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Formal synthesis of an unusual amino acid component of cyclosporin, involving stereocontrolled nucleophilic 1,4-addition

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Abstract: A *syn*-(2*R*)-amino-1,3,4-butanetriol derivative, readily available from D-isoascorbic acid, was utilized for the synthesis of MeBmt found in the immunosuppressive undecacyclopeptide cyclosporin. This new strategy involves diastereoselective nucleophilic 1,4-addition of lithium dimethylcuprate to a chiral α,β-unsaturated aldehyde, and elaboration of the terminal double bond, by Takai or Wittig method for the MeBmt or its 6*Z*-isomer, respectively. © 1997 Elsevier Science Ltd

(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-methylamino-6-octenoic acid (MeBmt)[1] is the unique C-9 amino acid constituent of the immunosuppressive undecacyclopeptide cyclosporin. MeBmt shows no biological activity, however, modification of the MeBmt moiety in cyclosporin greatly affects the immunosuppressive activity of this therapeutic agent. For example: modification at C-3 by acylation,[2] alkylation,[3] substitution by a thiol[4] of the hydroxyl group, modification at C-4 by demethylation,[5] methylation,[5] epimerization,[5,6] or modification of the carbon chain,[2,7,8] exhibits after incorporation into the undecacyclopeptide, a lower immunosuppressive activity relative to the peptide. However, isomerization of the Δ-6 double bond (6*Z*-MeBmt)[8,9] shows no loss of cyclosporin's activity. Since the first 24-step synthesis described by Wenger from L-(+)-diethyl tartrate,[10] several synthetic routes have been reported which involve three main strategies: transformation of chiral building block (D-glucose,[11] D-serine,[12] L-glutamic acid,[13] 2-deoxy-D-ribose[14]), aldolization reactions,[15] or regioselective opening of chiral epoxides.[16]

As part of our continuing investigations designed to explore the employment of the versatile *syn*-2*R*-amino-1,3,4-butanetriol derivative **1**, easily obtained on a multigram scale from D-isoascorbic acid,[17] we have recently developed efficient synthetic procedures for the synthesis of natural aminodiol,[17] 3-amino-4-hydroxyazepane and 3-amino-2-hydroxyacids.[18] Now, we would like to demonstrate that this highly functionalized enantiopure chiral building block **1** is a good precursor for MeBmt and its 6*Z*-isomer. The key steps of our approach involve the asymmetric 1,4-addition of a methyl group to the α,β-ethylenic aldehyde **2**, and subsequent elaboration of the terminal (*E*) or (*Z*) double bond (Scheme 1).

Althought the chemical outcome of conjugate additions to enoates or enones that bear γ-alkyl,[19] γ-alkoxy[20] or γ-amino[21] substituents has been intensively investigated, only a few examples of such additions of γ-oxido-substituted enal have ben described.[22]

Swern oxidation[23] of the free primary alcohol function of **1** (Scheme 2) into aldehyde followed by *in situ* Wittig reaction with formylmethylene triphenylphosphorane afforded the α,β-ethylenic aldehyde **2**[18] in 91% overall yield (E configuration exclusively). Addition of lithium dimethylcuprate to **2**[24] at −50°C led to a mixture of diastereomers **3a** and **3b** in 72% yield in a 80/20 ratio. After flash chromatography separation, each stereomer **3a** and **3b** was subsequently transformed into the corresponding azepane **8a** and **8b**, to determine the configuration of the newly created asymmetric carbon by NMR experiments.

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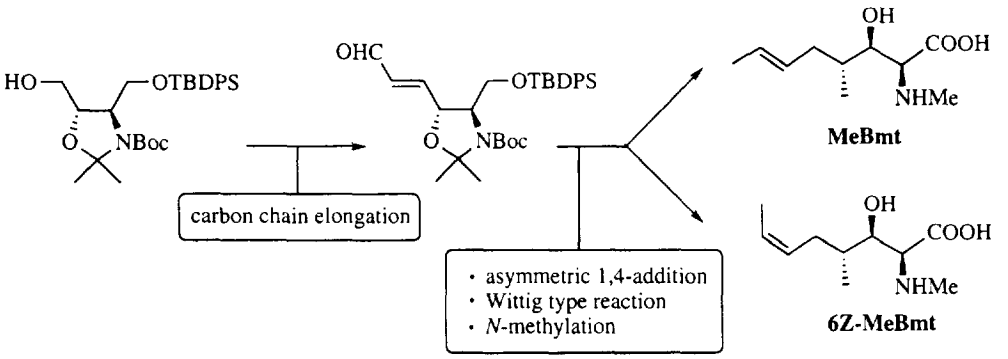
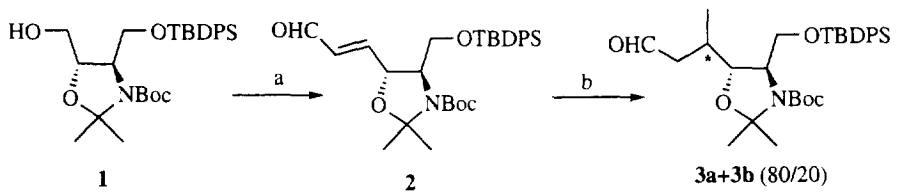
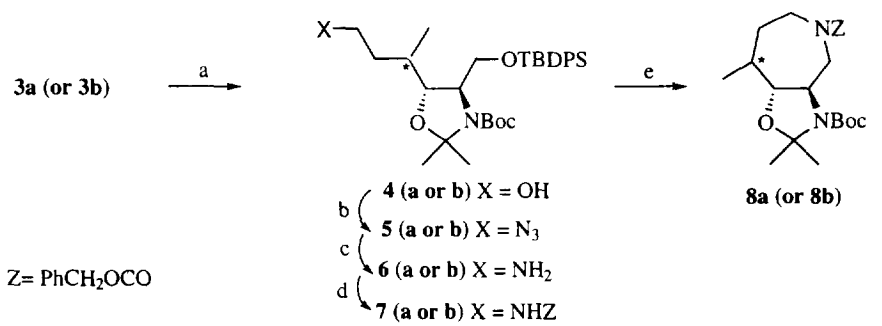


Scheme 1.



Scheme 2. a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 then $Ph_3P{=}CH{-}CHO$, CH_2Cl_2, 24h (91%). b) Me_2CuLi, Et_2O, −50°C (72%).

The azepane formation (Scheme 3) was accomplished, according to analogous described procedures[18,25] by reduction of the aldehyde and activation of the free hydroxyl group with triflic anhydride and substitution with *N,N'*-tetramethylguanidinium azide, transformation of the azido group into the *N*-benzyl carbamate, and subsequent cyclization after deprotection and mesylation of the primary alcohol function.



Scheme 3. a) H_2, Ni Raney, EtOH. b) $(CF_3SO_2)_2O$, $CHCl_3$, 2,6-lutidine then $(Me_2N)_2CNH_2^+\ N_3^-$ (48%) from **3a** or **3b**. c) H_2, Pd/C (10%), THF. d) $PhCH_2OCOCl$, NaOH, 1,4-dioxane (57%) from **5a** or **5b**. e) *i*: nBu_4NF, THF; *ii*: CH_3SO_2Cl, Et_3N, CH_2Cl_2; *iii*: *t*BuOK, THF (50%).

2D NOESY diagram of **8a**[26] with ^1H NMR spectrum (Figure 1) showed, notably, by cross signals of the methyl group (0.76 ppm) with H_3 (3.75 ppm), and H_5 (2.10 ppm) with H_4 (3.94 ppm), a *cis*-relationship between Me/H_3 and H_4/H_5, thus an *R* configuration for C_5 of the azepane **8a**. Likewise, 2D NOESY diagram of **8b** showed, notably, by cross signals of methyl (0.95 ppm) with H_4 (3.90 ppm), a *cis*-relationship between Me/H_4, thus an *S* configuration for C_5 of the azepane **8b**.

Since the transformation of **3a** into **8a**, or **3b** into **8b**, was carried out with retention of configuration,

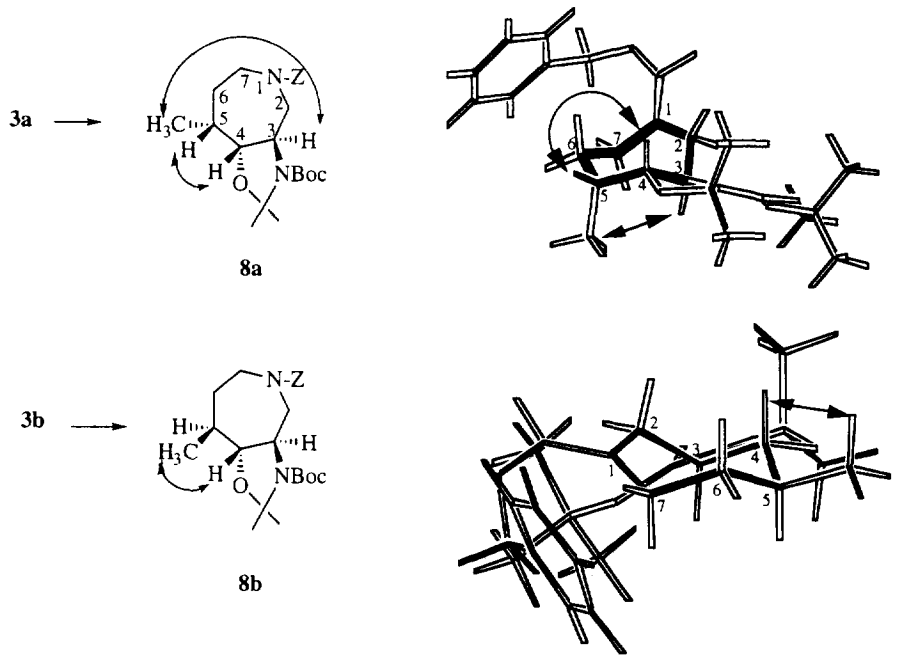
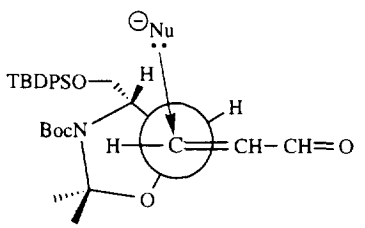


Figure 1. Main observed nOe (^{1}H NMR, 2D NOESY, 250 MHz, C_6D_6, 65°C) and stereoview of the minimized conformation from molecular dynamic simulations[26] of azepanes **8a** and **8b**.

these results showed that the absolute configuration of the newly created asymmetric carbon atom was *R* for the major diastereomer **3a**, and *S* for the minor one **3b**.

For a mechanistic point of view outcome of the addition of dimethylcuprate to enal **2** can be explained by a modified Felkin–Anh model for the transition state with a carbon–carbon bond formation *anti* to the γ-alkoxy group:

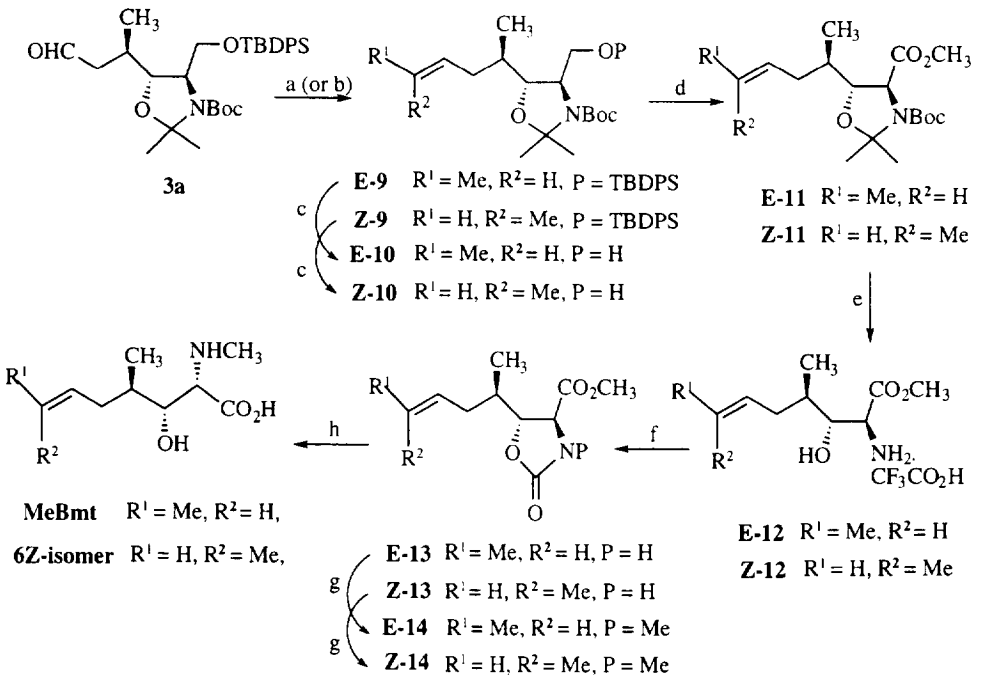


Having in hand the major stereomer **3a** possessing the *R* configuration at C–Me, we proceeded to the synthesis of MeBmt and its 6Z-isomer (Scheme 4).

For the transformation of the aldehyde **3a** into the olefin *E*-**9**, the Takai method,[27] by treatment with 1,1-diiodoethane in presence of chromium(II) chloride in excess, revealed to be the best one to have a good control of the stereochemistry (87% yield, *E*/*Z*≥95%, ^{1}H NMR analysis).[28]

On the other hand, Wittig reaction on the aldehyde **3a** with the ylide derived from ethyltriphenylphosphonium bromide, by treatment with butyllithium in diluted solution of THF at −78°C, afforded only the olefin *Z*-**9** (75% yield, *Z*/*E*≥95%, ^{1}H NMR analysis).

The final transformations were then carried out on each isomer (*E*-**9** and *Z*-**9**). Deprotection of the silylether followed by Swern oxidation of the primary alcohol to aldehyde, with further oxidation to carboxylic acid in the presence of sodium chlorite and sulfamic acid, and esterification led to the methyl ester *E*-**11** or *Z*-**11** in respectively 61% or 65% overall yield. *N*-Methylation was readily



Scheme 4. a) CH_3CHI_2, $CrCl_2$, THF (87%), E/Z≥95%. b) $Ph_3P^+CH_2CH_3$ Br^-, BuLi, THF, −78°C (75%) Z/E≥95%. c) nBu_4NF, THF (96% for *Z*-**10** and 90% for *E*-**10**). e) *i*: $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; *ii*: $NaClO_2/NH_2SO_3H$, 1,4-dioxane–H_2O; *iii*: CH_2N_2 (61% overall from *E*-**10** and 65% from *Z*-**10**). e) CF_3COOH–H_2O. f) $Cl_3COCOCl$, CH_2Cl_2/NEt_3 1/1 (61% from *E*-**11** and 55% from *Z*-**11**). g) MeI, Ag_2O, DMF (86%). h) see ref.[10]

performed by acidic hydrolysis of both oxazolidine and the *N*-carbamate protecting group leading to *E*-**12** or *Z*-**12**, followed by formation of the oxazolidinone using trichloromethyl chloroformate (TCF)[29] and subsequent methylation with methyliodide in presence of silver(I) oxide.[30] *E*-**14** is thus obtained with 53% overall yield from *E*-**11**, and *Z*-**14** with 47% overall yield from *Z*-**11**. Comparison of the physical and spectroscopic data of *E*-**14** and *Z*-**14** with those described[15b,f] were in good agreement. They could be easily converted into the final amino acid, MeBmt or its 6*Z*-isomer, respectively by hydrolysis according to the procedure of Wenger.[10]

In summary, we have presented here a practical synthesis of MeBmt present in the structure of immunosuppressive cyclosporin and its *Z*-isomer, *via* the enantiopure *syn*-2*R*-1,3,4-butanetriol derivative prepared from D-isoascorbic acid. The key steps of this new strategy involve the diastereoselective nucleophilic 1,4-addition of lithium dimethylcuprate to α,β-ethylenic aldehyde with preponderance of *anti*-orientated C-methyl product, and subsequent elaboration of the terminal double bond by the Takai or Wittig method. Our current efforts involve the study of this asymmetric 1,4-addition, and the obtention of other unusual amino acids.

Experimental section

Prior to use, tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. CH_2Cl_2 and ethyl acetate (EtOAc) were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR (62,9 MHz) spectra were recorded on a Bruker AM 250. Chemical shifts are reported in δ (ppm)[31] and coupling constants are given in Hertz. High Resolution Mass Spectra were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp at 20°C. All reactions were carried out under argon

atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Chromatography was performed with Merck Kieselgel 60 (200–500 μm) or 60H (5–40 μm). Spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

Addition of Me_2CuLi on α,β-ethylenic aldehyde **2**

To a suspension of cuprous iodide (3.49 g, 18.3 mmol) in ether was dropwise added methylithium (1.56 M in ether, 23.5 mL, 36.7 mmol). After stirred for 45 min at −30°C, the reaction mixture was cooled at −50°C and the aldehyde **2**[18] (3.20 g, 6.11 mmol) in ether (104 mL) was added. The mixture was warmed at 0°C and 50 mL of brine was added. After extraction with ether (3×60 mL), the organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 9/1) afforded 1.97 g of **3a** (60%, Rf 0.2) and 0.40 g of **3b** (12%, Rf 0.3).

*(4R,5R)-3-*N-tert-*Butyloxycarbonyl-4-*tert-*butyldiphenylsilyloxymethyl-5[(1″R)-1″-methyl propan-3″-al]-2,2-dimethyl-1,3-oxazolidine* ***3a***

$[\alpha]_D$ −19 (c 1.18, CH_2Cl_2). ^{1}H NMR (C_6D_6, 65°C) δ: 9.47 (1H, dd, H-3″, $J_{3'',2''a}$=1,5 Hz, $J_{3'',2''b}$=2 Hz), 7.84–7.16 (10H, 2m, Ph), 4.54–3.83 (4H, m, H-5,4,1′), 2.44 (1H, ddd, H-2″a, $J_{2''a,2''b}$=−16 Hz, $J_{2''a,3''}$=1.5 Hz, $J_{2''a,1''}$=4 Hz), 2.19–2.07 (1H, m, H-1″), 1.98 (1H, ddd, $H_{2''b}$, $J_{2''b,1''}$=8 Hz, $J_{2''a,2''b}$=−16 Hz, $J_{2''b,3''}$=2 Hz), 1.60, 1.55 (6H, 2s, CMe_2), 1.36 (9H, 2, O*t*Bu), 1.15 (9H, s, Si*t*Bu), 0.87 (3H, d, CH_3, $J_{CH3,H1''}$=6.5 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 199.9 (C-3″), 151.9 (NCO_2), 136.1, 133.9, 130.1, 128.2 (Ph), 94.7 (C-2), 81.9 (C-5), 79.7 ($(CH_3)_3CO$), 63.8 (C-1′), 62.1 (C-4), 47.0 (C-2″), 32.8 (C-1″), 28.5($OCMe_3$), 28.1, 27.6 (CMe_2), 27.2 (Me_3CSi), 19.5 (Me_3CSi), 17.5 (CH_3). HMRS for $C_{23}H_{28}NO_5Si$ ($M^+-C_8H_{17}$), calcd 426.1737, found 426.1736.

*(4R,5R)-3-*N-tert-*Butyloxycarbonyl-4-*tert-*butyldiphenylsilyloxymethyl-5-[(1S″)-1″-methyl propan-3″-al]-2,2-dimethyl-1,3-oxazolidine* ***3b***

$[\alpha]_D$ −10 (c 1.08, CH_2Cl_2). ^{1}H NMR (C_6D_6, 65°C) δ: 9.42 (1H, dd, H-3″, $J_{3'',2''a}$=2 Hz, $J_{3'',2''b}$=1.6 Hz), 7.92–7.18 (10H, 2m, Ph), 4.33–3.74 (4H, m, H-5,4,1′), 2.45–2.28 (2H, m, H-1″,2″a), 2.07–1.87 (1H, ddd, H-2″b, $J_{2''b,3''}$=1.6 Hz, $J_{2''a,2''b}$=−15 Hz, $J_{2''b,1''}$=7 Hz), 1.60, 1.57 (6H, 2s, CMe_2), 1.36 (9H, s, O*t*Bu), 1.15 (9H, s, Si*t*Bu), 0.87 (3H, d, CH_3, $J_{CH3,H1''}$=6.4 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 199.6 (C-3″), 152.0 (NCO_2), 136.1, 133.9, 130.1, 128.1 (Ph), 94.5 (C-2), 80.7 (C-5), 79.7 ($OCMe_3$), 63.4 (C-1′), 60.0 (C-4), 48.4 (C-2″), 31.1 (C-1″), 28.5 ($OCMe_3$), 28.3, 27.8 (CMe_2), 27.2 (Me_3CSi), 19.5 (Me_3CSi), 14.5 (CH_3). Anal. calcd for $C_{31}H_{45}NO_5Si$: C, 68.98; H, 8.40; N, 2.59. Found: C, 68.86; H, 8.36; N, 2.48.

*(4R,5R)-3-*N-tert-*Butyloxycarbonyl-4-*tert-*butyldiphenylsilyloxymethyl-5-[(1″R)-3″-hydroxy-1″-methylpropyl]-2,2-dimethyl-1,3-oxazolidine* ***4a***

A solution of **3a** (202 mg, 0.37 mmol) in EtOH (6 mL) was stirred for 4 h under hydrogen in the presence of a catalytic amount of Raney nickel (40 mg, P=3 atm). After filtration through a celite pad and concentration *in vacuo*, 133 mg (66%) of **4a** was obtained after flash chromatography (cyclohexane/EtOAc 8/2 Rf 0.2). ^{1}H NMR ($CDCl_3$) δ: 7.70–7.30 (10H, 2m, Ph), 4.08–3.50 (6H, m, H-5,4,3″,1″), 2.00–1.20 (18H, m, H-2″,1″,CMe_2, O*t*Bu), 1.03–0.80 (12H, m, Si*t*Bu,CH_3).

*(4R,5R)-3-*N-tert-*Butyloxycarbonyl-4-*tert-*butyldiphenylsilyloxymethyl-5-[(1″S)-3″-hydroxy-1″-methylpropyl]-2,2-dimethyl-1,3-oxazolidine* ***4b***

The reaction of the aldehyde **3b** (161 mg, 0.30 mmol) under the above experimental conditions furnished after flash chromatography (cyclohexane/EtOAc 8/2, Rf 0.2) 123 mg (76%) of **4b**. ^{1}H NMR ($CDCl_3$) δ: 7.70–7.25 (10H, 2m, Ph), 4.20–3.50 (6H, m, H-5,4,3″,1′), 1.95–1.20 (18H, m, H-2″,1″ CMe_2, O*t*Bu), 1.10–0.85 (12H, m, Si*t*Bu, CH_3).

*(4R,5R)-3-*N-tert-*Butyloxycarbonyl-4-*tert-*butyldiphenylsilyloxymethyl-5-[(1''R)-3''-*N-*benzyloxycarbonyl-1''-methylpropyl]-2,2-dimethyl-1,3-oxazolidine* **7a**

At −50°C, to a stirred solution of **4a** (125 mg, 0.23 mmol) in $CHCl_3$ was added trifluoromethanesulphonic anhydride (47 µL, 0.28 mmol), then after 5 min, 2,6-lutidine (32 µL, 0.28 mmol) and after 30 min tetramethylguanidiniumazide (TMGA 109 mg, 0.69 mmol). After stirring for 1 h at −50°C, the mixture was concentrated and filtered on pad of silice with EtOAc/cyclohexane (v/v 1/9) to discard the by-products. 94 mg of **5a** were obtained (72%).

A solution of **5a** (94 mg, 0.17 mmol) in THF (1 mL) was stirred under hydrogene in the presence of a catalytic amount of palladium on charcoal 10% (9 mg). After filtration through a celite pad and concentration *in vacuo* the crude amine was used without purification in the next step. To a solution of the amine in dioxane (1 mL), at 0°C, in the presence of NaOH (3 N, 166 µL, 0.50 mmol) was added dropwise benzylchloroformate (28 µL, 0.20 nmol). After stirring for 45 min the reaction mixture was poured into a saturated solution of ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give after chromatography (cyclohexane/EtOAc 8/2 Rf 0.3) 46 mg (57%) of **7a**. ^1H NMR ($CDCl_3$) δ: 7.70–7.30 (15H, 2m, Ph), 5.07 (2H, s, CH_2Ph), 4.75 (1H, *brs*, NH), 4.00–3.10 (H-5,4,3'',1'), 2.00–1.20 (18H, m, H-2'',1'',CMe_2,O*t*Bu), 1.10–0.80 (12H, m, Si*t*Bu,CH_3).

*(4R,5R)-3-*N-tert-*Butyloxycarbonyl-4-*tert-*butyldiphenylsilyloxymethyl-5-[(1''S)-3''-*N-*benzyloxycarbonyl-1''-methylpropyl]-2,2-dimethyl-1,3-oxazolidine* **7b**

The reaction of the alcohol **4b** (123 mg, 0.23 mmol) under the above experimental conditions furnished after purification 68 mg (53%) of **5b**.

The reaction of the azido **5b** (68 mg, 0.12 mmol) under the above experimental conditions furnished after purification (cyclohexane/EtOAc 8/2, Rf 0.3) 25 mg (31%) of **7b**. ^1H NMR ($CDCl_3$) δ: 7.70–7.30 (15H, 2m, Ph), 5.10 (2H, s, CH_2Ph), 4.74 (1H, brs, NH), 4.10–3.10 (6H, m, H-5, 4,3'',1'), 2.10–0.80 (30H, m, H-2'',1'', CMe_2, O*t*Bu, Si*t*Bu, CH_3).

*(3R,4R,5R)-3-*N-*Benzyloxycarbonyl-3,4-[3'-*N-tert-*butyloxycarbonyl-2',2'-dimethyl-1',3'-oxazolidinyl]-azepane* **8a**

At 20°C to a stirred solution of silylether **7a** (64 mg, 0.10 mmol) in THF (2 mL) was added dropwise *n*-tetrabutylammonium fluoride (104 µL, 0.11 mmol, 1M in THF). After stirring for 20 h and concentration *in vacuo*, water (1 mL) was added; after extraction with CH_2Cl_2 (3×2 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (EtOAc/cyclohexane 1/1 Rf 0.4) gave 36 mg (88%) of the corresponding alcohol.

To a solution of this alcohol above obtained (36 mg, 0.08 mmol) in CH_2Cl_2 (330 µL) in the presence of NEt_3 (17 µL, 0.10 mmol) was added at 0°C mesylchloride (8 µL, 0.10 mmol). After stirring for 20 min, the mixture was poured into water; after extraction with CH_2Cl_2 (3×2 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the corresponding mesylate which was used without purification in the next step.

At 20°C to the crude mesylate in THF (4.2 mL) was added a solution of tBuOK in THF (200 µL, 0.10 mmol, 0.5 M). After stirring for 2 h, 2 mL of ammonium chloride was added. After extraction with CH_2Cl_2 (3×3 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 8/2 Rf 0.4) gave 19 mg (56%) of **8a**. $[\alpha]_D$ −115 (c 1.00, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 7.35–7.00 (m, 10H, Ph), 5.10 (2H, AB, CH_2Ph, J_{AB}=−12.4 Hz), 4.34 (1H, dd, H-2a, $J_{2a,2b}$=−12.9 Hz, $J_{2a,3}$=5.3 Hz), 3.94 (1H, dd, H-4, $J_{3,4}$=9.3 Hz, $J_{4,5}$=3.4 Hz), 3.75 (1H, m, H-3), 3.65–3.32 (1H, m, H-2b,7b), 2.78 (1H, m, H-7a) 2.10 (1H, m, H-5), 1.90–1.12 (16H, m, H-6b, CMe_2, O*t*Bu), 1.06 (1H, m, H-6a), 0.76 (3H, d, CH_3, $J_{CH3,H5}$=7 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 155.8 (NCO_2Bn), 152.5 (NCO_2tBu), 94.3 (C-2'), 80.2 (C-5), 79.9 (O*C*Me$_3$), 67.3 (Ph*C*H$_2$), 54.8 (C-4), 49.5, 42.3, 32.0 (C-2,6,7), 28.5 (OC*Me*$_3$), 30.8, 26.0 (C*Me*$_2$), 13.0 (CH_3). HRMS for $C_{23}H_{34}N_2O_5$: (M^+) calcd 418.2468, found 418.2466.

*(3R,4R,5S)-3-*N*-Benzyloxycarbonyl-3,4-[-3'-*N*-tert-butyloxycarbonyl-2',2'-dimethyl-1',3'-oxazolidinyl]-azepane* ***8b***

The silylether **7b** under the above experimental conditions furnished after flash chromatography (cyclohexane/EtOAc 8/2 Rf 0.4) 4 mg (30% overall yield) of **8b**. $[\alpha]_D$ −83 (c 1.00, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 7.30–7.00 (5H, m, Ph), 5.12 (2H, AB, $PhCH_2$, J_{AB}=−12.5 Hz), 4.30 (1H, m, H-2a), 4.00–3.40 (5H, m, H-3,4,2b,7b), 2.50 (1H, m, H-7a), 1.75–1.20 (18H, m, CMe_2, OtBu, H-5,6), 0.95 (3H, d, CH_3, $J_{CH3,H5}$=6 Hz).

*(4R,5R)-3-*N*-tert-Butyloxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-5-[(1''R,3''E)-1''-methylpent-3''-enyl]-2,2-dimethyl-1,3-oxazolidine* E-***9***

To a chromium II chloride suspension (1.10 g, 8.91 mmol) in THF (22 mL) at room temperature was added a solution of the aldehyde **3a** (601 mg, 1.11 mmol) and 1,1-diiodoethane (2.24 µL, 2.22 mmol) in THF (3.4 mL). After stirring for 12 h, brine (10 mL) was added; after extraction with ethylacetate (3×10 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (EtOAc/cyclohexane 5/95, Rf 0.4) gave 534 mg (87%) of *E*-**9**. $[\alpha]_D$ −11 (c 1.00, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 7.88–7.10 (10H, 2m, Ph), 5.56–5.32 (2H, m, $H_{4'',3''}$), 4.20 (1H, dd, H-5, $J_{5,1''}$=3.5 Hz, $J_{5,4}$=8 Hz), 4.28–3.90 (3H, m, H-4,1'), 2.45 (1H, m, H-2''a), 1.97 (1H, m, H-2''b), 1.82–1.56 (10H, m, H-1'',5'', Me_2C), 1.38 (9H, s, O*t*Bu), 1.17 (9H, s, Si*t*Bu), 0.94 (3H, d, CH_3, $J_{CH3,H1''}$=6.7 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 152.0 (NCO_2), 136.1, 134.0, 130.1, 128.1 (Ph), 129.7 (C-3''), 126.6 (C-4''), 94.4 (C-2), 82.2 (C-5), 79.5 ($OCMe_3$), 63.9 (C-1'), 62.1 (C-4), 37.8 (C-1''), 35.6 (C-2''), 28.5 ($OCMe_3$), 28,1, 27.8 (CMe_2), 27.2 (Me_3CSi), 19.5 (Me_3CSi), 17.9 (CH_3), 16.5 (C-5''). Anal. calcd for $C_{33}H_{49}NO_4Si$: C, 71.83; H, 8.95; N, 2.54. Found: C, 71.86; H, 9.04; N, 2.54.

*(4R,5R)-3-*N*-tert-Butyloxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-5-[(1''R,3''Z)-1''-methylpent-3''-enyl]-2,2-dimethyl-1,3-oxazolidine* Z-***9***

To a suspension of the ethyltriphenylphosphonium bromide (1.80 g, 4.84 mmol) in THF (19 mL) at −78°C, was dropwise added *n*-butyllithium (1.4 M in hexane, 3.40 mL); red coloration progressively appeared. After 2 h stirring, a solution of aldehyde **3a** (870 mg, 1.61 mmol) in THF (16 mL) was dropwise added. The temperature was then raised to 20°C for 20 h. The reaction mixture was poured into an ammonium chloride aqueous solution (15 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane/EtOAc 96.5/3.5; Rf 0.3) to give 668 mg (75%) of *Z*-**9**. $[\alpha]_D$ −11 (c 1.35, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 7.84–7.18 (10H, 2m, Ph), 5.61–5.40 (2H, m, H-4'',3''), 4.21 (1H, dd, H-5, $J_{5,4}$=8 Hz, $J_{5,1''}$=3.6 Hz), 4.13–3.90 (3H, m, H-4,1'), 2.48 (1H, m, H-2''a), 2.10 (1H, m, H-2''b), 1.84–1.61 (7H, m, H-1'', CMe_2), 1.56 (3H, d, H-5'', $J_{5'',4''}$=6 Hz), 1.38 (9H, s, O*t*Bu), 1.14 (9H, s, Si*t*Bu), 0.94 (3H, d, CH_3, $J_{CH3,H1''}$=6.4 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 152.0 (NCO_2), 136.0, 134.0, 130.0, 128.1 (Ph), 128.8 (C-3''), 125.3 (C-4''), 94.3 (C-2), 82.2 (C-5), 79.5 ($OCMe_3$), 63.8 (C-1''), 62.2 (C-4), 38.0 (C-1''), 29.8 (C-2''), 28.5 ($OCMe_3$), 28.3, 27.6 (CMe_2), 27.2 ($SiCMe_3$) 19.5 ($SiCMe_3$), 16.5 (CH_3), 12.9 (C-5''). Anal. calcd for $C_{33}H_{49}NO_4Si$: C, 71.83; H, 8.95; N, 2.59. Found: C, 71.78; H, 8.89; N, 2.56.

*(4R,5R)-3-*N*-tert-Butyloxycarbonyl-4-hydroxymethyl-5-[(1''R,3''E)-1''-methyl-pent-3''-enyl]-2,2-dimethyl-1,3-oxazolidine* E-***10***

To stirred solution of *E*-**9** (454 mg, 0.82 mmol) in THF (19 mL) was added dropwise at 20°C *n*-tetrabutylammonium fluoride (905 µL, 0.91 mmol, 1M in THF). After stirring for 20 h, water (10 mL) was added; after extraction with CH_2Cl_2 (3×10 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 8/2 Rf 0.3) gave 233 mg (90%) of *E*-**10**. M.p.: 60–61°C. $[\alpha]_D$ −3(c 1.05, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 5.47–5.28 (2H, m, H-4'',3''), 3.88 (1H, m, H-4), 3.74–3.65 (2H, m, H-1'), 3.58 (1H, brt, H-5,

$J_{4,5}$=$J_{5,1''}$=6.7 Hz), 2.34 (1H, m, H-2''a), 1.96–1.80 (1H, m, H-2''b), 1.70–1.53 (10H, m, H-1'', 5'', CMe_2), 1.38 (9H, s, O*t*Bu), 0.84 (3H, d, CH_3, $J_{CH3,H1''}$=6.8 Hz). ^{13}C NMR δ: 153.6 (NCO_2), 129.6 (C-3''), 126.7 (C-4''), 94.3 (C-2), 81.5 (C-5), 80.4 ($OCMe_3$), 65.3 (C-1'), 63.6 (C-4), 37.5 (C-1''), 35.6 (C-2''), 28.5 (CMe_3), 28.3, 27.1 (CMe_2), 17.8 (CH_3), 16.0 (C-5'').

*(4*R,*5*R*)-3*-N-tert-*Butyloxycarbonyl-4-hydroxymethyl-5-[(1''*R,*3''*Z)-*1''-methyl-pent-3''-enyl]-2,2-dimethyl-1,3-oxazolidine* Z-***10***

The reaction of the silylether *Z*-**9** (247 mg, 0.45 mmol) in THF (10 mL) under the above experimental conditions furnished after chromatography 134 mg (96%) of the alcohol *Z*-**10**. M.p. 36–37°C. $[\alpha]_D$ +1 (c 1.20, CH_2Cl_2), $[\alpha]_{Hg365}$ +7 (c 1.20, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 5.57–5.32 (2H, m, H-4'', 3''), 3.94–3.84 (1H, m, H-4), 3.78–2.64 (2H, m, H-1'), 3.59 (1H, brt, H-5, $J_{5,4}$=$J_{5,1''}$=6.5 Hz), 2.35 (1H, m, H-2''a), 2.01 (1H, m, H-2''b), 1.72–1.50 (10H, m, H-1'', 5'', CMe_2), 1.38 (9H, s, O*t*Bu), 0.85 (3H, d, CH_3, $J_{CH3,H1''}$=6.8 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 153.7 (NCO_2), 128.8 (C-3''), 125.3 (C-4''), 94.3 (C-2), 81.6 (C-5), 80.4 ($OCMe_3$), 65.4 (C-1'), 63.7 (C-4), 37.8 (C-1''), 29.8 (C-2''), 28.4 ($OCMe_3$), 28.3, 27.1 (CMe_2), 16.0 (CH_3), 12.9 (C-5'').

*(4*S,*5*R*)-3*-N-tert-*Butyloxycarbonyl-4-methoxycarbonyl-5-[1''*R,*3''*E)-*1''-methyl-pent-3''-enyl]-2,2-dimethyl-1,3-oxazolidine* E-***11***

To a stirred solution of oxalyl chloride (19 μL, 0.22 mmol) in CH_2Cl_2 at −78°C was slowly added DMSO (31 μL, 0.43 mmol). The resulting complex was stirred for 15 min at −78°C prior to the addition of alcohol *E*-**10** (45 mg, 0.14 mmol) in CH_2Cl_2. After 45 min at −65°C, Et_3N (120 μL, 0.86 mmol) was added and the temperature was raised to 20°C. After stirring for 1.5 h, Et_2O was added and the salt (Et_3NHCl) was removed by filtration through a celite pad. The filtrate was concentrated *in vacuo* to give the crude aldehyde which was used without purification in the next step. To a solution of the aldehyde in a mixture of water–dioxane (v/v 1/3, 7.2 mL) cooled at 0°C were successively added sodium chloride (26 mg, 0.29 mmol) and sulfamic acid (14 mg, 0.24 mmol). After stirring for 45 min the reaction mixture was poured into brine (3 mL) and extracted with CH_2Cl_2 (3×10 mL); the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to gave the carboxylic acid. To the carboxylic acid in methanol (3 mL), diazomethane in ether was added until yellow coloration. After concentration *in vacuo*, flash chromatography of the residue (EtOAc/cyclohexane 5/95 Rf 0.3) gave 30 mg (61%) of *E*-**11**. $[\alpha]_D$ −13 (c 1.10, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 5.44–5.24 (2H, m, H-3'',4''), 4.40–4.15 (1H, brs, H-4), 3.99 (1H, t, H-5, $J_{5,4}$=$J_{5,1''}$=6.7 Hz), 3.40 (3H, s, OCH_3), 2.30 (1H, m, H-2''a), 1.94 (1H, m, H-2''b), 1.82–1.50 (10H, m, H-1'', 5'', CMe_2), 1.39 (9H, s, O*t*Bu), 0.90 (3H, d, CH_3, $J_{CH3,H1''}$=6.8 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 172.0 (CO_2), 151.6 (NCO_2), 129.2 (C-3''), 127.0 (C-4''), 95.3 (C-2), 82.2 (C-5), 80.2 ($OCMe_3$), 63.1 (C-4), 51.5 (OCH_3), 37.6 (C-1''), 35.6 (C-2''), 28.4 ($OCMe_3$), 27.3, 25.6 (CMe_2), 17.8 (CH_3), 15.2 (C-5'').

*(4*S,*5*R*)-3*-N-tert-*Butyloxycarbonyl-4-methoxycarbonyl-5-(1''*R,*3''*Z)-*1''-methyl-pent-3''-enyl-2,2-dimethyl-1,3-oxazolidine* Z-***11***

The reaction of alcohol *Z*-**10** (97 mg, 0.31 mmol) with oxalyl chloride (40 μL, 0.46 mmol), dimethyl sulfoxyde (166 μL, 0.93 mmol), triethylamine (258 μL, 1.86 nmol), then sodium chlorite (112 mg, 1.24 mmol), sulfamic acid (60 mg, 0.62 mmol), water/dioxane 1/3 (15.5 mL) under the above experimental conditions furnished after chromatography purification (cyclohexane/EtOAc 95/5, Rf 0.3) 69 mg (65%) of *Z*-**11**. $[\alpha]_D$ −14 (c 1.24, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ: 5.57–5.29 (2H, m, H-4'', 3''), 4.35–4.16 (1H, brs, H-4), 3.97(1H, t, H-5, $J_{5,1''}$=$J_{5,4}$=6.8 Hz), 3.40 (3H, s, OCH_3), 2.28 (1H, m, H-2''a), 2.02 (1H, m, H-2''b), 1.83–1.60 (7H, m, H-1'', CMe_2), 1.52 (3H, d, H-5'', $J_{5'',4''}$=6.2 Hz) 1.38 (9H, s, O*t*Bu), 0.89 (3H, d, CH_3, $J_{CH3,\ H1''}$=6.8 Hz). ^{13}C NMR (C_6D_6, 65°C) δ: 172.0 (CO_2Me), 151.6 (NCO_2), 128.3 (C-3''), 125.6 (C-4''), 95.4 (C-2), 82.4(C-5), 80.1 ($OCMe_3$), 63.4 (C-4), 51.6 (OCH_3), 37.9 (C-1''), 29.8 (C-2''), 28.4 ($OCMe_3$), 27.2, 25.5 (CMe_2), 15.2 (CH_3), 12.8 (C-5'').

(4S,5R)-4-Methoxycarbonyl-5-[1''R,3''E)-1''-methyl-pent-3''-enyl]-2,2-dimethyl-2-oxazo-lidinone E-***13***

At 0°C the oxazolidine *E*-**11** (61 mg, 0.20 mmol) was stirred for 5 h in trifluoroacetic acid/water 1/1 (2 mL); the mixture was then freeze-dried and the resulting ammonium trifluoroacetate was used without purification in the next step.

At −20°C to the ammonium trifluoroacetate in CH_2Cl_2/NEt_3 (1/1, 6 mL) was added trichloromethyl chloroformate (17 µL, 0.14 mmol). After stirring for 2 h, water (6 mL) was added. After extraction with CH_2Cl_2 (3×6 mL), the organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane/EtOAc 6/4, Rf 0.2) to give 27 mg (61%) of *E*-**13**. $[\alpha]_D$ +60 (c 1.00, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 6.19 (1H, s, NH), 5.56–5.26 (2H, m, H-4'', 3''), 4.46 (1H, dd, H-5, $J_{5,4}$=4.5 Hz, $J_{5,1''}$=5.8 Hz), 4.08 (1H, d, H-4, $J_{4,5}$=4.5 Hz), 3.78 (3H, s, OCH_3), 2.20 (1H, m, H-2''a), 2.00–1.80 (2H, m, H-2''b, 1''), 1.63 (3H, d, H-5'', $J_{5'',4''}$=6.0 Hz), 0.94 (3H, d, CH_3, $J_{CH3,\ H1''}$=6.4 Hz). ^{13}C NRM ($CDCl_3$) δ: 170.9 (C-1'), 158.4 (C-2), 128.1 (C-3''), 127.3 (C-4''), 82.3 (C-5), 56.0 (C-4), 53.0 (OCH_3), 37.6 (C-1''), 34.2 (C-2''), 17.9 (CH_3), 13.9 (C-5'').

(4S,5R)-4-Methoxycarbonyl-5-[(1''R,3''Z)-1''-methyl-pent-3''-enyl]-2,2-dimethyl-2-oxazolidinone Z-***13***

The reaction of the oxazolidine *Z*-**11** under the above experimental conditions furnished the oxazolidinone *Z*-**13** with 55% yield. $[\alpha]_D$ +74 (c 0.68, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 5.85 (1H, s, NH), 5.57 (1H, m, H-4''), 5.31 (1H, m, H-3''), 4.49 (1H, dd, H-5, $J_{5,1''}$=6.4 Hz, $J_{5,4}$=4.4 Hz), 4.10 (1H, d, H-4, $J_{4,5}$=4.4 Hz), 3.79 (3H, s, OCH_3), 2.25 (1H, m, H-2''a), 2.13–1.82 (2H, m, H-2''b, 1''), 1.60 (3H, d, H-5'', $J_{5'',4''}$=8 Hz), 0.97 (3H, d, CH_3, $J_{CH3,\ H1''}$=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.8 (C-1'), 158.4 (C-2), 126.7, 126.5 (C-3'', 4''), 82.5 (C-5), 56.2 (C-4), 53.0 (OCH_3), 37.6 (C-1''), 28.3 (C-2''), 14.6 (CH_3), 12.9 (C-5'').

*(4S,5R)-4-Methoxycarbonyl-2-*N*-methyl-5-[(1''R,3''E)-1''-methyl-pent-3''-enyl]-2,2-dimethyl-2-oxazolidinone* E-***14***

To the oxazolidinone *E*-**13** (40 mg, 0.18 mmol) and methyl iodide (87 µL, 1.41 mmol) in DMF (1.3 mL) at 20°C, silver oxide (163 mg, 0.70 mmol) was added. After stirring for 20 h in darkness, the mixture was filtered through celite, and water (4 mL) was added. After extraction with CH_2Cl_2 (3×6 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 6/4 Rf 0.3) gave 36 mg (86%) of *E*-**14**. $[\alpha]_D$ +38 (c 1.00, CH_2Cl_2), lit[15f] $[\alpha]_D$ +38.2 (c 1.36 CH_2Cl_2), lit[15b] $[\alpha]_D$ 37.1 (c 1.51, CH_2Cl_2). ^1H NMR δ ($CDCl_3$, 500 MHz): 5.46 (1H, td, H-4'', $J_{4'',3''}$=15 Hz, $J_{4'',5''}$=6.5 Hz), 5.33 (1H, m, H-3''), 4.25 (1H, dd, H-5, $J_{5,4}$=4.6 Hz, $J_{5,1''}$=6.3 Hz), 3.94 (1H, d, H-4, $J_{4,5}$=4.6 Hz), 3.79 (3H, s, OCH_3), 2.89 (3H, s, NCH_3), 2.18 (1H, m, H-2''a), 1.97–1.80 (2H, m, H-2''b, 1''), 1.64 (3H, d, H-5'', $J_{5'',4''}$=6.5 Hz), 0.92 (3H, d, CH_3, $J_{CH3,\ H1''}$=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.2 (C-1'), 157.2 (C-2), 128.0 (C-4''), 127.2 (C-3''), 79.2 (C-5), 61.6 (C-4), 52.8 (OCH_3), 37.5 (C-1''), 34.2 (C-2''), 30.0 (NCH_3), 17.9 (CH_3), 13.7 (C-5''). Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.75; H, 7.96; N, 5.72.

*(4S,5R)-4-Methoxycarbonyl-2-*N*-methyl-5-[(1''R,3''Z)-1''-methyl-pent-3''-enyl]-2,2-dimethyl-2-oxazolidinone* Z-***14***

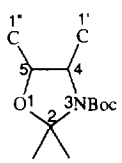
The *N*-methylation of the oxazolidinone *Z*-**13** (83 mg), 0.37 mmol) with methyl iodide (182 µL, 2.92 mmol) and silver oxide (339 mg, 1.46 mmol) in dimethylformamide (2.5 mL) under the above experimental conditions furnished after flash chromatography (cyclohexane/EtOAc 6/4 Rf 0.3) 44 mg (50%) of *Z*-**14**. $[\alpha]_D$ +45 (c 1.05, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 5.52 (1H, m, H-4''), 5.30 (1H, m, H-3''), 4.25 (1H, dd, H-5, $J_{5,4}$=4.8 Hz, $J_{5,1''}$=6.4 Hz), 3.96 (1H, d, H-4, $J_{4,5}$=4.8 Hz), 3.78 (3H, s, OCH_3), 2.88 (3H, s, NCH_3), 2.27–2.10 (1H, m, H-2''a), 2.08–1.74 (2H, m, H-2''b, 1''), 1.57 (3H, dd,

H-5″, $J_{5'',4''}$=6.8 Hz, $J_{5'',3''}$=0.8 Hz), 0.92 (3H, d, JCH_3, $H_{1''}$=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.2 (C-1′), 157.2 (C-2), 126.6, 126.5 (C-3″,4″), 79.5 (C-5), 61.9 (C-4), 52.9 (OCH_3), 37.8 (C-1″), 30.1 (NCH_3), 28.3 (C-2″), 14.0 (CH_3), 12.9 (C-5″). MS (EI, %) 241(20), 182(100), 138(40), 128(90), 100(40), 84(20); HRMS for $C_{12}H_{19}NO_4$: (M^+) calcd 241.1314, found 241.1314.

References

1. MeBmt is the IUPAC/IUB three-letter notation for (4*R*)-4-*N*-dimethyl-L-threonine.
2. Wenger, R.M. *Angew. Chem. Int. Ed. Engl.*, **1983**, *24*, 77–138.
3. (a) Eberle, M.K.; Hiestand, P.; Jutzi-Eme, A.-M.; Nuninger, F.; Zihlmann, H.R. *J. Med. Chem.*, **1995**, *38*, 1853–1864 and references cited therein. (b) Eberle, M.K.; Nuninger, F. *Tetrahedron Lett.*, **1994**, *35*, 6477–6480.
4. Eberle, M.K.; Nuninger, F.; Weber, H.-P. *J. Org. Chem.*, **1995**, *60*, 2610–2612.
5. Miller, K.E.; Rich, D.H. *J. Am. Chem. Soc.*, **1989**, *111*, 8351–8362.
6. Rich, D.H.; Sun, C.-Q.; Guillaume, D.; Dunlap, B.; Evans, D.A.; Weber, A.E. *J. Med. Chem.*, **1989**, *32*, 1982–1987.
7. Aebi, J.D.; Deyo, D.T.; Sun, C.Q.; Guillaume, D.; Dunlap, B.; Rich, D.H. *J. Med. Chem.*, **1990**, *33*, 999–1009.
8. Park, S.B.; Meier, G.P. *Tetrahedron Lett.*, **1989**, *30*, 4215–4218.
9. (a) Wenger, R.M. Patent EP 34567, A2, 810826. (b) Lubell, W.D.; Jamison, T.F.; Rapoport, H. *J. Org. Chem.*, **1990**, *55*, 3511–3522.
10. Wenger, R.M. *Helv. Chim. Acta* **1983**, *66*, 2308–2321.
11. (a) Rama Rao, A.V.; Yadav, J.S.; Chandrasekhar, S.; Drinivas Rao, C. *Tetrahedron Lett.* **1989**, *30*, 6769–6772. (b) Ogoroniidchuk, A.S.; Dybenko, A.G.; Romanova, V.P.; Shilin, V.V. *Ukr. Khim. Zh.* **1990**, *56*, 1203–1205.
12. Lubell, W.D.; Jamison, T.F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511–3522.
13. Yoda, H.; Shirai, T.; Katagiri, T.; Takabe, K.; Hosoya, K. *Chem. Express* **1992**, *7*, 477–480.
14. Lee, S.G.; Kim, Y.K.; Kim; S.K.; Yoon, Y.-Y.; Park, K.H. *J. Korean Chem. Soc.* **1995**, *39*, 123–126.
15. (a) Schmidt, V.; Siegel, W. *Tetrahedron Lett.* **1987**, *28*, 2849–2852. (b) Evans, D.A.; Weber, A.E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (c) Rich, D.H.; Sun, C.-Q.; Guillaume, D.; Dunlap, B.; Evans, D.E.; Weber, A.E. *J. Med. Chem.* **1989**, *2*, 1982–1987. (d) Aebi, J.D.; Dhaon, M.K.; Rich, D.H. *J. Org. Chem.* **1987**, *52*, 2881–2886. (e) Seebach, D.; Juaristi, E.; Miller, D.D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237–261. (f) Blaser, D.; Ko, S.Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230–6233. (g) Togni, A.; Pastor, S.D.; Rihs, G. *Helv. Chim. Acta* **1989**, *72*, 1471–1478.
16. (a) Rama Rao, A.V.; Murali Dhar, T.G.; Subhas Bose, D.; Chakraborty, T.K.; Gurjar, M.K. *Tetrahedron* **1989**, *45*, 7361–7370. (b) Savignac, M.; Durand, J.O.; Genêt, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 717–722. (c) Jung, R.D.; Rich, D.H. *Tetrahedron Lett.* **1987**, *28*, 1139–1142.
17. Tuch, A.; Sanière, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 897–906.
18. Tuch, A.; Sanière, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 2901–2909.
19. Dorigo, A.E; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524–6536.
20. (a) Hanessian, S.; Gai, Y.; Wang, W. *Tetrahedron Lett.* **1996**, *37*, 7443–7476. (b) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P.A. *Tetrahedron* **1995**, *51*, 12843–12858. (c) Nilsson, K.; Ullenius,C. *Tetrahedron* **1994**, *50*, 13173–13180.
21. (a) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C.-G.; Boulanger, T.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.*, **1991**, *56*, 5729–5733. (b) Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, *37*, 7477–7480.
22. (a) Roush, W.R.; Michaelides, M.R.; Tai, D.F.; Lesur, B.M.; Chong, W.K.M.; Hanis, D.J. *J. Am. Chem. Soc.* **1989**, *111*, 2984–2995. (b) Honda, Y; Hirai, S; Tsuchihashi, G.I. *Chem. Lett.* **1989**, 255–258.
23. Tidwel, T.T. *Organic Reactions*, John Wiley and Sons Inc., **1990**, *39*, 297–572.

24. For analogous reactions on achiral α,β-ethylenic aldehydes, see: Clive, D.L.J.; Farina, V.; Beaulieu, P.L. *J. Org. Chem.* **1982**, *47*, 2572–2582, and references cited therein.
25. Nicolaou, K.C.; Bunnage, M.E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402–8403.
26. In ^{1}H NMR (250 MHz), only the coupling constants $^3J_{H\text{-}3,H\text{-}4}$=9.3 and $^3J_{H\text{-}4,H\text{-}5}$=3.4 Hz for the azepane **8a** have been measured. These values, which suggest a *trans* relationship between H3–H4,and a *cis* one between H4–H5, are in good agreement with those based on molecular dynamics simulation using Insight II software (calculated: $J_{H\text{-}3,H\text{-}4}$=7.7–9.8 and 7.9–9.9, respectively for **8a** and **8b**; $J_{H\text{-}4,H\text{-}5}$=1.9–3.8 and $J_{H\text{-}4,H\text{-}5}$=9.5–10.3, respectively for **8a** and **8b**). ^{1}H NMR 2D NOESY diagram of **8a**: cross signals of CH3 with H-3, CH3 with H-4, CH_3 with H-7a, CH_3 with H-6a; H-6b with H-4, H-6b with H-5, H-6b with H-6a; H-2a with H-2b, H-2a with H-3; H-4 with H-5. 2D NOESY diagram of **8b**: cross signals of CH_3 with H-4; H-2a with H-3, H-2a with H-2b; H-2a with H-7a; H-7a with H-7b, H-7a with H-3.
27. Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953.
28. This method constitutes an alternative to the reduction of a propargylic derivative by the modified Corey–Fuchs procedure recently reported, see: D'Aniello, F.; Falorni, M.; Mann, A.; Taddei, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1217–1226.
29. Melon, D.; Gravier-Pelletier, C.; Le Merrer, Y.; Depezay, J.-C. *Bull. Soc. Chim. Fr.* **1992**, *129*, 585–593, and references cited therein.
30. Olsen, R.K. *J. Org. Chem.* **1970**, *35*, 1912–1915.
31. The numbering system used in this paper corresponds to the current CA index names for substructure 1. For details, see: *Chemical Abstracts Service Index Guide*, American Chemical Society:



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