THE HIGHLY STEREOCONTROLLED RADICAL-BASED ADDITION OF A 2,2-DICHLOROACYL FUNCTION TO A 2-OXAZOLONE HETEROCYCLE. A NEW APPROACH TO MeBmt, THE KEY COMPONENT OF CYCLOSPORIN

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Abstract - The intramolecular Ru(II)-catalyzed addition of the 2,2-dichloro-4-hexenoyl pendant group to an 2-oxazolone moiety followed by treatment with $(Me_3Si)_3SiH$-Et_3B provides a perfectly stereocontrolled approach to the unusual amino acid (2*S*, 3*R*, 4*R*, 6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt), which contains three contiguous stereogenic centers and is a key component of cyclosporin.

The unusual C_9-amino acid (2*S*, 3*R*, 4*R*, 6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt), found in the immunosuppressive peptide cyclosporin,[1] appears to play a critical role in the observed biological activity of this chemotherapeutic agent[2] and represents an ideal target compound for asymmetric synthesis.[3-9] A number of strategies for the multistep synthesis of MeBmt have appeared[3-9] and involve stereoselective transformations of a variety of chiral sources such as tartaric acid,[3] glucose[4] and serine[5] as well as a rationally designed aldehyde[6] and epoxides.[7,8]

This paper describes an entirely different synthetic approach to this unusual hydroxy amino acid, which contains three contiguous stereogenic centers, in which the efficient chiral functionalization of a simple heterocycle, 2-oxazolone, is involved in the key step.

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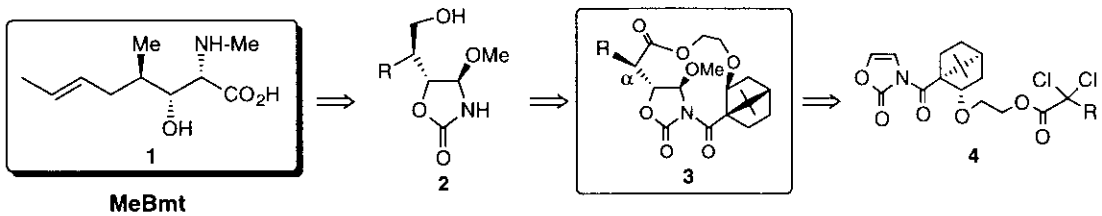
* Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

We previously demonstrated the versatility of 2-oxazolone as a building block for chiral hydroxy amino acids such as hydroxyglutamic acid,[10] statine[10,11] and the unusual amino acid components of amastatin and pepstatin.[12] Further investigation revealed an alternative method for the chiral synthesis of dichloro- and difluorostatines with adjacent chiral centers, involving the smooth intramolecular Ru(II)-catalyzed addition of the trihaloacetyl pendant groups to the 2-oxazolone moiety.[13] This promising strategy for intramolecular radical-based addition, which proceeds with complete diastereoselection, is now extended to the chiral construction of the three contiguous stereogenic centers found in MeBmt, as retrosynthetically shown in Scheme 1.



Scheme 1

The condensation of 2,2-dichloro-(4*E*)-hexenoic acid (**5**) and (1*R*,2*S*)-2-hydroxyethoxy-1-apocamphanecarboxylic ester (**6**)[14] gave the 1-apocamphanecarboxylic acid (**7**), whose sodium salts readily reacted with DPPOx (**8**)[15] to give the chiral 3-acyl-2-oxazolone (**9**) with a dichloroacyl pendant group. A benzene solution of **9** was refluxed in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ (0.1 eq.) for 168 h to give the 12-membered macrolide (**10**) in a diastereomeric ratio of 3.4:1, attributable to the Cα-isomers only. Methanolysis of the isomeric mixture (**10**) in refluxing methanol followed by treatment with $(Me_3Si)_3SiH$ under UV-irradiation gave the dechlorinated compound (**12**) with 99% de, while reduction with Bu_3SnH resulted in a lower selectivity of 87% de. The formation of small amounts of by-product, presumably an olefinic (*Z*)-isomer, was unavoidable under conditions of UV-irradiation. When Et_3B was used as an initiator instead of UV-irradiation, the reaction of **11** with $(Me_3Si)_3SiH$ proceeded smoothly to give a quantitative yield of the key intermediate (**12**) with perfectly controlled contiguous chiral centers with no detectable by-products.

The excellent selectivity thus observed can be rationalized by assuming an exclusive attack of the bulky reductant from the less hindered side to the carbon radicals generated *in situ*, as is schematically shown in Figure 1. This consideration is further supported by the stereochemistry of the macrolide (**12**), verified by positive and negative NOE differences between the *H*a and methylene protons, and the *H*a and *H*b-protons, respectively, as depicted in Figure 2.

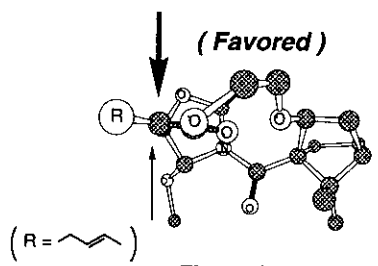


Figure 1

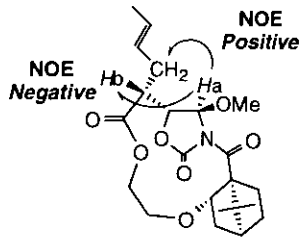
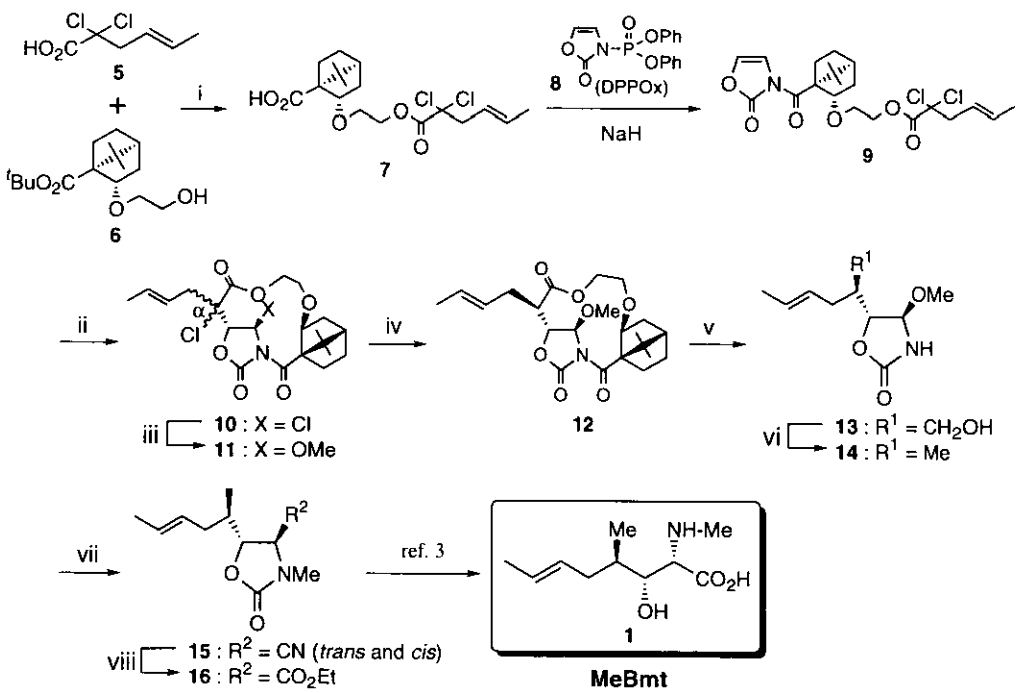


Figure 2

The apocamphanecarbonyl auxiliary was reductively cleaved by $LiBH_4$-MeOH (1:2)[16] to give the 2-oxazolidinone derivative (**13**), the hydroxymethyl function of which was converted to a methyl group by conventional procedures. The *N*-methylation of **14** thus formed followed by cyanation[10] gave the cyanides (**15**) as a mixture of *trans*- and *cis*-isomers (1.4:1), which were readily separable by chromatography. Treatment of the isomeric mixture (**15**) with K_2CO_3 in EtOH at room temperature followed by acidification gave the *trans*-ester (**16**) in 90% yield,[3] whose spectral and physical data were in good agreement with those previously reported,[3] except for optical rotatory data.[17] The hydrolytic conversion of **16** to MeBmt has been well established.[3]



i) 1) $SOCl_2$, 2) NaH/THF; rt, 3) TFA; ii) $RuCl_2(PPh_3)_3$/PhH; reflux; iii) MeOH; reflux; iv) $(TMS)_3SiH$, BEt_3/Toluene; -78 °C; v) $LiBH_4$-MeOH(1:2)/THF; 0 °C; vi) 1) MsCl, NEt_3/THF; rt, 2) NaI/DME; reflux, 3) Bu_3SnH, BEt_3/THF; -78 °C; vii) 1) MeI, NaH/THF; rt, 2) TMSCN, BF_3•OEt/CH_2Cl_2; -50 °C→rt; viii) 1) K_2CO_3/EtOH; rt, 2) 2N HCl; rt

Scheme 2

In conclusion, the intramolecular radical-based addition of the dichloroacyl pendant group to the 2-oxazolone heterocyclic moiety presented here provides a useful tool for the effective construction of chiral skeletons with three contiguous stereogenic centers, such as is found in MeBmt. This methodology has the potential for serving as a general synthetic method for a variety of 2-amino alcohols with multi-stereogenic centers of biological interest.

EXPERIMENTAL

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP 370 polarimeter. IR spectra were recorded on a JASCO IR Report-100 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard at 500 MHz on a JEOL ALPHA-500 spectrometer. MS and HRMS were obtained with a JEOL JMS-DX303HF mass spectrometer. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). All solvents were distilled prior to use; THF over Na/benzophenone, Et_2O over $LiAlH_4$, CH_2Cl_2 over CaH_2, MeOH over NaOMe and benzene over CaH_2.

2,2-Dichloro-(4*E*)-hexenoic acid (5). A solution of *t*-butyl dichloroacetate (2.76 g, 14.9 mmol) in THF (14 mL) was added dropwise to a solution of $HNEt_2$ (3.60 g, 49.3 mmol), BuLi (1.70 M in hexane; 26.4 mL, 44.8 mmol) and HMPA (2.68 g, 14.9 mmol) in THF (21 mL) under an argon atmosphere at -78 °C over a period of 30 min. After stirring at -78 °C for 30 min, a solution of *trans*-crotyl chloride[18] (2.70 g, 29.8 mmol), derived from *trans*-2-butenol[19] in THF (7 mL), was added at -78 °C, followed by stirring at rt for 10 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl, followed by the addition of 200 mL of EtOAc. The usual work-up followed by chromatography on silica gel (hexane → hexane:CH_2Cl_2 = 9:1) yielded *t*-butyl 2,2-dichloro-(4*E*)-hexenoate (2.20 g, 62%) as a colorless oil; bp 53.6 °C/2.5 mmHg. ^{1}H NMR δ 1.52 (9H, s), 1.71 (3H, d, J = 6.7 Hz), 3.06 (2H, d, J = 6.7 Hz), 5.45-5.51 (1H, m), 5.65-5.71 (1H, m). The *t*-butyl ester was treated with CF_3CO_2H (10.5 g, 92 mmol) in CH_2Cl_2 (3.6 mL) at rt for 3 h to give **5** (1.7 g, quant.) as a colorless oil; IR (neat) 3600-2400, 2970, 2920, 2850, 1740, 1720, 1635, 1420, 1260, 1210, 965, 700 cm^{-1}; ^{1}H NMR δ 1.73 (3H, d, J = 6.7 Hz), 3.12 (2H, d, J = 6.7 Hz), 5.48-5.55 (1H, m), 5.70-5.77 (1H, m), 7.21 (1H, br s); MS (FAB,

$CHCl_3$+NBA+NaI): m/z 227 ([M+2Na-H]$^+$), 205; HRMS (FAB, $CHCl_3$+NBA+NaI) calcd for $C_6H_7O_2Cl_2Na_2$ ([M+2Na-H]$^+$): m/z 226.9619, found: m/z 226.9602.

(1*R*,2*S*)-2-[2-(2,2-Dichloro-(4*E*)-hexenoyloxy)ethoxy]-7,7-dimethylbicyclo[2.2.1]-heptane-1-carboxylic acid (7). To a solution of **6**[14] (1.88 g, 6.60 mmol) in THF (33 mL) was added 2,2-dichloro-(4*E*)-hexenoyl chloride, derived from **5** (3.02 g, 16.5 mmol) and $SOCl_2$ (19.6 g, 165 mmol), in the presence of NaH (60% in oil; 0.66 g, 16.5 mmol) and the mixture was stirred at rt for 3 h. The reaction was quenched by passing the solution through a silica gel-pad with EtOAc (200 mL) as eluent. The usual work-up followed by chromatography on silica gel (hexane:CH_2Cl_2 = 9:1 → 2:8) yielded *t*-butyl (1*R*, 2*S*)-2-[2-(2,2-dichloro-(4*E*)-hexenoyloxy)ethoxy]-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (2.69 g, 91%) as a colorless oil; $[\alpha]_D^{27}$ +35.3 ° (*c* 1.03, $CHCl_3$); IR (neat) 2970, 2930, 2880, 1760, 1740, 1725, 1710, 1450, 1360, 1320, 1250, 1180, 1120, 1035, 965, 850 cm^{-1}; ^{1}H NMR δ 1.02-1.06 (1H, m), 1.04 (3H, s), 1.25 (3H, s), 1.37-1.44 (1H, m), 1.46 (9H, s), 1.60-1.72 (6H, m), 1.86-1.94 (2H, m), 3.09 (2H, dd, *J* = 1.2, 7.3 Hz), 3.64-3.70 (3H, m), 4.29-4.33 (2H, m), 5.46-5.51 (1H, m), 5.67-5.71 (1H, m); MS (FAB, $CHCl_3$+NBA+NaI): m/z 471 (MNa$^+$), 415, 375, 209, 57; HRMS (FAB, $CHCl_3$+NBA+NaI) calcd for $C_{22}H_{34}O_5Cl_2Na$ (MNa$^+$): m/z 471.1681, found: m/z 471.1703.

Subsequent treatment of the *t*-butyl ester (9.68 g, 21.5 mmol) with CF_3CO_2H (6.8 g, 60 mmol) in CH_2Cl_2 (6 mL) at rt for 3 h gave **7** (2.39 g, quant.) as a colorless oil; $[\alpha]_D^{26}$ +41.2 ° (*c* 1.00, $CHCl_3$); IR (neat) 3600-2400, 2950, 2900, 1740, 1710, 1690, 1450, 1380, 1250, 1100, 1035, 965, 860, 720 cm^{-1}; ^{1}H NMR δ 1.05 (3H, s), 1.08-1.35 (1H, m), 1.20 (3H, s), 1.25-1.33 (2H, m), 1.71 (3H, dd, *J* = 1.2, 6.7 Hz), 1.80-1.87 (3H, m), 2.00-2.04 (1H, m), 2.36-2.41 (1H, m), 3.10 (2H, d, *J* = 6.7 Hz), 3.76 (1H, ddd, *J* = 3.1, 6.1, 12.2 Hz), 3.84 (1H, dd, *J* = 3.1, 6.7 Hz), 3.86 (1H, ddd, *J* = 3.1, 6.1, 12.2 Hz), 4.38 (1H, ddd, *J* = 3.1, 6.1, 12.2 Hz), 4.45 (1H, ddd, *J* = 3.1, 6.1, 12.2 Hz), 5.30-5.50 (1H, m), 5.67-5.72 (1H, m); MS (FAB, $CHCl_3$+NBA+NaI): m/z 437 ([M+2Na-H]$^+$), 415 (MNa$^+$), 375, 209; HRMS (FAB, $CHCl_3$+NBA+NaI) calcd for $C_{18}H_{26}O_5Cl_2Na$ (MNa$^+$): m/z 415.1055, found: m/z 415.1042.

3-[(1*R*,2*S*)-2-[2-(2,2-Dichloro-(4*E*)-hexenoyloxy)ethoxy]-7,7-dimethylbicyclo[2.2.1]-heptane-1-carbonyl]-2-oxazolone (9). To the mixture of sodium carboxylate derived from **7** (1.21 g, 3.1 mmol) and NaH (60% in oil; 0.14 g, 3.4 mmol) in THF (10 mL), DPPOx[15] (**8**) (diphenyl 2-oxo-3-oxazolinylphosphonate; 0.98 g, 3.1 mmol) in THF (13 mL) was added at 0 °C followed by stirring at rt for 2 h. The solution was passed through a silica gel-pad (EtOAc as eluent) followed by evaporation and column chromatography on silica gel (hexane:CH_2Cl_2 = 5:5 → CH_2Cl_2) to give the 2-oxazolone derivative

(**9**) (1.30 g, 92%) as a colorless oil; $[\alpha]_D^{27}$ +42.4 ° (c 1.01, $CHCl_3$); IR (neat) 3150, 2940, 2880, 1790, 1760, 1745, 1710, 1355, 1280, 1230, 1120, 1070, 968, 912, 837, 702 cm^{-1}; ^1H NMR δ 1.14 (3H, s), 1.17-1.21 (1H, m), 1.33 (3H, s), 1.70 (3H, dd, *J* = 1.2, 6.7 Hz), 1.70-1.84 (4H, m), 1.93-1.97 (1H, m), 2.36-2.40 (1H, m), 3.03 (2H, d, *J* = 6.7 Hz), 3.52 (1H, dt, *J* = 4.3, 11.6 Hz), 3.65 (1H, dt, *J* = 4.3, 11.6 Hz), 4.23 (2H, t, *J* = 4.3 Hz), 4.79 (1H, q, *J* = 3.7 Hz), 5.43-5.49 (1H, m), 5.62-5.68 (1H, m), 6.78 (1H, d, *J* = 2.4 Hz), 7.27 (1H, d, *J* = 2.4 Hz); MS (FAB, $CHCl_3$+NBA+NaI): m/z 482 (MNa^+), 375, 209; HRMS (FAB, $CHCl_3$+NBA+NaI) calcd for $C_{21}H_{27}NO_6Cl_2Na$ (MNa^+): m/z 482.1113, found: m/z 482.1111.

Intramolecular Cyclization to the Macrolide (10). A mixture of **9** (8.29 g, 18.0 mmol) and $RuCl_2(PPh_3)_3$ (1.73 g, 1.80 mmol) in benzene (360 mL) was refluxed for 168 h. The mixture was passed through a silica gel-pad with EtOAc as eluent. Evaporation of the eluate followed by chromatography on silica gel (hexane:CH_2Cl_2 = 8:2 → 4:6) afforded the macrolide (**10**) (4.65 g, 56%) as colorless crystals; mp 187-190 °C (from hexane-CH_2Cl_2). The ^1H NMR spectrum showed a diastereomeric mixture in a ratio of 3.4:1. IR (nujol) 1795, 1740, 1700, 1280, 1115, 975, 915 cm^{-1}; ^1H NMR δ 1.15-1.26 (1H, m), 1.20 (3H, s), 1.21 (3H, s), 1.63-1.68 (2H, m), 1.73 (3H, d, *J* = 6.1 Hz), 1.83-1.93 (3H, m), 2.24-2.32 (1H, m), 2.74-3.00 (2H, m), 3.28 and 3.30 (1H, dt, *J* = 1.8, 11.6 Hz), 3.75-3.93 (2H, m), 4.31 (1H, q, *J* = 3.7 Hz), 4.78 and 4.85 (1H, d, *J* = 1.2 Hz), 4.89 and 4.97 (1H, dt, *J* = 1.8, 11.6 Hz), 5.30-5.50 (1H, m), 5.70-5.77 (1H, m), 6.22 and 6.38 (1H, d, *J* = 1.2 Hz); MS (FAB, $CHCl_3$+NBA+NaI): m/z 482 (MNa^+), 176; HRMS (FAB, $CHCl_3$+NBA+NaI) calcd for $C_{21}H_{27}NO_6Cl_2Na$ (MNa^+): m/z 482.1113, found: m/z 482.1116.

Methanolysis to 11. A solution of **10** (4.65 g, 10.1 mmol) in methanol (200 mL) was refluxed for 3 h and usual work-up gave diastereomeric mixture **11** (4.58 g, quant.) as colorless crystals; mp 112-122 °C (from hexane-CH_2Cl_2); IR (nujol) 1798, 1740, 1696, 1280, 1240, 1200, 1115, 1095, 975, 917, 727 cm^{-1}; ^1H NMR δ 1.13-1.22 (7H, m), 1.62-1.66 (2H, m), 1.72 (3H, d, *J* = 6.1 Hz), 1.79-1.84 (2H, m), 1.88-1.94 (1H, m), 2.32-2.39 (1H, m), 2.67 and 2.78 (1H, dd, *J* = 7.9, 14.7 Hz), 2.95 and 2.98 (1H, dd, *J* = 6.7, 14.7 Hz), 3.29 and 3.31 (1H, t, *J* = 11.6 Hz), 3.53 and 3.59 (3H, s), 3.73 and 3.75 (1H, d, *J* = 11.6 Hz), 3.82 and 3.92 (1H, d, *J* = 11.6 Hz), 4.35 (1H, q, *J* = 3.7 Hz), 4.42 and 4.49 (1H, s), 4.87 and 4.92 (1H, dt, *J* = 1.8, 11.6 Hz), 5.45-5.55 (1H, m), 5.52 and 5.55 (1H, s), 5.66-5.74 (1H, m); MS (FAB, $CHCl_3$+NBA+NaI): m/z 478 (MNa^+), 424, 329, 176; HRMS (FAB, $CHCl_3$+NBA+NaI) calcd for $C_{22}H_{30}NO_7ClNa$ (MNa^+): m/z 482.1609, found: m/z 478.1598.

Reductive Dechlorination to 12. To a mixture of **11** (3.83 g, 8.41 mmol) and tris(trimethylsilyl)-silane (2.30 g, 9.25 mmol) in toluene (168 mL), triethylborane (1.04 M in hexane; 2.43 mL, 2.52 mmol) was added at -78 °C under an argon atmosphere followed by stirring for 5 h. The solution was then passed through a silica gel-pad (EtOAc as eluent). The usual work-up of the eluate afforded **12** (3.55 g, quant.) as colorless crystals; mp 101.5-102.0 °C (from hexane); $[\alpha]_D^{28}$ +26.7 ° (c 1.00, $CHCl_3$); IR (nujol) 1783, 1740, 1695, 1280, 1240, 1180, 1110, 980, 770, 720 cm^{-1}; ^1H NMR δ 1.13-1.21 (1H, m), 1.20 (3H, s), 1.22 (3H, s), 1.58-1.65 (2H, m), 1.67 (3H, dd, *J* = 1.2, 6.7 Hz), 1.81-1.93 (3H, m), 2.15 (1H, quintet, *J* = 7.3 Hz), 2.37 (1H, ddd, *J* = 3.6, 9.2, 12.2 Hz), 2.49 (1H, ddd, *J* = 6.1, 7.9, 12.2 Hz), 2.86 (1H, ddd, *J* = 3.6, 7.9, 9.2 Hz), 3.22 (1H, dt, *J* = 1.8, 11.6 Hz), 3.50 (3H, s), 3.666 (1H, t, *J* = 11.6 Hz), 3.670 (1H, t, *J* = 11.6 Hz), 4.33 (1H, q, *J* = 3.7 Hz), 4.40 (1H, dd, *J* = 1.2, 3.6 Hz), 4.98 (1H, dt, *J* = 1.8, 11.6 Hz), 5.32-5.38 (1H, m), 5.52 (1H, d, *J* = 1.2 Hz), 5.54-5.60 (1H, m). Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.64; H, 7.49; N, 3.42.

The optical purity was in excess of 99% de, as evidenced by HPLC analysis on a DAICEL CHIRALCEL-AD column with hexane-IPA (99:1) as an eluent.

(4*R*, 5*R*)-5-[(1*S*, 3*E*)-1-Hydroxymethyl-3-pentenyl]-4-methoxy-2-oxazolidinone (13). A solution of **12** (1.28 g, 3.04 mmol) in THF (36 mL) was treated with $LiBH_4$ (2.0 M in THF; 7.6 mL, 15.2 mmol) and MeOH (0.97 g, 30.4 mmol) at 0 °C under an argon atmosphere for 3 h. The mixture was then passed through a silica gel-pad with EtOAc as the eluent. The usual work-up of the eluate followed by chromatography on silica gel (hexane:AcOEt = 1:1 → 1:9) afforded, in addition to the oily 2-*exo*-hydroxyethoxy-1-apocamphanemethanol (0.66 g, quant.), the deacylated 2-oxazolidinone (**13**) (0.44 g, 67%) as colorless crystals; mp 104-105 °C (from hexane-CH_2Cl_2); $[\alpha]_D^{28}$ +121.0 ° (c 0.50, $CHCl_3$); IR (nujol) 3330, 1750, 1725, 1235, 1100, 1060, 1030, 1010, 970, 940 cm^{-1}; ^1H NMR δ 1.67 (3H, d, *J* = 6.1 Hz), 1.79-2.18 (3H, m), 3.34 (3H, s), 3.64 (1H, dd, *J* = 6.7, 11.0 Hz), 3.74 (1H, dd, *J* = 3.7, 11.0 Hz), 4.52 (1H, dd, *J* = 1.8, 5.5 Hz), 5.03 (1H, s), 5.36-5.44 (1H, m), 5.48-5.60 (1H, m), 7.16 (1H, br s). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.97; H, 8.03; N, 6.47.

(4*R*,5*R*)-5-[(1*S*,3*E*)-1-Methanesulfonyloxymethyl-3-pentenyl]-4-methoxy-2-oxazolidinone. To a mixture of **13** (1.03 g, 4.80 mmol) and triethylamine (0.73 g, 7.20 mmol) in THF (60 mL), methanesulfonyl chloride (0.60 g, 5.28 mmol) in THF (10 mL) was added at 0 °C followed by stirring at rt for 30 min. The solution was passed through a silica gel-pad (EtOAc as eluent) followed by evaporation *in vacuo*. Column chromatography on silica gel (CH_2Cl_2:EtOAc = 4:1 → 1:1) afforded the

mesylate (1.41 g, quant.) as colorless crystals; mp 67-69 °C (from hexane-CH_2Cl_2); $[\alpha]_D^{28}$ +101.5 ° (c 1.02, $CHCl_3$); IR (nujol) 3270, 1750, 1720, 1363, 1225, 1180, 995, 975, 840 cm^{-1}; ^1H NMR δ 1.68 (3H, d, *J* = 7.3 Hz), 2.05-2.11 (1H, m), 2.15-2.24 (2H, m), 3.04 (3H, s), 3.35 (3H, s), 4.15 (1H, dd, *J* = 7.3, 10.4 Hz), 4.30 (1H, dd, *J* = 4.3, 10.4 Hz), 4.52 (1H, dd, *J* = 1.8, 4.9 Hz), 4.90 (1H, d, *J* = 1.8 Hz), 5.32-5.38 (1H, m), 5.53-5.60 (1H, m), 7.11 (1H, br s). Anal. Calcd for $C_{11}H_{19}NO_6S$: C, 45.04; H, 6.53; N, 4.77. Found: C, 44.94; H, 6.56; N, 4.75.

(4*R*, 5*R*)-5-[(1*R*, 3*E*)-1-Iodomethyl-3-pentenyl]-4-methoxy-2-oxazolidinone. A mixture of (4*R*, 5*R*)-5-[(1*S*, 3*E*)-1-methanesulfonyloxymethyl-3-pentenyl]-4-methoxy-2-oxazolidinone (1.41 g, 4.78 mmol) and sodium iodide (1.43 g, 9.57 mmol) in dimethoxyethane (96 mL) was refluxed for 1 h. The solution was then passed through a silica gel-pad (EtOAc as eluent) followed by evaporation *in vacuo*. Column chromatography on silica gel (CH_2Cl_2:EtOAc = 9:1 → 4:1) afforded the iodide (1.48 g, 95%) as colorless crystals; mp 68.0-68.5 °C (from hexane-CH_2Cl_2); $[\alpha]_D^{27}$ +83.0 ° (c 0.76, $CHCl_3$); IR (nujol) 3290, 1742, 1710, 1235, 1082, 1065, 1008, 968, 958 cm^{-1}; ^1H NMR δ 1.68 (3H, d, *J* = 5.5 Hz), 1.76-1.83 (1H, m), 2.11 (1H, quintet, *J* = 7.3 Hz), 2.26-2.30 (1H, m), 3.21 (2H, dd, *J* = 1.2, 7.3 Hz), 3.36 (3H, s), 4.54 (1H, dd, *J* = 1.8, 4.9 Hz), 4.82 (1H, d, *J* = 1.8 Hz), 5.29-5.35 (1H, m), 5.57-5.63 (1H, m), 6.99 (1H, br s). Anal. Calcd for $C_{10}H_{16}NO_3I$: C, 36.94; H, 4.96; N, 4.31. Found: C, 36.92; H, 4.89; N, 4.28.

(4*R*, 5*R*)-4-Methoxy-5-[(1*R*, 3*E*)-1-methyl-3-pentenyl]-2-oxazolidinone (14). To a mixture of (4*R*, 5*R*)-5-[(1*R*, 3*E*)-1-iodomethyl-3-pentenyl]-4-methoxy-2-oxazolidinone (0.59 g, 1.83 mmol) and tributyltin hydride (0.64 g, 2.19 mmol) in THF (36 mL), triethylborane (1.04 M in hexane; 0.53 mL, 0.55 mmol) was added at -78 °C under an argon atmosphere followed by stirring for 1 h. The solution was then passed through a silica gel-pad (EtOAc as eluent) followed by evaporation *in vacuo*. Column chromatography on silica gel (CH_2Cl_2:EtOAc = 9:1 → 7:3) afforded **14** (0.36 g, quant.) as colorless crystals; mp 66.2-66.5 °C (from hexane); $[\alpha]_D^{27}$ +109.1 ° (c 0.98, $CHCl_3$); IR (nujol) 3270, 1740, 1712, 1230, 1110, 1070, 1020, 970, 950, 920 cm^{-1}; ^1H NMR δ 0.93 (3H, d, *J* = 6.7 Hz), 1.67 (3H, dd, *J* = 1.2, 6.7 Hz), 1.78-1.84 (1H, m), 1.91-1.97 (1H, m), 2.19-2.22 (1H, m), 3.33 (3H, s), 4.19 (1H, dd, *J* = 1.8, 7.3 Hz), 4.76 (1H, t, *J* = 1.8 Hz), 5.34-5.40 (1H, m), 5.46-5.52 (1H, m), 7.31 (1H, br s). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.58; H, 8.64; N, 7.08.

(4*R*, 5*R*)-4-Methoxy-3-methyl-5-[(1*R*, 3*E*)-1-methyl-3-pentenyl]-2-oxazolidinone. To a mixture of **14** (0.28 g, 1.41 mmol) and iodomethane (0.80 g, 5.63 mmol) in THF (14 mL), NaH (60% in

oil; 0.09 g, 2.11 mmol) was added at 0 °C followed by stirring at rt for 1 h. The solution was passed through a silica gel-pad (EtOAc as eluent) followed by evaporation *in vacuo*. Column chromatography on silica gel (CH_2Cl_2:EtOAc = 9:1 → 7:3) afforded (4*R*, 5*R*)-4-methoxy-3-methyl-5-[(1*R*, 3*E*)-1-methyl-3-pentenyl]-2-oxazolidinone (0.30 g, quant.) as a colorless oil; $[\alpha]_D^{27}$ +71.9 ° (c 0.89, $CHCl_3$); IR (neat) 2960, 2920, 1770, 1430, 1395, 1220, 1040, 970 cm^{-1}; ^1H NMR δ 0.93 (3H, d, *J* = 6.7 Hz), 1.67 (3H, dd, *J* = 1.2, 6.1 Hz), 1.73-1.80 (1H, m), 1.91-1.97 (1H, m), 2.17-2.22 (1H, m), 2.92 (3H, s), 3.30 (3H, s), 4.08 (1H, dd, *J* = 1.8, 7.3 Hz), 4.70 (1H, d, *J* = 1.8 Hz), 5.30-5.39 (1H, m), 5.46-5.52 (1H, m); MS (EI): m/z 213 (M^+), 198, 182, 156, 126, 85; HRMS (EI) calcd for $C_{11}H_{19}NO_3$ (M^+): m/z 213.13648, found: m/z 213.13670.

(4*S*,5*R*)- and (4*R*,5*R*)-3-methyl-5-[(1*R*,3*E*)-1-methyl-3-pentenyl]-2-oxo-4-oxazolidinecarbonitrile (15). To a solution of (4*R*, 5*R*)-4-methoxy-3-methyl-5-[(1*R*, 3*E*)-1-methyl-3-pentenyl]-2-oxazolidinone (0.30 g, 1.38 mmol) and trimethylsilyl cyanide (0.27 g, 2.76 mmol) in CH_2Cl_2 (14 mL), BF_3•OEt_2 (0.20 g, 1.38 mmol) in CH_2Cl_2 (1.4 mL) was added at -78 °C under an argon atmosphere followed by stirring at rt for 10 h. The mixture was passed through a silica gel-pad with EtOAc as the eluent. Concentration of the eluate *in vacuo* followed by chromatography on silica gel (CH_2Cl_2 → CH_2Cl_2:EtOAc = 19:1) afforded **15** as a mixture of *trans*- and *cis*-isomers which were readily separable by column chromatography on silica gel (hexane:EtOAc = 4:1 → 3:2).

***trans*-15** ((4*S*)-form; lower polarity)**:** 0.14 g (52%) as colorless crystals; mp 42.5-43.0 °C (from hexane-CH_2Cl_2); $[\alpha]_D^{27}$ +35.6 ° (c 0.71, $CHCl_3$); IR (neat) 2960, 2920, 2850, 1760, 1425, 1390, 1220, 1140, 1120, 1040, 965, 823 cm^{-1}; ^1H NMR δ 0.98 (3H, d, *J* = 6.1 Hz), 1.69 (3H, dd, *J* = 1.2, 6.1 Hz), 1.91-1.99 (1H, m), 2.00-2.06 (1H, m), 2.18-2.23 (1H, m), 2.99 (3H, s), 4.22 (1H, d, *J* = 6.1 Hz), 4.49 (1H, t, *J* = 6.1 Hz), 5.33-5.39 (1H, m), 5.51-5.58 (1H, m). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.42; H, 7.74; N, 13.21.

***cis*-15** ((4*R*)-form; higher polarity)**:** 0.11 g (38%) as colorless crystals; mp 68.5-69.5 °C (from hexane-CH_2Cl_2); $[\alpha]_D^{28}$ -7.8 ° (c 0.77, $CHCl_3$); IR (neat) 2960, 2920, 2850, 1760, 1425, 1390, 1220, 1140, 1120, 1040, 965, 823 cm^{-1}; ^1H NMR δ 0.99 (3H, d, *J* = 6.7 Hz), 1.68 (3H, d, *J* = 7.3 Hz), 2.02-2.09 (1H, m), 2.12-2.18 (1H, m), 2.41-2.46 (1H, m), 3.01 (3H, s), 4.21 (1H, dd, *J* = 7.3, 10.4 Hz), 4.49 (1H, d, *J* = 7.3 Hz), 5.36-5.42 (1H, m), 5.51-5.58 (1H, m). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.38; H, 7.89; N, 13.30.

Ethyl (4*S*,5*R*)-3-Methyl-5-[(1*R*,3*E*)-1-methyl-3-pentenyl]-2-oxo-4-oxazolidinecarboxylate (16). A mixture of *trans*- and *cis*- **15** (0.12 g, 0.57 mmol) and K_2CO_3 (0.16 g, 1.16 mmol) in EtOH (17 mL) was stirred at rt for 2 h and then acidified with a solution of 2N HCl (1.75 mL, 3.49 mmol). After stirring for an additional 1 h, the solution was neutralized with a saturated solution of $NaHCO_3$. After removal of the solvents, EtOAc (100 mL) was added, followed by washing (brine, 20 mL × 3) and concentrated *in vacuo*. Column chromatography on silica gel (hexane:EtOAc = 8:2) afforded **16** (0.13 g, 90%) as a colorless oil; $[\alpha]_D^{28}$ +34.0 ° (c 1.31, $CHCl_3$) (lit.,[3] $[\alpha]_D$ +29.5 ° (c 1.0, $CHCl_3$)); IR (neat) 2970, 2930, 1762, 1750, 1440, 1400, 1220, 1140, 1045, 970 cm^{-1}; ^1H NMR δ 0.94 (3H, d, *J* = 6.7 Hz), 1.32 (3H, t, *J* = 6.7 Hz), 1.66 (3H, dd, *J* = 1.2, 6.1 Hz), 1.84-1.90 (1H, m), 1.95 (1H, quintet, *J* = 7.3 Hz), 2.18-2.25 (1H, m), 2.91 (3H, s), 3.95 (1H, d, *J* = 4.9 Hz), 4.23-4.31 (3H, m), 5.33-5.39 (1H, m), 5.45-5.53 (1H, m); MS (EI): m/z 255 (M^+), 198, 182, 128, 100, 55; HRMS (EI) calcd for $C_{13}H_{21}NO_4$ (M^+): m/z 255.1470, found: m/z 255.1462.

In addition to **16**, the 4,5-*cis*-carboxylate was isolated in 1% yield (2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, d, *J* = 6.7 Hz), 1.32 (3H, t, *J* = 6.7 Hz), 1.66 (3H, d, *J* = 6.1 Hz), 1.69-1.76 (1H, m), 1.94-2.00 (1H, m), 2.33-2.39 (1H, m), 2.84 (3H, s), 4.18 (1H, d, *J* = 7.3 Hz), 4.23-4.35 (3H, m), 5.32-5.38 (1H, m), 5.47-5.53 (1H, m). The *cis*-stereochemistry was verified by differential NOE analysis.

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17. This discrepancy might come from possible contamination with the *cis*-isomer.[7]

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Received, 1st June, 1998