

**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  $(\text{Me}_3\text{Si})_3\text{SiH-Et}_3\text{B}$  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.

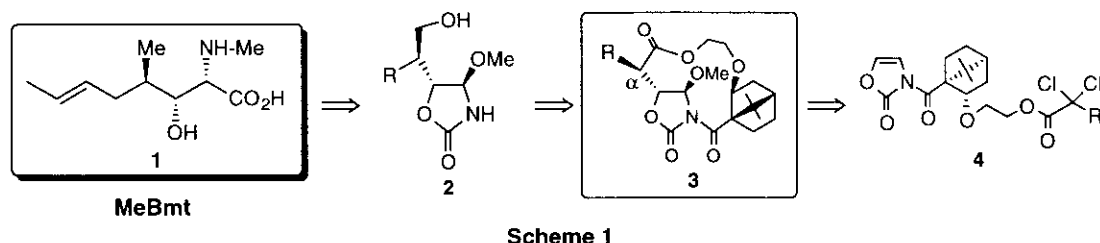
The unusual C<sub>9</sub>-amino acid (2*S*, 3*R*, 4*R*, 6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt), found in the immunosuppressive peptide cyclosporin,<sup>1</sup> appears to play a critical role in the observed biological activity of this chemotherapeutic agent<sup>2</sup> and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

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,<sup>10</sup> statine<sup>10,11</sup> and the unusual amino acid components of amastatin and pepstatin.<sup>12</sup> 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.<sup>13</sup> 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.



The condensation of 2,2-dichloro-(4*E*)-hexenoic acid (**5**) and (1*R*,2*S*)-2-hydroxyethoxy-1-apocamphane-carboxylic ester (**6**)<sup>14</sup> gave the 1-apocamphanecarboxylic acid (**7**), whose sodium salts readily reacted with DPPOx (**8**)<sup>15</sup> to give the chiral 3-acyl-2-oxazolone (**9**) with a dichloroacetyl pendant group. A benzene solution of **9** was refluxed in the presence of a catalytic amount of RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (0.1 eq.) for 168 h to give the 12-membered macrolide (**10**) in a diastereomeric ratio of 3.4:1, attributable to the C $\alpha$ -isomers only. Methanolysis of the isomeric mixture (**10**) in refluxing methanol followed by treatment with (Me<sub>3</sub>Si)<sub>3</sub>SiH under UV-irradiation gave the dechlorinated compound (**12**) with 99% de, while reduction with Bu<sub>3</sub>SnH 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<sub>3</sub>B was used as an initiator instead of UV-irradiation, the reaction of **11** with (Me<sub>3</sub>Si)<sub>3</sub>SiH 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 *Ha* and methylene protons, and the *Ha* and *Hb*-protons, respectively, as depicted in Figure 2.

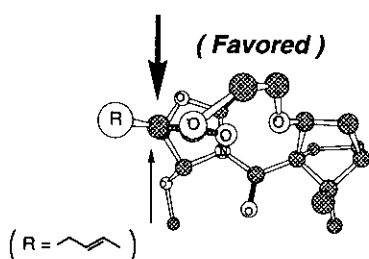


Figure 1

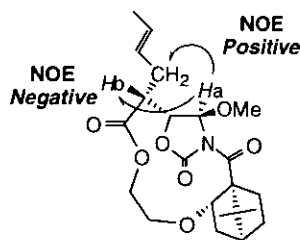
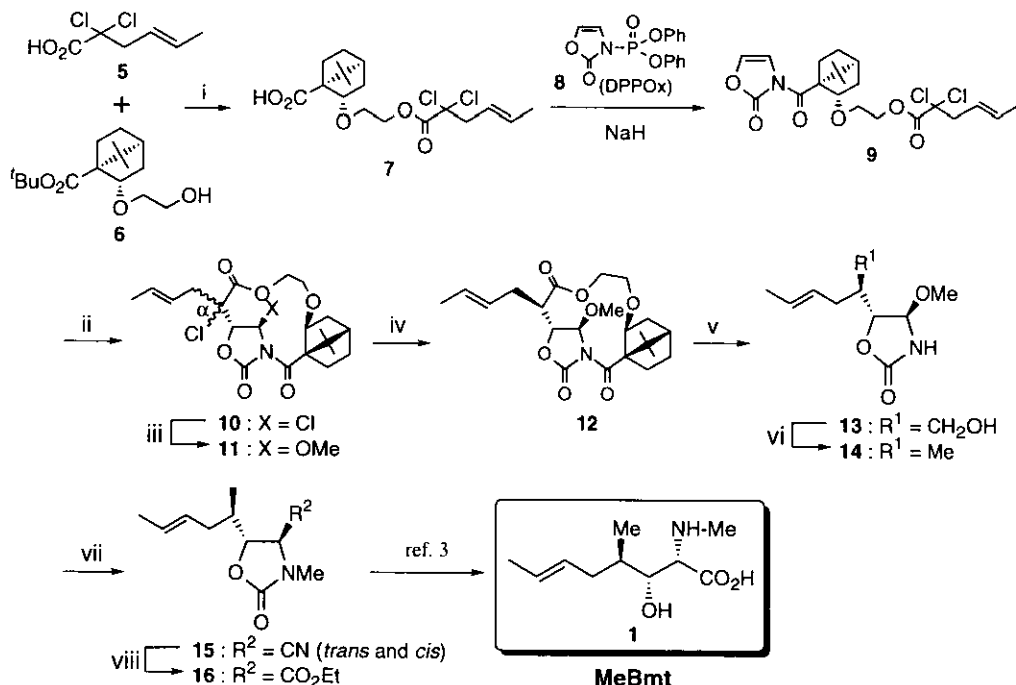


Figure 2

The apocamphanecarbonyl auxiliary was reductively cleaved by  $\text{LiBH}_4\text{-MeOH}$  (1:2)<sup>16</sup> 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<sup>10</sup> 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  $\text{K}_2\text{CO}_3$  in EtOH at room temperature followed by acidification gave the *trans*-ester (**16**) in 90% yield,<sup>3</sup> whose spectral and physical data were in good agreement with those previously reported,<sup>3</sup> except for optical rotatory data.<sup>17</sup> The hydrolytic conversion of **16** to MeBmt has been well established.<sup>3</sup>



i) 1)  $\text{SOCl}_2$ , 2)  $\text{NaH/THF}$ ; rt, 3) TFA; ii)  $\text{RuCl}_2(\text{PPh}_3)_3/\text{PhH}$ ; reflux; iii) MeOH; reflux; iv)  $(\text{TMS})_3\text{SiH}$ ,  $\text{BEt}_3/\text{Toluene}$ ;  $-78^\circ\text{C}$ ; v)  $\text{LiBH}_4\text{-MeOH}$ (1:2)/THF;  $0^\circ\text{C}$ ; vi) 1)  $\text{MsCl}$ ,  $\text{NEt}_3/\text{THF}$ ; rt, 2)  $\text{NaI/DME}$ ; reflux, 3)  $\text{Bu}_3\text{SnH}$ ,  $\text{BEt}_3/\text{THF}$ ;  $-78^\circ\text{C}$ ; vii) 1)  $\text{MeI}$ ,  $\text{NaH/THF}$ ; rt, 2)  $\text{TMSCN}$ ,  $\text{BF}_3\cdot\text{OEt}/\text{CH}_2\text{Cl}_2$ ;  $-50^\circ\text{C}\rightarrow\text{rt}$ ; viii) 1)  $\text{K}_2\text{CO}_3/\text{EtOH}$ ; rt, 2)  $2\text{N HCl}$ ; 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.  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  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,  $\text{Et}_2\text{O}$  over  $\text{LiAlH}_4$ ,  $\text{CH}_2\text{Cl}_2$  over  $\text{CaH}_2$ , MeOH over NaOMe and benzene over  $\text{CaH}_2$ .

**2,2-Dichloro-(4E)-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  $\text{HNET}_2$  (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  $-78^\circ\text{C}$  over a period of 30 min. After stirring at  $-78^\circ\text{C}$  for 30 min, a solution of *trans*-crotyl chloride<sup>18</sup> (2.70 g, 29.8 mmol), derived from *trans*-2-butenol<sup>19</sup> in THF (7 mL), was added at  $-78^\circ\text{C}$ , followed by stirring at rt for 10 h. The reaction was quenched by the addition of a saturated solution of  $\text{NH}_4\text{Cl}$ , followed by the addition of 200 mL of EtOAc. The usual work-up followed by chromatography on silica gel (hexane  $\rightarrow$  hexane: $\text{CH}_2\text{Cl}_2$  = 9:1) yielded *t*-butyl 2,2-dichloro-(4E)-hexenoate (2.20 g, 62%) as a colorless oil; bp  $53.6^\circ\text{C}/2.5$  mmHg.  $^1\text{H}$  NMR  $\delta$  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  $\text{CF}_3\text{CO}_2\text{H}$  (10.5 g, 92 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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,

$\text{CHCl}_3+\text{NBA}+\text{NaI}$ ):  $m/z$  227 ( $[\text{M}+2\text{Na}-\text{H}]^+$ ), 205; HRMS (FAB,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ) calcd for  $\text{C}_6\text{H}_7\text{O}_2\text{Cl}_2\text{Na}_2$  ( $[\text{M}+2\text{Na}-\text{H}]^+$ ):  $m/z$  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**<sup>14</sup> (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  $\text{SOCl}_2$  (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: $\text{CH}_2\text{Cl}_2$  = 9:1  $\rightarrow$  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;  $[\alpha]_{\text{D}}^{27} +35.3^\circ$  ( $c$  1.03,  $\text{CHCl}_3$ ); IR (neat) 2970, 2930, 2880, 1760, 1740, 1725, 1710, 1450, 1360, 1320, 1250, 1180, 1120, 1035, 965, 850  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ):  $m/z$  471 ( $\text{MNa}^+$ ), 415, 375, 209, 57; HRMS (FAB,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ) calcd for  $\text{C}_{22}\text{H}_{34}\text{O}_5\text{Cl}_2\text{Na}$  ( $\text{MNa}^+$ ):  $m/z$  471.1681, found:  $m/z$  471.1703.

Subsequent treatment of the *t*-butyl ester (9.68 g, 21.5 mmol) with  $\text{CF}_3\text{CO}_2\text{H}$  (6.8 g, 60 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL) at rt for 3 h gave **7** (2.39 g, quant.) as a colorless oil;  $[\alpha]_{\text{D}}^{26} +41.2^\circ$  ( $c$  1.00,  $\text{CHCl}_3$ ); IR (neat) 3600-2400, 2950, 2900, 1740, 1710, 1690, 1450, 1380, 1250, 1100, 1035, 965, 860, 720  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  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,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ):  $m/z$  437 ( $[\text{M}+2\text{Na}-\text{H}]^+$ ), 415 ( $\text{MNa}^+$ ), 375, 209; HRMS (FAB,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ) calcd for  $\text{C}_{18}\text{H}_{26}\text{O}_5\text{Cl}_2\text{Na}$  ( $\text{MNa}^+$ ):  $m/z$  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<sup>15</sup> (**8**) (diphenyl 2-oxo-3-oxazoliny]phosphonate; 0.98 g, 3.1 mmol) in THF (13 mL) was added at 0  $^\circ\text{C}$  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: $\text{CH}_2\text{Cl}_2$  = 5:5  $\rightarrow$   $\text{CH}_2\text{Cl}_2$ ) to give the 2-oxazolone derivative

(**9**) (1.30 g, 92%) as a colorless oil;  $[\alpha]_D^{27} +42.4^\circ$  (c 1.01,  $\text{CHCl}_3$ ); IR (neat) 3150, 2940, 2880, 1790, 1760, 1745, 1710, 1355, 1280, 1230, 1120, 1070, 968, 912, 837, 702  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$  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,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ):  $m/z$  482 ( $\text{MNa}^+$ ), 375, 209; HRMS (FAB,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ) calcd for  $\text{C}_{21}\text{H}_{27}\text{NO}_6\text{Cl}_2\text{Na}$  ( $\text{MNa}^+$ ):  $m/z$  482.1113, found:  $m/z$  482.1111.

**Intramolecular Cyclization to the Macrolide (10).** A mixture of **9** (8.29 g, 18.0 mmol) and  $\text{RuCl}_2(\text{PPh}_3)_3$  (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: $\text{CH}_2\text{Cl}_2 = 8:2 \rightarrow 4:6$ ) afforded the macrolide (**10**) (4.65 g, 56%) as colorless crystals; mp 187-190  $^\circ\text{C}$  (from hexane- $\text{CH}_2\text{Cl}_2$ ). The  $^1\text{H NMR}$  spectrum showed a diastereomeric mixture in a ratio of 3.4:1. IR (nujol) 1795, 1740, 1700, 1280, 1115, 975, 915  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$  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,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ):  $m/z$  482 ( $\text{MNa}^+$ ), 176; HRMS (FAB,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ) calcd for  $\text{C}_{21}\text{H}_{27}\text{NO}_6\text{Cl}_2\text{Na}$  ( $\text{MNa}^+$ ):  $m/z$  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  $^\circ\text{C}$  (from hexane- $\text{CH}_2\text{Cl}_2$ ); IR (nujol) 1798, 1740, 1696, 1280, 1240, 1200, 1115, 1095, 975, 917, 727  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$  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,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ):  $m/z$  478 ( $\text{MNa}^+$ ), 424, 329, 176; HRMS (FAB,  $\text{CHCl}_3+\text{NBA}+\text{NaI}$ ) calcd for  $\text{C}_{22}\text{H}_{30}\text{NO}_7\text{ClNa}$  ( $\text{MNa}^+$ ):  $m/z$  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);  $[\alpha]_D^{28} +26.7^\circ$  (c 1.00, CHCl<sub>3</sub>); IR (nujol) 1783, 1740, 1695, 1280, 1240, 1180, 1110, 980, 770, 720 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>22</sub>H<sub>31</sub>NO<sub>7</sub>: 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.

**(4R, 5R)-5-[(1S, 3E)-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<sub>4</sub> (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<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{28} +121.0^\circ$  (c 0.50, CHCl<sub>3</sub>); IR (nujol) 3330, 1750, 1725, 1235, 1100, 1060, 1030, 1010, 970, 940 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>10</sub>H<sub>17</sub>NO<sub>4</sub>: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.97; H, 8.03; N, 6.47.

**(4R,5R)-5-[(1S,3E)-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<sub>2</sub>Cl<sub>2</sub>:EtOAc = 4:1 → 1:1) afforded the

mesylate (1.41 g, quant.) as colorless crystals; mp 67-69 °C (from hexane-CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{28} +101.5^\circ$  (c 1.02, CHCl<sub>3</sub>); IR (nujol) 3270, 1750, 1720, 1363, 1225, 1180, 995, 975, 840 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>11</sub>H<sub>19</sub>NO<sub>6</sub>S: C, 45.04; H, 6.53; N, 4.77. Found: C, 44.94; H, 6.56; N, 4.75.

**(4R, 5R)-5-[(1R, 3E)-1-Iodomethyl-3-pentenyl]-4-methoxy-2-oxazolidinone.** A mixture of (4R, 5R)-5-[(1S, 3E)-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<sub>2</sub>Cl<sub>2</sub>:EtOAc = 9:1 → 4:1) afforded the iodide (1.48 g, 95%) as colorless crystals; mp 68.0-68.5 °C (from hexane-CH<sub>2</sub>Cl<sub>2</sub>);  $[\alpha]_D^{27} +83.0^\circ$  (c 0.76, CHCl<sub>3</sub>); IR (nujol) 3290, 1742, 1710, 1235, 1082, 1065, 1008, 968, 958 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>10</sub>H<sub>16</sub>NO<sub>3</sub>I: C, 36.94; H, 4.96; N, 4.31. Found: C, 36.92; H, 4.89; N, 4.28.

**(4R, 5R)-4-Methoxy-5-[(1R, 3E)-1-methyl-3-pentenyl]-2-oxazolidinone (14).** To a mixture of (4R, 5R)-5-[(1R, 3E)-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<sub>2</sub>Cl<sub>2</sub>:EtOAc = 9:1 → 7:3) afforded **14** (0.36 g, quant.) as colorless crystals; mp 66.2-66.5 °C (from hexane);  $[\alpha]_D^{27} +109.1^\circ$  (c 0.98, CHCl<sub>3</sub>); IR (nujol) 3270, 1740, 1712, 1230, 1110, 1070, 1020, 970, 950, 920 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.58; H, 8.64; N, 7.08.

**(4R, 5R)-4-Methoxy-3-methyl-5-[(1R, 3E)-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<sub>2</sub>Cl<sub>2</sub>: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; [ $\alpha$ ]<sub>D</sub><sup>27</sup> +71.9 ° (c 0.89, CHCl<sub>3</sub>); IR (neat) 2960, 2920, 1770, 1430, 1395, 1220, 1040, 970 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sup>+</sup>), 198, 182, 156, 126, 85; HRMS (EI) calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>3</sub> (M<sup>+</sup>): *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-oxazolidine-carbonitrile (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<sub>2</sub>Cl<sub>2</sub> (14 mL), BF<sub>3</sub>•OEt<sub>2</sub> (0.20 g, 1.38 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> → CH<sub>2</sub>Cl<sub>2</sub>: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<sub>2</sub>Cl<sub>2</sub>); [ $\alpha$ ]<sub>D</sub><sup>27</sup> +35.6 ° (c 0.71, CHCl<sub>3</sub>); IR (neat) 2960, 2920, 2850, 1760, 1425, 1390, 1220, 1140, 1120, 1040, 965, 823 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: 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<sub>2</sub>Cl<sub>2</sub>); [ $\alpha$ ]<sub>D</sub><sup>28</sup> -7.8 ° (c 0.77, CHCl<sub>3</sub>); IR (neat) 2960, 2920, 2850, 1760, 1425, 1390, 1220, 1140, 1120, 1040, 965, 823 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: 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<sub>2</sub>CO<sub>3</sub> (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<sub>3</sub>. 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; [α]<sub>D</sub><sup>28</sup> +34.0 ° (c 1.31, CHCl<sub>3</sub>) (lit.,<sup>3</sup> [α]<sub>D</sub> +29.5 ° (c 1.0, CHCl<sub>3</sub>)); IR (neat) 2970, 2930, 1762, 1750, 1440, 1400, 1220, 1140, 1045, 970 cm<sup>-1</sup>; <sup>1</sup>H 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<sup>+</sup>), 198, 182, 128, 100, 55; HRMS (EI) calcd for C<sub>13</sub>H<sub>21</sub>NO<sub>4</sub> (M<sup>+</sup>); *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); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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.

## REFERENCES

1. M. Dreyfuss, E. Harri, H. Hofmann, H. Kobel, W. Pache, and H. Tschertter, *Eur. J. Appl. Microbiol.*, 1976, **3**, 125; R. M. Wenger, 'Cyclosporin A', ed. by D. J. G. White, Elsevier Biomedical, Amsterdam, 1982.
2. K. E. Miller and D. H. Rich, *J. Am. Chem. Soc.*, 1989, **111**, 8351; D. H. Rich, M. K. Dhaon, B. Dunlap and S. P. F. Miller, *J. Med. Chem.*, 1986, **29**, 978.
3. R. M. Wenger, *Helv. Chim. Acta*, 1983, **66**, 2308; R. M. Wenger, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 77.
4. A.V. Rama Rao, J. S. Yadav, S. Chandrasekhar, and C. Srinivas Rao, *Tetrahedron Lett.*, 1989, **30**, 6769.
5. W. D. Lubell, T. F. Jamison, and H. Rapoport. *J. Org. Chem.*, 1990, **55**, 3511.

6. D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1986, **108**, 6757; D. Seebach, E. Juaristi, D. D. Miller, C. Schickli, and T. Weber, *Helv. Chim. Acta*, 1987, **70**, 237; J. D. Aebi, M. K. Dhaon, and D. H. Rich, *J. Org. Chem.*, 1987, **52**, 2881; U. Schmidt and W. Siegel, *Tetrahedron Lett.*, 1987, **28**, 2849; A. V. Rama Rao, T. G. Murali Dhar, T. K. Chakraborty, and M. K. Gurjar, *Tetrahedron Lett.*, 1988, **29**, 2069; A. Togni, S. D. Pastor, and G. Rihs, *Helv. Chim. Acta*, 1989, **72**, 1471; D. Blaser, S. Y. Ko, and D. Seebach, *J. Org. Chem.*, 1991, **56**, 6230.
7. R. D. Tung and D. H. Rich, *Tetrahedron Lett.*, 1987, **28**, 1139.
8. C. -Q. Sun and D. H. Rich, *Tetrahedron Lett.*, 1988, **29**, 5205; J. P. Genet, J. O. Durand, M. Savignac, and D. Pons, *Tetrahedron Lett.*, 1992, **33**, 2497.
9. S. W. McCombie, B. B. Shankar, and A. K. Ganguly, *Tetrahedron Lett.*, 1989, **30**, 7029; A. V. Rama Rao, M. K. Gurjar, D. S. Bose, and R. Revathi Devi, *J. Org. Chem.*, 1991, **56**, 1320.
10. T. Kunieda, T. Ishizuka, T. Higuchi, and M. Hirobe, *J. Org. Chem.*, 1988, **53**, 3381. For reviews, see: T. Ishizuka and T. Kunieda, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 118; T. Ishizuka, S. Ishibuchi, and T. Kunieda, *Tetrahedron*, 1993, **49**, 1841; T. Kunieda and T. Ishizuka, '*Studies in Natural Products Chemistry, Stereoselective Synthesis (Part H)*', ed. by Atta-ur-Rahman, Elsevier Science Publishers, Amsterdam, 1993, pp. 411-444; T. Kunieda and T. Ishizuka, '*Reviews on Heteroatom Chemistry*', Vol. 15, ed. by S. Oae, MYU, Tokyo, 1996, pp. 227-241.
11. S. Ishibuchi, Y. Ikematsu, T. Ishizuka, and T. Kunieda, *Tetrahedron Lett.*, 1991, **32**, 3523.
12. S. Ishibuchi, T. Nagatani, T. Ishizuka, and T. Kunieda, *Natural Products Letters*, 1992, **1**, 21.
13. T. Yamamoto, S. Ishibuchi, T. Ishizuka, M. Haratake, and T. Kunieda, *J. Org. Chem.*, 1993, **58**, 1997.
14. T. Ishizuka, K. Kimura, S. Ishibuchi, and T. Kunieda, *Chem. Pharm. Bull.*, 1990, **38**, 1717.
15. T. Kunieda, Y. Abe, T. Higuchi, and M. Hirobe, *Tetrahedron Lett.*, 1981, **22**, 1257; T. Kunieda and M. Hirobe, *J. Synth. Org. Chem. Jpn.*, 1983, **41**, 77; T. Nagamatsu and T. Kunieda, *Tetrahedron Lett.*, 1987, **28**, 2375; T. Kunieda, T. Nagamatsu, T. Higuchi, and M. Hirobe, *ibid.*, 1988, **29**, 2203; T. Kunieda, *Yakugaku Zasshi*, 1988, **108**, 593.

16. H. Matsunaga, K. Kimura, T. Ishizuka, M. Haratake, and T. Kunieda, *Tetrahedron Lett.*, 1991, **32**, 7715; H. Matsunaga, T. Ishizuka, N. Marubayashi, and T. Kunieda, *Chem. Pharm. Bull.*, 1992, **40**, 1077.
17. This discrepancy might come from possible contamination with the *cis*-isomer.<sup>7</sup>
18. R. M. Magid, O. S. Fruchey, W. L. Johnson, and T. G. Allen, *J. Org. Chem.*, 1981, **46**, 1232.
19. K. Mori, M. Amaike, and H. Watanabe, *Liebigs Ann. Chem.*, 1993, 1287; S. E. Denmark and T. K. Jones, *J. Org. Chem.*, 1982, **47**, 4595.

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