate NH was selected as all attempts to protect the oxazoline NH effectively with either another Boc group or with more bulkier silyl groups had failed (the use of LiHMDS at higher temperatures led to decomposition of the oxazoline). Without the TMS protection step, all oxidation methods involving proton abstraction from the oxazoline with KHMDS (or LDA) led to poor yields, even with an excess of the reagents.

The $CuBr_2$/HMTA/DBU oxidation and the KHMDS/I_2 oxidation gave nearly identical yields of the oxazoles **4** and **20**. Both oxidation methods also yielded the same, isomeric side products.[42] We were able to improve the combined yield of the product and the side product up to 82%, but the formation of the side products could not be completely suppressed.[43] The fact that the side products were formed also with the KHMDS/I_2 oxidation was thought to be the result of an incomplete reaction at the TMS protection step.[44,45] However, all attempts at improving this step (changing the temperature, the use of TMSOTf instead of TMSCl, or the use of in situ quench conditions[46]) failed.

The $CuBr_2$/HMTA/DBU oxidation has been proposed to proceed via one-electron transfers from the copper enolate of the oxazoline (Figure 4).[39] The KHMDS/I_2 oxidation also proceeds via the corresponding ester enolate, and it is highly conceivable that similar one-electron transfers accompanied with proton abstraction by the base are also operating in this oxidation. Overall, these two oxidation methods gave the cleanest reactions and best yields.

Conclusion

A successful route to the $C_{26}-C_{32}$ oxazole fragment **4** of calyculin C and its C_{32} epimer **20** has been developed. For the *syn* isomer **4**, the route involves seven steps starting from Boc-D-alaninal (21% overall yield), and for the *anti* isomer **20**, six steps from Boc-L-alaninal (16% overall yield). The oxidation of the sensitive oxazolines **18** and **19** to the corresponding oxazoles provided an excellent test case for current oxidation methods. As the route employed for **4** has provided us with a sufficient supply of the required oxazole fragment in high purity, studies toward the total synthesis of calyculin C are ongoing and progress will be reported in due course.

Experimental Section

General. Melting points are uncorrected. Optical rotations were measured at 22 °C. ^1H and ^{13}C NMR spectra were

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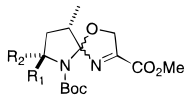
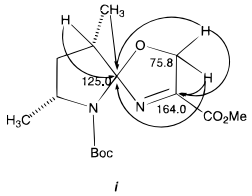
(42) The structures of the side products have tentatively been assigned as **i** and **ii** (both being mixtures of diastereomers due to the presence of an additional chiral spiro atom):



i R_1 = H, R_2 = Me
ii R_1 = Me, R_2 = H

Complete listings of ^1H NMR, ^{13}C NMR, and IR resonances as well as the HRMS data are given in the Supporting Information. For **i**, indicative long-range $^1H-^{13}C$ couplings and the corresponding ^{13}C chemical shifts are given below; similar correlations are also observed for **ii**. The absence of N−H stretching in their IR spectra at 3400 cm^{-1} and their isomeric composition with the oxazoles **4** and **20** (as evidenced by the HRMS data) are also indicative evidence for their structures.



i

(43) In contrast with the results obtained by Peña and co-workers (see ref 41), in our case all oxidations with iodine proceeded to completion, with no traces of the starting oxazoline left. The $CuBr_2$/HMTA/DBU oxidations also proceeded to completion within 2−3 h.

(44) Our failure to prevent **i** and **ii** from forming despite our attempts to improve the N-silylation step could also be explained if they are formed as follows: intramolecular silyl transfer to the enolate anion (Brook rearrangement), cyclization of the resulting carbamate nitrogen-centered anion, and final loss of TMS from the ester. We thank the anonymous reviewer for pointing out this possibility.

(45) The two methyl substituents are likely to considerably enhance the rate of cyclization and thus favor the formation of the side product. For an excellent discussion of this *reactive rotamer effect*, see: (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232. For recent studies of this effect with other than *gem*-dialkyl substituents, see: (b) De Corte, F.; Nuyttens, F.; Cauwberghs, S.; De Clercq, P. *Tetrahedron Lett.* **1993**, *34*, 1831−1832. (c) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 4509−4512.

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Table 1. Oxidation of Oxazolines 18 or 19 to the Corresponding Oxazoles 4 or 20

entry	substrate	product	reagents and conditions	reaction time	yield (%)	reference
1	**18**	**4**	MnO_2, PhH, cat. pyridine, 55 °C	18 h	0[a]	35
2	**18**	**4**	NiO_2, CH_2Cl_2, cat. DBU	48 h	27−39[b]	36, 37
3	**18**	**4**	NiO_2, PhH, rfx	10−20 h	20−30[c]	36
4	**18**	**4**	CuBr, $Cu(OAc)_2$, t-BuOOBz, PhH, rfx	9 h	27[d]	38
5	**18**	**4**	(1) (i) LiHMDS, (ii) TMSCl, (iii) KHMDS, (iv) PhSeBr; THF, −78 °C; (2) H_2O_2, pyr, CH_2Cl_2, 0 °C	(1) i−iv: 10−20 min each; (2): 2 h	42[e]	7, 40, this work
6	**18**	**4**	(i) LiHMDS, (ii) TMSCl, (iii) KHMDS, (iv) I_2; THF, −78 to −60 °C (i−iv) to 0 °C (iv)	i−iii: 10−20 min each (iv): 30 min−4 h	42[f]	40, 41, this work
7	**19**	**20**	$CuBr_2$, DBU, HMTA; CH_2Cl_2, rt	3 h	42[g]	39

[a] The reaction fails also with activated MnO_2. [b] The yields were not reproducible. [c] Extensive decomposition observed. [d] The product was difficult to purify, and polymerization and decomposition of the starting material were also observed. [e] The use of LDA instead of KHMDS gave **4** in a similar yield. [f] The side product i was also isolated in 26% yield. [g] The side product ii was also isolated in 40% yield. Prolonged reaction times led to loss of yield (20−25% instead of 42%).

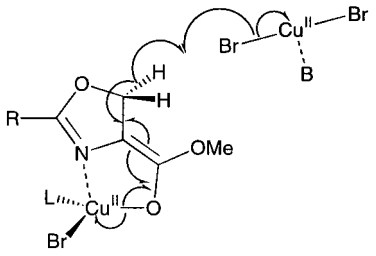

Figure 4.

recorded in $CDCl_3$. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent.

Analytical thin-layer chromatography was performed on Merck 0.25 mm silica gel 60 F plates. For visualization, UV light and ninhydrin solution followed by heating were used. Flash chromatography was performed on Merck silica gel 60 (230−400 mesh).

All reactions involving nonaqueous media were conducted under a positive pressure of argon, and the solvents and reagents were dried prior to use. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. *N*-Methyl morpholine, toluene, and benzene were distilled from sodium metal. Acetonitrile was distilled from phosphorus pentoxide. Dichloromethane was distilled from calcium hydride. Ethyl acetate was distilled from potassium carbonate. Methanol was distilled from $Mg(OMe)_2$. Triethylamine was distilled prior to use. All other commercial reagents were used as received.

N-(*tert*-Butoxycarbonyl)-D-alaninal (10). Acetyl chloride (12.0 mL, 13.26 g, 0.169 mol, 167 mol %) was added dropwise to dry methanol (200 mL) at 5 °C. To this was added D-alanine (8.98 g, 0.101 mol, 100 mol %), and the mixture was heated to reflux for 5 days. Concentration afforded the crude methyl ester hydrochloride (14.2 g, 101% mass balance) as a white solid, which was used in the next step without further purification.

The crude ester obtained above was dissolved in a mixture of dichloromethane (200 mL) and methanol (10 mL), and the mixture was cooled to 5 °C. To this was added triethylamine (17.4 mL, 12.7 g, 0.125 mol, 125 mol %) and di-*tert*-butyl dicarbonate (22.04 g, 0.101 mol, 100 mol %). The mixture was allowed to warm to rt. After 1 h, the mixture was warmed to 35 °C and stirred at that temperature overnight. After concentration, the mixture was partitioned between 7% citric acid solution (150 mL) and diethyl ether (300 mL). The aqueous layer was extracted twice more with 50-mL portions of diethyl ether. The combined extracts were washed with saturated $NaHCO_3$ (2 × 40 mL) and brine, dried ($MgSO_4$), and concentrated to afford the protected ester (19.39 g, 95%) as a solid, which was employed in the next step without further purification.

The crude protected ester obtained above (18.30 g, 90 mmol, 100 mol %) was dissolved in toluene (200 mL) and cooled to −80 °C. To this was added precooled (−70 °C) diisobutylaluminum hydride (162 mL, 1 M solution in toluene, 0.162 mol, 170 mol %) via cannula over a period of 45 min while maintaining the internal temperature below −69 °C. The mixture was stirred for 15 min, and precooled (−75 °C) methanol (60 mL) was added via cannula. During the addition, the reaction mixture was maintained below −69 °C. The mixture was then allowed to warm to 5 °C, and 200 g of ice was added with heavy agitation, followed by 100 mL of 2 M HCl. The cloudy, gellike mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The crude product thus obtained was allowed to solidify and then washed with cold hexane (20 mL) to give the first crop of **10**. Concentration of the mother liquor and dry flash chromatography (100 g of silica, 15% EtOAc:hexanes to 33% EtOAc:hexanes) afforded a further crop of the aldehyde **10** as a white crystalline solid; combined yield 11.06 g (71%). $[\alpha]_D = +36.2$ ($c = 1.00$, MeOH), mp 88 °C (lit.[21] $[\alpha]^{18}_D = +35.2$ ($c = 1.00$, MeOH), mp 90−91 °C), ^{1}H NMR (200 MHz) δ 9.57 (s, 1 H), 5.11 (m, 1 H), 4.25 (m, 1 H), 1.46 (s, 9 H), 1.34 (d, 1 H, $J = 7.2$ Hz).

[2*E*,4*S*]-4-((*tert*-Butoxycarbonyl)amino)-2-methyl-2-pentenoic Acid, Methyl Ester (7). To a solution of phosphorane **6** (1.92 g, 5.5 mmol, 110 mol %) in dichloromethane (10 mL) at rt was added aldehyde **5** (0.87 g, 5.0 mmol, 100 mol %) dissolved in CH_2Cl_2 (7 mL). An exothermic reaction ensued. After 1 h at rt, the reaction mixture was concentrated and then triturated with EtOAc:hexanes (1:5, 30 mL) to induce crystallization. Filtration (3 × 10 mL 1:5 EtOAc:hexanes rinse), concentration, and purification of the residue by flash chromatography (4 × 5 cm silica, gradient of 17% EtOAc:hexanes to 33% EtOAc:hexanes) afforded the crude product as a solid (1.15 g, 95%). Recrystallization from hexanes afforded the pure (*E*)-isomer **7** (985 mg, 81%): mp 79 °C (lit.[21] mp 79−80 °C), ^{1}H NMR (200 MHz) δ 6.52 (dq, 1 H, $J = 8.7$, 1.4 Hz), 4.52 (m, 2 H), 3.74 (s, 3 H), 1.92 (d, 3 H, $J = 1.4$ Hz), 1.43 (s, 9 H), 1.22 (d, 3 H, $J = 6.5$ Hz).

[2*S*/*R*,4*S*]-4-((*tert*-Butoxycarbonyl)amino)-2-methylpentanoic Acid, Methyl Ester (8a/8b). To a solution of ester **7** (10.49 g, 43.1 mmol) in ethyl acetate (300 mL) was added 10% Pt/C (0.44 g), and the flask was then flushed with argon and finally with hydrogen. The reaction mixture was hydrogenated under atmospheric pressure at rt for 14 h, after which it was filtered through a pad of Celite (3 × 40 mL EtOH rinse) and concentrated. Trituration with isooctane (50 mL) induced solidification, yielding, after drying, the product as a 2:1 diastereomer mixture of **8a**/**8b** (10.54 g, 100%): $[\alpha]_D = +17.3$ ($c = 1.78$, MeOH); mp 41−49 °C; IR ($CDCl_3$) 3442, 2979, 1708, 1503, 1455, 1367, 1251, 1163 cm^{-1}; major diastereomer **8a**: ^{1}H NMR (200 MHz) δ 4.30 (m, 1 H), 3.72 (m, 1 H), 3.67 (s, 3 H), 2.52 (app dq, 1 H, $J = 7.0$ Hz), 1.78 (m, 1 H), 1.48 (m, 1 H), 1.42 (s, 9 H), 1.16 (d, 3 H, $J = 7.1$ Hz), 1.10 (d, 3 H, $J = 6.6$ Hz); minor diastereomer **8b** ^{1}H NMR δ 4.30 (m, 1 H), 3.72 (m, 1 H), 3.66 (s, 3 H), 2.52 (app dq, 1 H, $J = 7.0$ Hz), 1.78 (m, 2 H), 1.42 (s, 9 H), 1.17 (d, 3 H, $J = 6.9$ Hz), 1.12 (d, 3 H, $J =$

6.6 Hz). Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.80; H, 9.82, N, 5.76.

[2*S*,4*S*]-4-((*tert*-Butoxycarbonyl)amino)-2-methylpentanoic Acid (9a). To a solution of ester **8a**/**8b** (2:1 mixture of two diastereomers) (2.36 g, 9.36 mmol, 100 mol %) in 1:1 THF/methanol (40 mL) at rt was added 1 M NaOH (14.4 mL, 14.4 mmol, 154 mol %), and the resulting clear solution was stirred at rt for 16 h. The solution was cooled in ice, acidified with 1 M HCl (20 mL), and extracted with EtOAc (4 × 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The clear oil thus obtained solidified in high vacuum, yielding the crude product as a white solid (2.22 g, 100%). The major product **9a** was obtained by recrystallization from Et_2O: hexanes (1:1) as a white crystalline solid (1.36 g, 61%): mp 112−114 °C, $[\alpha]_D = +21.5$ ($c = 1.00$, MeOH); IR ($CDCl_3$) 3437, 2980, 1744, 1708, 1513, 1455, 1368, 1252, 1163 cm^{-1}; ^1H NMR (400 MHz) δ 4.53 (m, 1 H), 3.77 (m, 1 H), 2.53 (m, 1 H), 1.79 (m, 1 H), 1.45 (m, 1 H), 1.45 (s, 9 H), 1.19 (d, 3 H, $J = 6.8$ Hz), 1.15 (d, 3 H, $J = 6.5$ Hz); ^{13}C NMR (100 MHz) δ 179.1, 156.7, 80.4, 45.0, 42.8, 36.8, 28.3, 21.5, 17.7. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.37; H, 9.49; N, 6.12.

[2*Z*,4*R*]-4-((*tert*-Butoxycarbonyl)amino)-2-methyl-2-pentenoic Acid, Methyl Ester (12). Potassium carbonate (29.59 g, 0.214 mol, 600 mol %) and 18-crown-6 (18.86 g, 71.4 mmol, 200 mol %) were stirred at rt in toluene (100 mL) and acetonitrile (10 mL) for 1 h, and the mixture was cooled to −12 °C. To this was added a solution of aldehyde **10** (6.18 g, 35.7 mmol, 100 mol %) and phosphonate **11** (11.85 g, 35.7 mmol, 100 mol %) in toluene (45 mL). The reaction mixture was stirred at −12 °C for 5 h and then quenched with 200 mL of 25% citric acid solution. Extraction with EtOAc (3 × 150 mL), followed by washing of the combined extracts with brine (100 mL), drying ($MgSO_4$), and concentration afforded an oil which was purified by flash chromatography (5 × 20 cm of silica, 18% EtOAc:hexanes) to afford the ester **12** as a white, crystalline solid (8.37 g, 96%): $[\alpha]_D = -66.9$ ($c = 1.00$, MeOH); mp 49−50 °C; IR ($CDCl_3$) 3445, 2981, 1712, 1497, 1454, 1368, 1230, 1156, 1048 cm^{-1}; ^1H NMR (200 MHz) δ 5.80 (br d, 1 H, $J = 8.3$ Hz), 4.95 (m, 1 H), 4.56 (m, 1 H), 3.75 (s, 3 H), 1.90 (d, 3 H, $J = 1.3$ Hz), 1.45 (s, 9 H), 1.24 (d, 3 H, $J = 6.8$ Hz); ^{13}C NMR (50 MHz) δ 187.9, 155.1, 145.0, 126.7, 79.3, 51.5, 45.9, 28.4, 20.8, 20.4. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.09; H, 8.66; N, 5.75.

[5*R*]-*N*-(*tert*-Butoxycarbonyl)-3,5-dimethyl-3-pyrrolin-2-one (13). To a solution of ester **12** (1.92 g, 7.89 mmol, 100 mol %) in acetonitrile (15 mL) were added 4-(dimethylamino)pyridine (116 mg, 0.95 mmol, 12 mol %) and di-*tert*-butyl dicarbonate (1.90 g, 8.70 mmol, 110 mol %). The solution was stirred for 48 h at rt, during which time it gradually turned red. More 4-(dimethylamino)pyridine (60 mg, 0.49 mmol, 6 mol %) and di-*tert*-butyl dicarbonate (1.32 g, 6.05 mmol, 77 mol %) were added, and the mixture was stirred for a further 72 h at rt. Concentration followed by purification of the residue by flash chromatography (4 × 18 cm silica, 1:4 EtOAc: hexanes) afforded the lactam **13** as a crystalline solid (1.40 g, 84%): $[\alpha]_D = -117.1$ ($c = 1.00$, MeOH); mp 67−68 °C; IR ($CDCl_3$) 2982, 1771, 1721, 1371, 1350, 1330, 1282, 1161 cm^{-1}; ^1H NMR (200 MHz) δ 6.72 (dq, 1 H, $J = 1.7$, 2.1 Hz), 4.47 (dq, 1 H, $J = 2.1$, 6.6 Hz), 1.66 (t, 3 H, $J = 1.7$ Hz), 1.56 (s, 9 H), 1.39 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz) δ 169.9, 149.6, 144.8, 133.5, 82.6, 56.0, 28.1, 18.3, 10.8. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.47; H, 7.80; N, 6.44.

[3*S*/*R*,5*R*]-*N*-(*tert*-Butoxycarbonyl)-3,5-dimethyl-2-pyrrolidone (14a/14b). To a solution of lactam **13** (1.79 g, 8.47 mmol) of in 50 mL of EtOH was added 10% Pd/C (110 mg), and the round-bottomed flask was then flushed with argon and finally with hydrogen. The mixture was hydrogenated at atmospheric pressure for 24 h, filtered through Celite (followed by 4 × 15 mL EtOH rinse), and concentrated to give the pyrrolidones **14a**/**14b** as a 10:1 mixture of diastereomers (GC) (1.82 g, 100%): colorless oil, $[\alpha]_D = -55.2$ ($c = 1.00$, MeOH); IR ($CDCl_3$) 2979, 2936, 1775, 1714, 1457, 1370, 1343, 1292, 1257, 1154 cm^{-1}; ^1H NMR (200 MHz) δ 4.03 (app dq, 1 H, $J = 6.1$ Hz), 2.59−2.33 (m, 2 H), 1.54 (s, 9 H), 1.39 (d, 3 H, $J = 6.1$ Hz), 1.25 (d, 3 H, $J = 6.9$ Hz), 1.25 (m, 1 H); ^{13}C NMR (50 MHz) δ 177.1, 150.5, 82.7, 52.2, 37.6, 34.5, 28.1, 22.1, 16.4. HRFABMS calcd for MH^+ ($C_{11}H_{20}NO_3$) 214.1443, found: 214.1436, $\Delta = 3.3$ ppm.

[2*S*/*R*,4*R*]-4-((*tert*-Butoxycarbonyl)amino)-2-methylpentanoic Acid (15a/15b). Hydrogen peroxide (30% solution, 7.0 mL, 400 mol %) and lithium hydroxide monohydrate (1.45 g, 34.6 mmol, 200 mol %) were added to a solution of pyrrolidones **14a**/**14b** (3.67 g, 17.2 mmol, 100 mol %, 10:1 mixture of diastereomers) in 4:1 THF:water (125 mL) at 0 °C. The resultant cloudy mixture was stirred at 0 °C for 12 h. Saturated Na_2SO_3 (50 mL) and 1 M NaOH (100 mL) were then added, and the solution was washed with CH_2Cl_2 (2 × 200 mL). After acidification to pH = 2 with 0.5 M phosphoric acid, the mixture was extracted with EtOAc (5 × 100 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated to afford acid **15a**/**15b** as a clear oil, which solidified to a white crystalline mass (3.65 g, 92%): $[\alpha]_D = +1.8$ (for the mixture of diastereomers **15a** and **15b**, $c = 1.00$, MeOH), mp 73 °C (for an isolated crystal of **15a**); IR ($CDCl_3$) 3438, 2979, 1708, 1504, 1455, 1393, 1368, 1248, 1163, 1072 cm^{-1}; ^1H NMR (200 MHz) δ 11.19 (br s, 1 H), 4.41 (m, 1 H), 3.72 (m, 1 H), 2.48 (m, 1 H), 1.82 (m, 1 H), 1.50−1.36 (obs m, 1 H), 1.41 (s, 9 H), 1.22−1.13 (m, 3 H), 1.10 (d, 3 H, $J = 6.6$ Hz); HRFABMS calcd for MH^+ ($C_{11}H_{22}NO_4$): 232.1549, found: 232.1531, $\Delta = 7.8$ ppm. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 56.81; H, 9.27; N, 6.05.

[2*S*,2(2*S*,4*R*)]-Methyl 2-[4-((*tert*-Butoxycarbonyl)amino)-2-methyl-1-oxopentyl)amino]-3-hydroxypropionate (16a). To a solution of acid **15a**/**15b** (4.22 g, 18.2 mmol, 100 mol %, 10:1 mixture of diastereomers) in THF (120 mL) at −25 °C was added *N*-methylmorpholine (2.05 mL, 1.88 g, 18.6 mmol, 105 mol %), followed by isobutyl chloroformate (2.41 mL, 2.54 g, 18.6 mmol, 105 mol %). The resultant cloudy mixture was stirred at −25 °C for 10 min, and L-serine methyl ester hydrochloride (2.90 g, 18.6 mmol, 105 mol %) was then added, followed by *N*-methylmorpholine (2.35 mL, 2.16 g, 21.4 mmol, 120 mol %). The mixture was allowed to gradually warm to rt. After 16 h, the mixture was quenched with 7% $NaHCO_3$ solution (300 mL) and extracted with EtOAc (5 × 150 mL). The combined extracts were dried (Na_2SO_4) and concentrated to afford a viscous oil which was purified by flash chromatography (6 × 20 cm of silica, linear gradient of 17% acetone: $CHCl_3$ to 30% acetone:$CHCl_3$) to yield diastereomerically pure **16a** as a white, crystalline solid (4.89 g, 81%): $[\alpha]_D = +16.0$ ($c = 1.38$, MeOH); mp 124 °C; IR ($CDCl_3$) 3442, 2979, 1745, 1684, 1506, 1369, 1249, 1163, 1077 cm^{-1}; ^1H NMR (200 MHz) δ 6.92 (d, 1 H, $J = 7.7$ Hz), 4.70 (m, 2 H), 4.21 (app t, 1 H, $J = 7.0$ Hz), 3.99 (m, 2 H), 3.79 (s, 3 H), 3.60 (m, 1 H), 2.44 (ddq, 1 H, $J = 4.9$, 7.0, 10.2 Hz), 1.92 (app ddd, 1 H, $J = 4.9$, 10.2 Hz), 1.44 (m, 1 H), 1.42 (s, 9 H), 1.24 (d, 3 H, $J = 6.9$ Hz), 1.16 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR δ 175.5, 171.1, 155.7, 80.0, 63.0, 54.7, 52.5, 45.2, 41.6, 39.2, 28.4, 20.3, 18.8. Anal. Calcd for $C_{15}H_{28}N_2O_6$: C, 54.20; H, 8.49; N, 8.43. Found: C, 53.97; H, 8.42; N, 8.33.

[2*S*,2(2*S*,4*S*)]-Methyl 2-[4-((*tert*-Butoxycarbonyl)amino)-2-methyl-1-oxopentyl)amino]-3-hydroxypropionate (17). Following the procedure given for **16a**, acid **9a** (4.22 g, 18.3 mmol, 100 mol %) afforded, after recrystallization of the product from Et_2O−hexanes, the dipeptide **17** as a crystalline solid (4.79 g, 79%): $[\alpha]_D = +6.4$ ($c = 1.01$, MeOH); mp 126 °C; IR ($CDCl_3$) 3434, 3303, 2980, 1748, 1672, 1513, 1456, 1437, 1368, 1249, 1161, 1085 cm^{-1}; ^1H NMR (400 MHz) δ 7.91 (br d, 1 H, $J = 7.0$ Hz), 4.50 (m, 2 H), 4.06−3.91 (m, 3 H), 3.76 (s, 3 H), 3.20 (unresolved t, 1 H, $J = 5.9$ Hz), 2.40 (m, 1 H), 1.78 (app ddd, 1 H, $J = 2.7$, 11.3, 14.0 Hz), 1.43 (s, 9 H), 1.30 (app t, 1 H, $J = 11.5$ Hz), 1.16−1.12 (two overlapping doublets, 6 H, $J = 6.7$, 8.6 Hz); ^{13}C NMR (100 MHz) δ 176.3, 170.8, 156.8, 80.1, 63.0, 55.4, 52.4, 44.8, 43.9, 37.1, 28.4, 22.2, 17.9. Anal. Calcd for $C_{15}H_{28}N_2O_6$: C, 54.20; H, 8.49; N, 8.43. Found: C, 54.33; H, 8.63; N, 8.42.

[4*S*,2(1*S*,3*R*)]-2-[3-((*tert*-Butoxycarbonyl)amino)-1-methylbutyl]-2-oxazoline-4-carboxylic Acid, Methyl Ester (18). To dipeptide **16a** (2.49 g, 7.49 mmol, 100 mol %)

dissolved in THF (100 mL) at 0 °C was added Burgess reagent (2.05 g, 8.61 mmol, 115 mol %) over a period of 10 min, and the resulting solution was stirred for a further 15 min at 0 °C. The solution was then heated to reflux for 2 h, allowed to cool, and stirred at rt for 8 h. Evaporation of the solvent left a residue which was partitioned between saturated NH_4Cl (75 mL) and benzene (75 mL). The layers were separated, and the aqueous layer was extracted with benzene (2 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting oil was purified by flash chromatography (5 × 19 cm silica, 70% EtOAc:hexanes), giving 1.97 g (84%) of oxazoline **18** as a colorless oil: $[\alpha]_D = +109.8$ (c = 1.28, MeOH); IR ($CDCl_3$) 3439, 2979, 1740, 1706, 1653, 1506, 1438, 1367, 1216, 1161 cm^{-1}; ^1H NMR (400 MHz) δ 4.71 (dd, 1 H, J = 10.7, 7.8 Hz), 4.45 (t, 1 H, J = 8.6 Hz), 4.42 (m, 1 H), 4.39 (dd, 1 H, J = 8.6, 10.7 Hz), 3.78 (s, 3 H), 3.72 (m, 1 H), 2.59 (app dq, 1 H, J = 7.0 Hz), 1.83 (ddd, 1 H, J = 7.0, 10.2, 13.7 Hz), 1.54 (m, 1 H), 1.41 (s, 9 H), 1.21 (d, 3 H, J = 7.0 Hz), 1.12 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (100 MHz) δ 174.4, 171.8, 155.3, 79.0, 69.3, 67.8, 52.6, 44.6, 41.4, 30.8, 28.4, 22.1, 17.7; HRFABMS calcd for MH^+ ($C_{15}H_{27}N_2O_5$): 315.1920, found 315.1877, Δ = 14 ppm.

[4*S*,2(1*S*,3*S*)]-2-[3-((*tert*-Butoxycarbonyl)amino)-1-methylbutyl]-2-oxazoline-4-carboxylic Acid, Methyl Ester (19). Following the procedure given for **18**, dipeptide **17** (1.00 g, 3.01 mmol) similarly afforded oxazoline **19** as a colorless oil (0.78 g, 82%): $[\alpha]_D = +104.4$ (c = 1.62, MeOH); IR ($CDCl_3$) 3443, 2979, 1740, 1707, 1656, 1503, 1438, 1367, 1216, 1174 cm^{-1}; ^1H NMR (400 MHz) δ 4.71 (dd, 1 H, J = 7.8, 10.5 Hz), 4.45 (m, 1 H), 4.44 (t, 1 H, J = 8.6 Hz), 4.38 (dd, 1 H, J = 8.6, 10.5 Hz), 3.76 (s, 3 H), 3.70 (m, 1 H), 2.64 (m, 1 H), 1.80 (m, 1 H), 1.60 (m, 1 H), 1.41 (s, 9 H), 1.18 (d, 3 H, J = 7.0 Hz), 1.11 (d, 3 H, J = 6.7 Hz); ^{13}C NMR (100 MHz) δ 173.8, 171.7, 155.1, 79.0, 69.2, 67.9, 52.5, 44.8, 40.7, 30.5, 28.4, 20.8, 17.9; HRFABMS calcd for MH^+ ($C_{15}H_{27}N_2O_5$): 315.1920, found 315.1917, Δ = 1.0 ppm.

[4*S*,2(1*S*,3*R*)]-2-[3-((*tert*-Butoxycarbonyl)amino)-1-methylbutyl]-2-oxazole-4-carboxylic Acid, Methyl Ester (4). A solution of lithium hexamethyldisilazide in THF was prepared as follows: To a solution of hexamethyldisilazane (1.45 mL, 1.11 g, 6.89 mmol, 110 mol %) in THF (15 mL) at −78 °C was added *n*-butyllithium (2.35 M solution in hexanes, 2.95 mL, 6.89 mmol, 110 mol %), and the resulting clear solution was then warmed to 0 °C for 30 min and recooled to −78 °C. This solution was then added, via cannula, to a solution of oxazoline **18** (1.97 g, 6.27 mmol, 100 mol %) in THF (20 mL) held at −78 °C. After 15 min at −78 °C, trimethylsilyl chloride (835 mL, 715 mg, 6.58 mmol, 105 mol %) was added to the reaction mixture, and the solution was allowed to warm to −60 °C over a period of 10 min and then recooled to −78 °C. Upon addition of solid potassium hexamethyldisilazide (1.56 g, 7.83 mmol, 125 mol %), the solution turned pale yellow. After 20 min, a solution of iodine (1.99 g, 7.83 mmol, 125 mol %) in THF (15 mL) was added via cannula, resulting in immediate decolorization at first and then gradual darkening of the reaction mixture. The solution was allowed to warm to −20 °C over a period of 4 h. Saturated NH_4Cl (150 mL) and 10% $Na_2S_2O_3$ (50 mL) were then added, and the mixture was extracted with EtOAc (3 × 100 mL). The organic extracts were dried (Na_2SO_4) and concentrated to afford an oil which was purified by flash chromatography (4 × 18 cm of silica, linear gradient of 30% EtOAc:hexanes to 35% EtOAc:hexanes), yielding the side product i as a colorless oil (500 mg, 26%), followed by oxazole **4** as a solid (840 mg, 42%): $[\alpha]_D = +35.4$ (c = 1.00, MeOH); mp 55−56 °C (Et_2O/hexanes) (lit.[47] for *ent*-**4**: $[\alpha]^{27}_D = -30.6$ (c = 0.9, MeOH); mp 50−53 °C); IR ($CDCl_3$) 3438, 2979, 1708, 1597, 1503, 1440, 1368, 1326, 1246, 1159, 1112 cm^{-1}; ^1H NMR (400 MHz) δ 8.13 (s, 1 H), 4.24 (m, 1 H), 3.88 (s, 3 H), 3.75 (m, 1 H), 3.10 (app dq, 1 H, J = 6.7 Hz), 1.94 (ddd, 1 H, J = 6.2, 9.6, 14.0 Hz), 1.68 (m, 1 H), 1.39 (s, 9 H), 1.36 (d, 3 H, J = 7.0 Hz), 1.12 (d, 3 H, J = 6.5 Hz); ^{13}C NMR (100 MHz) δ 169.2, 161.7, 155.2, 143.6, 133.0, 79.1, 52.0, 44.4, 42.2, 31.0, 28.3, 22.0, 18.2. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C; 57.68, H; 7.74; N; 8.97. Found: C; 57.91, H; 7.85, N, 9.06.

[4*S*,2(1*S*,3*S*)]-2-[3-((*tert*-Butoxycarbonyl)amino)-1-methylbutyl]-2-oxazole-4-carboxylic Acid, Methyl Ester (20). To a suspension of $CuBr_2$ (721 mg, 3.23 mmol, 400 mol %) in degassed CH_2Cl_2 (20 mL) at rt was added hexamethylenetetramine (453 mg, 3.23 mmol, 400 mol %) as a solid, followed by addition of DBU (483 mL, 492 mg, 3.23 mmol, 400 mol %). The reaction mixture turned dark brown. After cooling to 0 °C, a solution of oxazoline **19** (254 mg, 0.808 mmol, 100 mol %) in degassed CH_2Cl_2 (10 mL) was added via cannula. The reaction mixture was allowed to gradually warm to rt. After 3.5 h, a 1:1 solution of saturated NH_4Cl and 25% aqueous NH_3 (50 mL) was added, and the blue mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The crude product thus obtained was purified by flash chromatography (3 × 17 cm, linear gradient of 30% EtOAc:hexanes to 35% EtOAc:hexanes) to afford the side product ii as a solid mass (100 mg, 40%), followed by oxazole **20** as a colorless oil (105 mg, 42%): $[\alpha]_D = +42.5$ (c = 0.84, MeOH); IR ($CDCl_3$) 3442, 2980, 1708, 1587, 1502, 1440, 1367, 1326, 1161, 1113 cm^{-1}; ^1H NMR (400 MHz) δ 8.14 (s, 1 H), 4.29 (m, 1 H), 3.90 (s, 3 H), 3.68 (m, 1 H), 3.14 (app dq, 1 H, J = 7.0 Hz), 2.00 (ddd, 1 H, J = 5.9, 8.3, 14 Hz), 1.75 (m, 1 H), 1.40 (s, 9 H), 1.35 (d, 3 H, J = 7.0 Hz), 1.11 (d, 3 H, J = 6.7 Hz); ^{13}C NMR (100 MHz) δ 168.9, 161.8, 155.0, 143.6, 133.1, 79.1, 52.0, 44.7, 41.8, 30.9, 28.3, 21.0, 18.8; HRFABMS calcd for MH^+ ($C_{15}H_{25}N_2O_5$): 313.1763, found 313.1747, Δ = 5.1 ppm.

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Supporting Information Available: ^1H and ^{13}C spectra of new compounds and characterization data for the side products **i** and **ii** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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