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A Short Synthesis of the Unusual Amino Acid of Cyclosporine (4R)-4-[(E)-2-butenyl]-4,N-Dimethyl-L-Threonine (MeBmt)

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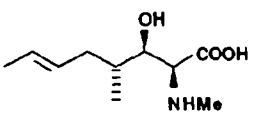
Abstract : MeBmt **1** was prepared in four steps from the optically pure (2Z, 4R) 4-methyloct-6-yn-2-en-1-ol **8**, Z allylic alcohol containing an alkynyl group at the γ position. The two stereogenic centers C-2 and C-3 in the product were controlled using Sharpless' epoxidation and subsequent ring opening at C-2 of the epoxy acid **10** with methylamine.

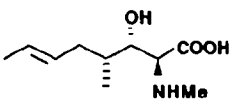
Introduction

β-Hydroxy-α-amino acids are an important class of compounds, appearing in nature both as natural products (threonine, serine, 4-hydroxyproline) and as components of more complex natural compounds such as cyclic polypeptides (e.g. vancomycine, edeine).[1] A representative of this class, MeBmt **1**, is an unusual C-9 amino acid found in the immuno-suppressive undecapeptide cyclosporine A, which appears to be critically involved in the biological activity of this chemotherapeutic agent. Several syntheses of MeBmt have recently been reported.[2]

In connection with our continued work on the asymmetric synthesis of *syn* or *anti* β-hydroxy-α-amino acids and analogues by asymmetric hydrogenation[3] and electrophilic[4] or nucleophilic amination[5], we recently reported in an earlier paper the synthesis of MeBma **2**[6] via the Sharpless epoxidation of the enantiomerically pure (4R,2E,6E)-4-methylocta-4-dien-1-ol followed by nucleophilic opening with methylamine of corresponding epoxy acid.



1



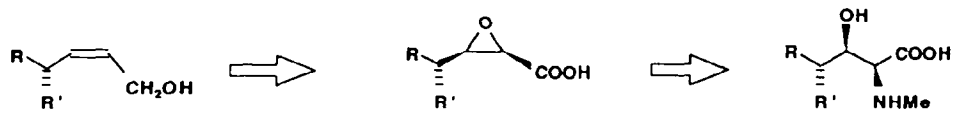
2

We now present a short synthesis of (2S,3S,4R) 2-methylamino-3-hydroxy-4-methyloct-6-enoic acid (MeBmt) **1**, using a similar approach.

Results[7] and Discussion

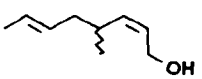
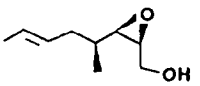
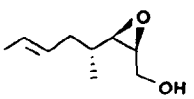
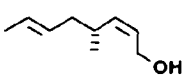
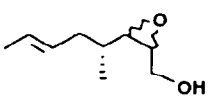
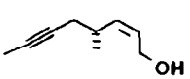
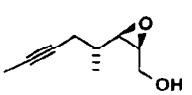
We considered chiral cis α,β-epoxy acids **4** as key intermediates because the regioselective ring opening[8] with methylamine sets up the desired *syn* relationship present in the MeBmt **1**. The absolute configuration is controlled by Sharpless epoxidation[9] of the corresponding allylic alcohol **3**.

Retrosynthetic Scheme

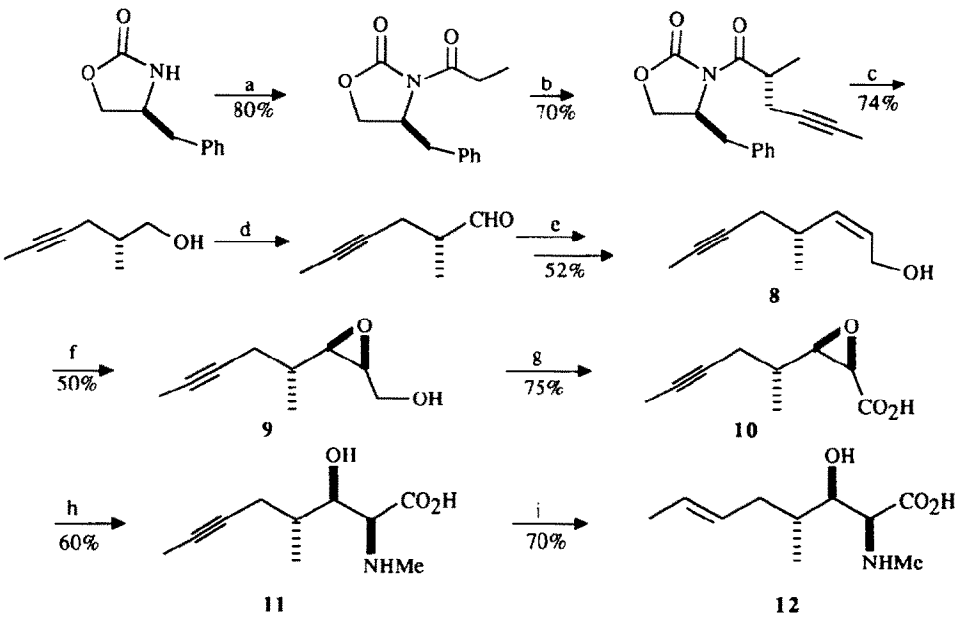


3 **4** **5**

However the Sharpless technology suffers from one limitation in that low asymmetric induction is obtained upon epoxidation of hindered Z allylic alcohols.[10] Indeed, in a first attempt, the asymmetric epoxidation of the racemic dienol **6** was carried out under catalytic conditions with 2.5 eq of TBHP and (+) diethyltartrate at -20°C. A kinetic resolution is observed (entry 1). Epoxidation is more difficult on the (R) alcohol than on the (S) enantiomer.

Entry	Substrate	Reagent	Product	de	Yield
1	 (R,S) **6**	2.5 eq. tBuOOH 10% Ti (OiPr)$_4$, 15% L(+) DET	 64%  36% + enantiomers	28%	60%
2	 (R) **7**	2.5 eq. tBuOOH 10% Ti (OiPr)$_4$, 15% L(+)DET		8%	60%
		2.2 eq. tBuOOH 1.05 eq. Ti(OiPr)4, 1.05 eq. L(+)DET		17%	32%
3	 (R) **8**	2.5 eq. tBuOOH 10% Ti (OiPr)$_4$, 15% L(+)DET		40%	60%
		2.2 eq. tBuOOH 1.05 eq. Ti(OiPr)$_4$, 1.05 eq.L(+)DET	 **9** + diastereoisomer	70%	70%

The (R) 2-methylhex-4-en-1-ol **7** did not epoxide selectively either under catalytic or stoichiometric conditions due to steric hinderance (entry 2). It has been demonstrated by Ganem[11] that when R = R' = CH_3, asymmetric Sharpless epoxidation proceeded with moderate enantiomeric excess (66%). So we anticipated that a less bulky alkynyl side chain at γ position could overcome this problem. We were pleased to find that the epoxidation under catalytic conditions gives a significant increase of the diastereoselection up to 40%. Interestingly under stoichiometric epoxidation conditions, an acceptable diastereoselectivity (70%) is observed. The diastereoisomers were separated by medium pressure liquid chromatography to give enantiomerically pure (2S,3R,4R) 2,3-epoxy-4-methyloct-6-yn-1-ol **9** (50%). So our strategy could be applied to the MeBmt synthesis and the overall sequence is showed in the following scheme :



a)$CH_3CH_2CO_2H$, Et_3N 1.2 eq, THF b)NaHMDS, $CH_3C{\equiv}CCH_2Br$, THF c)$LiAlH_4$, Et_2O, 0°C
d) $(COCl)_2$, DMSO, -78°C; Et_3N, -30°C e) i) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$; KHMDS
18-Crown-6, THF, -78°C; ° ii) Dibal; Et_2O -78°C f) tBuOOH; $Ti(OiPr)_4$; L(+)DET ; CH_2Cl_2; -20°C
g) PDC; DMF; 20°C h)$MeNH_2$ H_2O , 90°C; HCl 6N;  EtOH ; 90°C i) Li, NH_3, -78°C ⟶ -20°C

To fix the C-4 configuration, the Evans' procedure[2] is used. The chiral oxazolidinone is coupled with propionic acid (80%) and asymmetric alkylation of the oxazolidinone with butynyl bromide gives after reduction, the 2-methylhex-4-yn-1-ol. Swern oxidation leads to the aldehyde which is allowed to react immediately under Still modified Horner-Emmons conditions to afford the Z/E esters in a 9 to 1 ratio. The Z isomer could be separated by flash chromatography (60% overall). Reduction followed by catalytic asymmetric epoxidation and PDC oxidation product the epoxy acid **10**. Subsequent stereocontrolled opening with methylamine at C-2 furnished the (2S,3S,4R) 2-methylamino-3-hydroxy-4-methyloct-6-ynoic acid **11** (60%)

which gave after reduction (Li, NH_3) the cristalline MeBmt (m.p. 250°C, $[\alpha]_D$ = +11.8 c = 0.5, phosphate buffer pH=7, Literature $[\alpha]_D$ = 11.5) with 9% overall yield from the (2R)-2-methyl-4-hexyn-1-al.

Conclusion

This synthetic route provides a short, useful and general method for obtaining γ-dialkylbranched, *syn* β-hydroxy-α-amino acids such as MeBmt. We have found that the low asymmetric induction in Sharpless epoxidation of γ-dialkyl substituted Z allylic alcohols can be partially overcome by using a γ alkynyl group. The overall procedure allows synthesis of all the analogues of MeBmt just by changing the starting α-alkylated chiral aldehyde and the tartrate.

Acknowledgements : JO. Durand thanks the Ministry of Research (MRE) for a grant (1990-1992)

References and notes

Infrared spectra (IR) were taken using a Bruker 45 FTIR instrument; ^1H and ^{13}C NMR spectra were recorded using a Brucker AC200 spectrometer. Column chromatography was carried out over Merck silica gel 60 (40-63 µm). MPLC was carried out over Merck silica gel 60 (25-50 µm). (2R)-2-Methyl-4-hexyn-1-al was prepared from (4S)-4-(phenylmethyl) oxazolidin 2-one by Evans protocol[2] in four steps as describe in synthetic scheme with 35 % overall yield.

Methyl (2Z, 4R) 4-methyl oct-6-yn-2-enoate : A solution of 3.34 g (10.5 mmol) of methyl bis-(trifluoroethyl)phosphonoacetate, 11.1 g (42 mmol) of 18-Crown-6 in 150 mL of THF was cooled to -78°C and treated with 10.5 mmol of KHMDS (20.9 mL, 0.5 M) in toluene. Then, 1.15 g (10.5 mmol) of (2R)-2-methyl-4-hexynal was added and the reaction mixture was stirred for 1 h at -78°C, then quenched by the addition of saturated ammonium chloride. The aqueous phase was extracted into three 100 mL portions of Et_2O, the combinated organic phases were washed and dried over $MgSO_4$, then concentrated in vacuo. Isomer ratio was measured by NMR integration : E/Z = 13/87. Separation by flash chromatography (C_6H_{12}/Et_2O : 92/8) gave 1.1 g of Z isomer (63%), $[\alpha]_D$= 93 (c = 1, CH_2Cl_2) and 0.15 g of E isomer (12%). IR (KBr, cm-1) 1724, 1653 (ν CO, ν C=C). ^1H NMR (200 MHz, $CDCl_3$) δ 6.2-6.1 (1H, dd, ^3J = 11.5 Hz, ^3J = 9.8 Hz), 5.8-5.7 (1H, dd, ^3J = 11.5 Hz, ^4J = 1.5 Hz), 3.7 (3H, s), 3.75-3.5 (1H, m), 2.2-2.1 (2H, qd, ^3J = 8.5 Hz, ^5J = 2.5 Hz), 1.7 (3H, t, ^5J = 1Hz), 1.1 (3H, d, ^3J = 6.7 Hz). ^{13}C NMR(50 MHz, $CDCl_3$) δ 166.5 (OCH_3), 154 (C=C), 118 (C=C), 77.1 (C alkyne), 76.3 (C alkyne), 51 ($COOCH_3$), 31.9 (CH), 25.8 (CH_2), 19.3 (CH_3), 3.4 (CH_3).

(2Z, 4R) 4-Methyl oct-6-yn-2-en-1-ol 8 : To a solution of 1.25 g (7.53 mmol) of methyl (2Z, 4R) 4-methyl-6-octyn-2-enoate in 25 mL of anhydrous Et_2O at -78°C under argon was added dropwise 22.3 mL (22.3 mmol) of DIBAL-H 1M in hexane. The reaction mixture was stirred for 4 h, then quenched by slow addition of 10 mL of methanol. The mixture was stirred at room temperature until a white precipitate was formed, the precipitate was filtered through a pad of Celite, washed with Et_2O and the solvent was removed in vacuo. The residue was distilled under reduced pressure to give 0.860 g of colorless liquid (82%). b.p.$_{1.5}$ 90°C $[\alpha]_D$ = 37 (c = 1.08, CH_2Cl_2). IR (cm^{-1}) 3500-3100 (ν OH). 1H NMR (200MHz,$CDCl_3$) δ 5.8–5.6 (1H, td, ^3J= 7Hz, ^3J = 10.9 Hz), 5.5–5.35 (1H, t, ^3J = 10.9 Hz), 4.4-4.1 (2H, m), 2.9-2.6 (1H, m), 2.3-2.2 (2H, m), 1.9-1.8 (3H, t, ^5J = 2.4 Hz), 1.5-1.4 (1H, s large), 1.1 (3H, d, ^3J = 6.6 Hz). ^{13}C NMR DEPT (50 MHz, $CDCl_3$) δ 137.6(C=), 127.9 (=C), 58.5 (CH_2OH), 31.9 (CH), 26.6 (CH_2), 20.6 (CH_3), 3.32 (CH_3).

(2S, 3R, 4R) 2,3-Epoxy-4-methyl oct-6-yn-1-ol ***9*** *:* A mixture of powdered, commercially activated 4Å molecular sieves (0.576 g) and 80 mL of dichloromethane was cooled to -20°C. 1.36 mL of L-(+)-diethyltartrate (1.64 g, 7.96 mmol, 1.05 eq). 1.05 g (7.6 mol) of alcohol **8**, then 2.37 mL (2.26 g, 7.96,mmol, 1.05 eq) of titanium (IV) isopropoxide were added sequentially. After 3 min of stirring at -20°C, 5.76 mL (2.2 eq) of a 3.5 M solution of *ter*-butyl hydroperoxide were added. The mixture was stirring 60 h and neutralized with 21.7 mL of a 10% solution of tartric acid. After 30 min stirring at -20°C, the reaction mixture was allowed to warm to room temperature, stirred 1 h and decanted. The aqueous phase was extracted with CH_2Cl_2 and the organic solvent was concentrated. The residue was dissolved in 60 mL of Et_2O and hydrolysis of the tartrate was effected by adding 20 mL of a 1M aqueous solution of sodium hydroxyde at 0°C. After 30 min of vigorous stirring, the organic layer was separated and the aqueous layer was extracted with Et_2O.The organic phase was concentrated and the residue was purified by flash chromatography. The two diastereoisomers were separated by MPLC on silica gel (Et_2O/C_6H_{12} 1/1) to give 0.55 g of colorless oil (50%). $[\alpha]_D$ = 9.3 (c = 1.33, $CHCl_3$) IR (cm^{-1}) 3500-3100, 1200 (ν OH, ν C-O). ^1H NMR (200 MHz, $CDCl_3$) δ 4-3.8 (1H, dd, ^3J = 4.2 Hz, ^2J = 12Hz), 3.7-3.6 (1H, dd, ^3J = 5.2 Hz, ^2J = 12 Hz), 3.3-3.15 (1H, td, ^3J = 4.2 Hz, ^3J = 7 Hz), 3-2.8 (1H, dd, ^3J = 9.5Hz, ^3J = 4.2 Hz), 2.5-2.2 (2H, m), 2.1 (1H, s), 1.85 (3H, t, ^5J = 2.5 Hz), 1.7-1.5 (1H, m), 1.1 (3H, d, ^3J = 6.9 Hz). ^{13}C (50 MHz, $CDCl_3$) d 77.3 (C alkyne), 75.9 (C alkyne), 60.9 (CH_2OH), 60.8 (CHO), 57 (CHO), 32.1 (CH), 23.9 (CH_2), 15.6 (CH_3), 3.4 (CH_3).

(2R, 3R, 4R) 2,3-Epoxy-4-methyl oct-6-ynoic acid ***10*** *:* 11.2 g of pyridium dichromate were dissolved in 15 mL of DMF. 0.65 g of **9** were added and the mixture was stirred at room temperature for 48 h. 100 mL of water were added and the aqueous layer was extracted with Et_2O. The organic phase was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by chromatography (florisil, Et_2O/C_6H_{12}/HCOOH 35:64:1) to give 0.54 g of yellow oil (75%). $[\alpha]_D$ = 14.9 (c = 1.14, CH_2Cl_2).IR (cm^{-1}) 3500-2400, 1730, 1200 (ν OH, ν CO, ν C-O). ^1H NMR (200 MHz, $CDCl_3$) δ 3.6 (1H, d, ^3J = 4.7 Hz), 3.2-3.1 (1H, dd, ^3J = 4.7 Hz, ^3J = 9.4 Hz), 2.5-2.4 (2H, m), 1.8 (3H, t, ^5J = 2.5 Hz), 1.75-1.6 (1H, m), 1.1 (3H, d, ^3J = 6.9 Hz) ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.1 (COOH), 77.8 (C alkyne), 75.2 (C alkyne), 61.3 (CO), 52.5 (CO), 31.3 (CH), 23.6 (CH_2), 15.2 (CH_3), 3.4 (CH_3).

(2S,3S,4R) 2-Methylamino-3-hydroxy-4-methyl oct-6-ynoic acid ***11*** *:* 0.16 g of epoxy acid **10** was stirred with 5 mL of an aqueous solution of methylamine at 90°C for 5 h in a scelled tube. The water and excess of methylamine were evaporated, the residue was washed with Et_2O, then acidified with 2 mL of a 6N solution of HCl. After concentration in vacuo the solid was dissolved in 3 mL of ethanol, 2 mL of propylene oxide were added and the mixture was refluxed 10 min. 0.108 g of a white solid was obtained (54%)
mp 250°C $[\alpha]_D$ = 30.6 (c = 0.75, phosphate buffer Tritisol pH = 7). IR (cm^{-1}) 3650-2400, 3296, 3241, 1653, 1598 (ν NH, ν OH, δ NH_2^+, ν CO). ^1H NMR (200 MHz, D_2O) δ 3.75-3.65 (1H, dd, ^3J = 4.7 Hz, ^3J = 7.5 Hz), 3.5-3.45 (1H, d, ^3J = 4.7 Hz), 2.55 (3H, s), 2.3-1.9 (2H, m), 1.8-1.6 (1H, m), 1.6 (3H, t), 0.9-0.85 (3H, d, ^3J = 6.8 Hz). ^{13}C NMR (50 MHz, D_2O/NaOD) δ 183 (COOH), 80.7 (C alkyne), 80.5 (C alkyne), 78 (CH-N), 69.2 CH-O), 37.2 (CH), 36.3 (NH-CH_3), 23.8 (CH_2), 17.9 (CH_3), 4.6 (CH_3).

(2S,3S,4R) 2-Methylamino 3-hydroxy-4 methyl oct 6-enoic acid (MeBmt) : To a stirred solution of 0.033 g of Li in 21 mL of liquid ammoniac was added 0.046 g of **11** at -78°C under argon. The reaction mixture was heated to reflux at -20°C for 5 min. then quenched at -78°C by dropwise addition of 1 mL of water. The solvent was evaporated and the solid was neutralized with 1.5 mL of a 3.5N solution of HCl. After concentration, the residue was purified by chromatography through Mitsubishi HP20SS polymer resin with H2O then H_2O/MeOH 70:30 to give 0.032 g of white solid recrystallized in H_2O/EtOH (70%). mp 250°C $[\alpha]_D$ = 11.8 (c = 0.5, phosphate buffer Tritisol pH = 7) Lit.: $[\alpha]_D$ = 11.5 IR (cm^{-1}) 3214, 3000-2200, 1620, 1588 (ν OH, δ NH^+, C=C, δ NH, ν CO). ^1H NMR (200 MHz, D_2O) δ 5.5-5.2 (2H, m) 3.62-3.5 (1H, t, ^3J = 6.1 Hz), 3.46-3.43 (1H, d, ^3J = 5.8 Hz). 2.55 (3H, s), 2.2-2 (1H, m), 1.8-1.6 (1H, m), 1.6-1.5 (1H, m), 1.45 (3H, d, ^3J = 5 Hz), 0.75 (3H, d, ^3J = 6.7 Hz). ^{13}C NMR (50 MHz, D_2O/phosphate Tritisol ph 7) δ 173 (COOH), 130 (C=), 129.8 (C=), 75.2 (C-OH), 67.8 (C-NH), 36.6 (CH), 37.7 (CH_2), 33.7 (NH-CH_3), 18.3 (CH_3), 16.5 (CH_3) HRMS (EI) calcd 202.1440, found 202.1444

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