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Asymmetric synthesis of the β-amino acid methyl ester derivative of Onchidin: (2*S*,3*S*)-methyl-3-amino-2-methyl-7-octynoate and its enantiomer[1]

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Abstract: The asymmetric synthesis of the methyl ester of the natural β-amino acid of Onchidin (2*S*,3*S*)-methyl-3-amino-2-methyl-7-octynoate and its enantiomer is described. The preparation of an enantiomerically pure β-hydroxy acid through an enantioselective aldol condensation reaction and an intramolecular nucleophilic displacement to form a β-lactam intermediate are the key steps. © 1997 Elsevier Science Ltd

β-Amino acids have gained considerable interest among organic chemists along the last few years, mainly because of their occurrence in nature, either in free form or as a part of complex molecules.[2] They have also been successfully used as intermediates in the synthesis of β-lactams[3] and in peptidomimetics.[4] Particularly, marine organisms have revealed as a very abundant source of non proteinogenic amino acids, either by chemical modification of ordinary α-amino acids or as completely new structures. In addition, hydroxy acids are frequently found together with amino acids as part of depsipeptides.

Whereas several approaches towards the synthesis of β-amino acids have appeared in the literature[5] only a few of them have been developed well enough to cover a wide range of possible structures. Moreover, most of them seem to be unable to prepare all possible stereoisomers of a given β-amino acid in stereochemically pure form. In addition, the difficulties increase when α-substituted β-amino acids are required enantiomerically pure since two contiguous stereocenters have to be controlled.[6]

Recently, a very small amount of Onchidin **1** (Figure 1), a dimeric cyclic depsipeptide from the marine mollusc *Onchidium sp,* has been isolated.[7] Onchidin is formed by two identical chains linked in a head to tail way. Thus, the compound presents C_2 symmetry and only half the proton and carbon resonances are present in the NMR spectra. Each chain contains two units of 2-hydroxy isovaleric acid, valine and N-methyl valine together with an α-methyl-β-amino acid with an unusual side chain: 3-amino-2-methyl-7-octynoic acid **2** (AMO). Onchidin's structure has been elucidated from spectroscopic data and chemical degradation studies. The absolute configuration (2*S*,3*S*) of the β-amino acid AMO could only be proposed on the basis of nOe studies and NMR proton coupling constants analysis.

In addition, a β-hydroxy acid, 3-hydroxy-2-methyl-7-octynoic acid **7**, with the same carbon skeleton as **2**, has been identified in Onchidin B, another depsipeptide isolated from the same organism.[8] The absolute configuration of natural **7** has been determined to be (2*R*,3*R*) by comparison with all four possible stereoisomers properly derivatised. This finding made the synthesis of β-amino acids from β-hydroxy acids attractive to us in order to confirm the proposed structures of Onchidin and Onchidin B by total synthesis.

In this paper we present our work towards the synthesis of the enantiomerically pure (2*S*,3*S*)-methyl-3-amino-2-methyl-7-octynoate together with its enantiomer by parallel routes.

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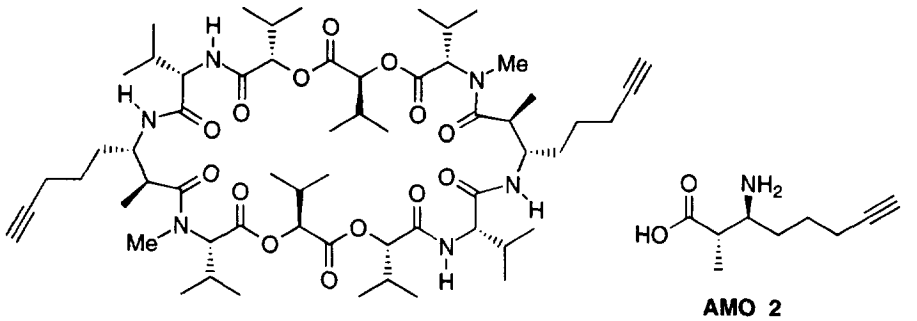
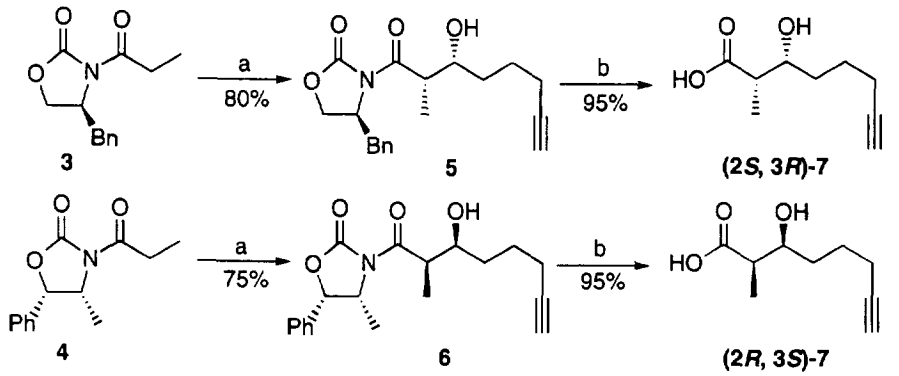


Figure 1.

Our synthetic plan started with the enantiopure preparation of the two stereoisomers (2*S*,3*R*) and (2*R*,3*S*) of 3-hydroxy-2-methyl-7-octynoic acid **7** as the key intermediates, making use of the powerful Evans' methodology[8,9] (Scheme 1).



a) 1) $(nBu)_2BOTf$, Et_3N, CH_2Cl_2, 0° C; 2) 5-hexynal, CH_2Cl_2, -70° C. b) LiOH, H_2O_2, THF-H_2O, 0° C

Scheme 1.

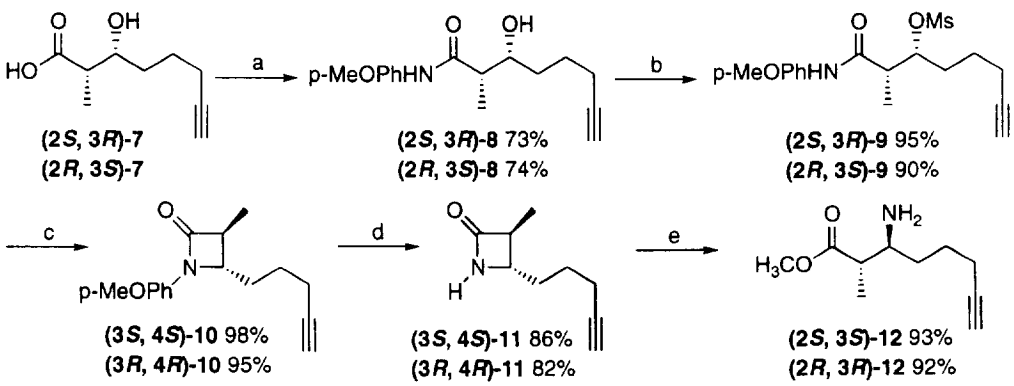
Thus, in the synthesis of (2*S*,3*R*)-**7** and (2*R*,3*S*)-**7** the presence of diastereoisomers of aldols **5** and **6** could not be detected by ^{1}H-NMR. The absolute configuration of aldol **6** was unambiguously confirmed to be (4*R*,5*S*,2′*R*,3′*S*) by single crystal X-ray analysis.[10] Since aldol **5** could not be crystallised, its absolute configuration was assumed to be (2*S*,3*R*) by considering previous studies in this type of reaction. An additional proof of the fact that **5** and **6** have enantiomeric configurations at positions 2′ and 3′ is the opposite sign of the specific rotation of the two β-hydroxy acids **7**, obtained from **5** and **6** respectively. Consequently, aldols **5** and **6** were hydrolysed following Evans' conditions[11] obtaining the enantiomeric β-hydroxy acids (2*S*,3*R*)-**7** ($[\alpha]_D$=+6.2 (*c* 2.0 $CHCl_3$)) and (2*R*,3*S*)-**7** ($[\alpha]_D$=−6.0 (*c* 1.3 $CHCl_3$)) in very high yield. All spectroscopic data for both enantiomers were identical.

From this point onwards both enantiomers were submitted to the same sequence of reactions in order to get (2*S*,3*S*)-AMO and (2*R*,3*R*)-AMO. The key step in these transformations was the displacement of the hydroxyl group at C-3 with a nucleophilic nitrogen in order to produce the inversion of the configuration on this carbon. Initially we considered the azide ion as a source of nitrogen, but when we tried to react sodium azide with the β-mesyl ester derivatives in DMSO at room temperature we only recovered starting material. More severe conditions, like raising the temperature, led to the elimination product. When the reaction was carried out using the well-known reagents, tetrabutyl ammonium azide, tetramethyl guanidinium azide[12] or the recently proposed system DPPA–DBU,[13] the results

did not improve. Several attempts using Mitsunobu conditions (DEAD, Ph_3P, DPPA)[14] also yielded starting material even after a few days of reaction.

With these disappointing results in hand we considered the intramolecular attack of an amide ion to a good leaving group. Finally, we chose the cyclization of the p-methoxyanilide anion with a sulfonate as the leaving group to produce a β-lactam.[15]

Accordingly, the corresponding hydroxy amides were prepared by reaction of the β-hydroxy acids with p-anisidine (Scheme 2). When the reaction between β-hydroxy acids **7** and p-anisidine was carried out with DCC as the coupling reagent, we obtained the β-hydroxy amides (2*S*,3*R*)-**8** and (2*R*,3*S*)-**8** in moderate yield along with other by-products. This yield could be increased to more than 70% using the tandem Ph_3P–2,2′-dipyridyl disulfide as the coupling agent.[16] These amides **8** were then mesylated under standard conditions (MsCl, Et_3N, CH_2Cl_2) giving the corresponding β-mesyl amides (2*S*,3*R*)-**9** and (2*R*,3*S*)-**9** in nearly quantitative yield. Treatment of these β-mesyl amides with potassium tert-butoxide at low temperature cleanly gave the corresponding trans β-lactams (3*S*,4*S*)-**10** and (3*R*,4*R*)-**10** in high yield. In fact, the product from the competitive elimination reaction could not be detected. We attributed the selectivity of this reaction to the steric hindrance on the proton in position α to the carboxyl group due to the presence of the methyl bonded to C-2.



a)Ph_3P, 2,2'-dipyridyl disulfide, p-anisidine, CH_2Cl_2, r.t. b) MsCl, Et_3N, CH_2Cl_2, 0° C. c) KOtBu, THF, -15° C. d) $(NH_4)_2Ce(NO_3)_6$, H_2O, CH_3CN, -15° C. e) MeOH, HCl (g).

Scheme 2.

Nitrogen deprotection of β-lactams **10** was performed oxidatively with ammonium cerium (IV) nitrate[17] at low temperature, obtaining (3*S*,4*S*)-**11** and (3*R*,4*R*)-**11** in good yield. This reaction proved to be very sensitive to the experimental conditions. Thus, when the temperature is raised or the reaction time is increased, yields are reduced and by-products appear. The major by-product was identified as the product resulting from the O-demethylation of the starting β-lactam.[18]

The relative trans stereochemistry of the β-lactams **10** and **11** was confirmed from the small value of the coupling constant (J=2.1 Hz) between protons at positions 3 and 4. In addition, no other diastereoisomers could be detected by ^{1}H-NMR, either after the lactam formation or after the lactam deprotection. Finally, the deprotected β-lactams **11** were opened in acidic methanol, producing in nearly quantitative yields the desired β-amino methyl esters (2*S*,3*S*)-**12** and (2*R*,3*R*)-**12** as unstable oils which were readily characterised.

Unfortunately, the scarcity of natural material made impossible the comparison between the natural and the synthesised amino acids. Both this reason and Onchidin's potential as cytotoxic agent led us to set up a program towards its total synthesis which is currently being developed.

Experimental

General

(1*S*,2*R*)-Norephedrine, L-phenylalanine, propionyl chloride, 5-hexyn-1-ol, dibutylboron triflate and 2,2-dipyridyl disulfide were purchased from Aldrich Chemical Company and were used without further purification. All solvents were distilled under argon following standard literature procedures. Flash column chromatography was performed using Kieselgel 60 230–400 mesh SiO_2 gel into glass columns. Melting points were determined using a Buchi apparatus and are uncorrected. All NMR spectra were recorded at room temperature in deuteriochloroform using Bruker AMX 300 and Bruker AMX 500 (Centro de Resonancia Magnética, Xunta de Galicia) or Bruker ARX 400 (CACTI, Universidad de Vigo) spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (δ 0.00 ppm) and coupling constants (J) are measured in Hertz. ^{1}H-NMR spectra were referenced either to TMS or to the residual signal of chloroform as internal standards. ^{13}C-NMR spectra were referenced with respect to the central peak of the carbon signal of $CDCl_3$ (δ 77.0 ppm). Infrared spectra were recorded using a FTIR GRAMS/386 spectrometer. Mass spectra were obtained either on a Kratos MS-50 or on a Hewlett–Packard spectrometer with the electronic impact (EI) technique. High resolution mass spectra were recorded on a Fisons Autospec M spectrometer (CACTI, Universidad de Vigo). Optical rotations were recorded on a Jasco DIP-370 digital polarimeter.

Preparation of (4*S*,2′*S*,3′*R*)-3-(3′-hydroxy-2′-methyl-7′-octynoyl)-4-(phenylmethyl)-2-oxazolidinone **5**, (4*R*,5*S*,2′*R*,3′*S*)-3-(3′-hydroxy-2′-methyl-7′-octynoyl)-5-phenyl-4-methyl-2-oxazolidinone **6**, (2*S*, 3*R*)-3-hydroxy-2-methyl-7-octynoic acid (2*S*,3*R*)-**7** and (2*R*,3*S*)-3-hydroxy-2-methyl-7-octynoic acid (2*R*,3*S*)-**7** is described elsewhere.[6]

(2S,3R)-3-Hydroxy-2-methyl-N-(4-methoxyphenyl)-7-octynamide (2S,3R)-8

A solution of triphenylphosphine (550 mg, 2.1 mmol) and 2,2′-dipyridyl disulfide (470 mg, 2.1 mmol) in dichloromethane (5 mL) was treated with a solution of the β-hydroxy acid (2*S*,3*R*)-**7** (275 mg, 1.61 mmol) in dichloromethane (5 mL). The resulting mixture was stirred for 30 min at room temperature and a solution of p-anisidine (258 mg, 2.1 mmol) in dichloromethane (5 mL) was added. The reaction was stirred for 16 hours at room temperature. Then, the mixture was washed with 1.5 M HCl (25 mL), 5% $NaHCO_3$ (25 mL) and brine (40 mL). The organic phase was dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (EtOAc–hexanes 1:3) yielding the β-hydroxy amide (2*S*,3*R*)-**8** as a white solid (325 mg, 73% yield). M.p.=131–133°C; $[\alpha]_D$=−14.2 (c 0.7, $CHCl_3$); ^{1}H-NMR: δ 1.27 (d, J=7.1 Hz, 3H, -HC-C*H*$_3$), 1.54–1.79 (m, 4H, -C*H*$_2$-C*H*$_2$-), 1.96 (t, J=2.6 Hz, 1H, -CC*H*), 2.23–2.28 (m, 2H, -C*H*$_2$CCH), 2.48 (m, J=7.1, 2.7 Hz, 1H, -*H*C-CH$_3$), 3.17 (d, J=3.4 Hz, 1H, -O*H*), 3.79 (s, 3H, C*H*$_3$O-), 4.00 (m, 1H, -*H*C-OH), 6.86 (d, J=9.0 Hz, 2H, Ar*H*), 7.40 (d, J=8.9 Hz, 2H, Ar*H*), 7.63 (broad s, 1H, N*H*); ^{13}C-NMR: δ 11.7 (CH_3), 18.6 (CH_2), 25.3 (CH_2), 32.9 (CH_2), 46.1 (CH), 69.1 (CH), 72.1 (CH), 84.5 (C), 114.5 (CH), 122.3 (CH), 131.0 (C), 157.0 (C), 174.5 (CO); MS: m/e (%), 275 (M^+, 50), 224 (3), 208 (2), 179 (14), 149 (11), 123 (100), 108 (40), 95 (5), 57 (7). HRMS: calculated for $C_{16}H_{21}NO_3$ 275.1521, found 275.1518.

(2R,3S)-3-Hydroxy-2-methyl-N-(4-methoxyphenyl)-7-octynamide (2R,3S)-8

Enantiomeric (2*R*,3*S*)-**8** was prepared using the same procedure described above for (2*S*,3*R*)-**8**. Thus, a solution of triphenylphosphine (244 mg, 0.92 mmol) and 2,2′-dipyridyl disulfide (203 mg, 0.92 mmol) in dichloromethane (5 mL) was treated with a solution of the β-hydroxy acid (2*R*,3*S*)-**7** (120 mg, 0.70 mmol) in dichloromethane (3 mL). The resulting mixture was stirred for 30 min at room temperature and a solution of p-anisidine (111 mg, 0.9 mmol) in dichloromethane (2 mL) was added. After work-up and purification, β-hydroxy amide (2*R*,3*S*)-**8** was obtained as a white solid (143 mg, 74% yield). $[\alpha]_D$=+11.8 (c 1.1 $CHCl_3$). Spectral data are identical to those obtained for the enantiomeric β-hydroxy amide.

(2S,3R)-3-Mesyl-2-methyl-N-(4-methoxyphenyl)-7-octynamide (2S,3R)-9

A solution of the β-hydroxy amide (2*S*,3*R*)-**8** (95 mg, 0.34 mmol) in dichloromethane (6 mL) was cooled to 0°C and was sequentially treated with mesyl chloride (0.05 mL, 0.69 mmol) and triethylamine (0.09 mL, 0.69 mmol). The reaction mixture was stirred for 30 min and then it was washed with H_2O (20 mL), 1 M H_3PO_4 (20 mL), 5% $NaHCO_3$ (25 mL) and brine (40 mL). The organic phase was dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (EtOAc–hexanes 1:3) yielding the β-mesylamide (2*S*,3*R*)-**9** as a white solid (115 mg, 95% yield). M.p.=98–100°C; $[\alpha]_D$=+35.7 (c 1.0, $CHCl_3$); ^{1}H-NMR: δ 1.29 (d, J=7.0 Hz, 3H, -HC-C*H*$_3$), 1.53–1.93 (m, 4H, -C*H*$_2$C*H*$_2$-), 1.95 (t, J=2.6 Hz, 1H, -CC*H*), 2.24 (m, J=6.9, 2.5 Hz, 2H, -C*H*$_2$-CCH), 2.99 (m, 1H, *H*C-CH$_3$), 3.06 (s, 3H, O-SO$_2$-C*H*$_3$), 3.79 (s, 3H, C*H*$_3$O), 4.90 (m, 1H, *H*C-O-SO$_2$CH$_3$), 6.86 (d, J=8.9 Hz, 2H, Ar*H*), 7.45 (d, J=8.9 Hz, 2H, Ar*H*), 7.64 (broad s, 1H, N*H*); ^{13}C-NMR: δ 13.5 (CH_3), 18.3 (CH_2), 25.0 (CH_2), 29.6 (CH_2), 39.2 (CH), 45.9 (CH), 55.9 (CH_3O), 69.6 (CH), 83.8 (C), 84.5 (CH_3-SO_2-O), 114.5 (CH), 121.9 (CH), 130.7 (C), 156.6 (C), 170.9 (CO); MS: m/e (%), 353 (M^+, 10), 257 (13), 218 (5), 177 (3), 149 (73), 134 (16), 123 (100), 108 (31), 91 (14), 79 (23). HRMS calculated for $C_{17}H_{23}NO_5S$ 353.1296, found 353.1291.

(2R,3S)-3-Mesyl-2-methyl-N-(4-methoxyphenyl)-7-octynamide (2R,3S)-9

β-Hydroxy amide (2*R*,3*S*)-**8** was mesylated using the same procedure described above for (2*S*,3*R*)-**8**. Thus a solution of (2*R*,3*S*)-**8** (140 mg, 0.5 mmol) in CH_2Cl_2 (7 mL) was cooled to 0°C and was sequentially treated with mesyl chloride (0.07 mL, 1 mmol) and Et_3N (0.14 mL, 1 mmol). After work-up and purification β-mesyl amide (2*R*,3*S*)-**9** was obtained as a white solid (159 mg, 90% yield). $[\alpha]_D$=−31.5 (c 1.1 $CHCl_3$). Spectral data are identical to those obtained for the enantiomeric β-mesyl amide.

(3S,4S)-3-Methyl-1-(4-methoxyphenyl)-4-(4'-pentynyl)-azetidin-2-one (3S,4S)-10

A solution of the β-mesyl amide (2*S*,3*R*)-**9** (150 mg, 0.42 mmol) in THF (15 mL) was cooled to −15°C and treated with potassium tert-butoxide (55 mg, 0.46 mmol). The reaction was stirred for 2 hours at −15 °C and then it was quenched with an aqueous saturated solution of NH_4Cl (20 mL). The organic phase was separated, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (EtOAc–hexanes 1:5) yielding the β-lactam (3*S*,4*S*)-**10** as a yellowish oil (108 mg, 98% yield). R.f.=0.5 (EtOAc/hexanes 1:1); $[\alpha]_D$=+22.6 (c 2.0 $CHCl_3$); ^{1}H-NMR: δ 1.37 (d, J=7.3 Hz, 3H, -HC-C*H*$_3$), 1.58–1.88 (m, 4H, -C*H*$_2$-C*H*$_2$-), 1.98 (t, J=2.6 Hz, 1H, -CC*H*), 2.23–2.28 (m, 2H, -C*H*$_2$-CCH), 2.94 (m, J=7.3, 2.1 Hz, 1H, *H*C-CH$_3$), 3.64 (m, 1H, *H*C-N-Ar), 3.78 (s, 3H, C*H*$_3$O.), 6.87 (d, J=9.0 Hz, 2H, Ar*H*), 7.30 (d, J=9.0 Hz, 2H, Ar*H*); ^{13}C-NMR: δ 13.8 (CH_3), 18.7 (CH_2), 24.3 (CH_2), 31.2 (CH_2), 50.2 (CH), 55.9 (CH), 59.7 (CH_3O), 69.6 (CH), 83.7 (C), 114.8 (CH), 118.9 (CH), 131.5 (C), 156.4 (C), 167.8 (CO); MS: m/e (%), 257 (M^+, 53), 200 (3), 186 (2), 170 (2), 149 (100), 134 (22), 106 (4), 92 (3), 77(4), 64 (2); IR (cm^{-1}): 828, 1036, 1161, 1243, 1293, 1394, 1448, 1513, 1735, 2941, 3294. HRMS: calculated for $C_{16}H_{19}NO_2$ 257.1415, found 257.1420.

(3R,4R)-3-Methyl-1-(4-methoxyphenyl)-4-(4'-pentynyl)-azetidin-2-one (3R,4R)-10

β-Lactam (3*R*,4*R*)-**10** was prepared following the same procedure described above for the enantiomeric β-lactam (3*S*,4*S*)-**10**. Thus, a solution of the β-mesyl amide (2*R*,3*S*)-**9** (90 mg, 0.25 mmol) in THF (10 mL) was cooled to −15°C and treated with potassium tert-butoxide (29 mg, 0.25 mmol). After work-up and purification β-lactam (3*R*,4*R*)-**10** was obtained as a yellowish oil (62 mg, 95% yield). $[\alpha]_D$=−21.8 (c 1.7 $CHCl_3$). Spectral data are identical to those obtained for the enantiomeric β-lactam.

(3S,4S)-3-Methyl-4-(4'-pentynyl)-azetidin-2-one (3S,4S)-11

A solution of ammonium cerium (IV) nitrate (868 mg, 1.56 mmol) in water (15 mL) was added dropwise to a solution of the β-lactam (3*S*,4*S*)-**10** (135 mg, 0.52 mmol) in acetonitrile (5 mL) cooled to

−15°C. The resulting solution was stirred at −10°C for 25 minutes and then was poured into a mixture of diethyl ether–aqueous saturated $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with ether (3×20 mL) and the combined organic extracts were washed with 10% Na_2SO_3 solution, 5% $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (EtOAc–hexanes 1:2) yielding the deprotected β-lactam (3*S*,4*S*)-**11** as a yellowish oil (68 mg, 86% yield). $[\alpha]_D$=−11.5 (c 0.8 $CHCl_3$); ^{1}H-NMR: δ 1.30 (d, J=7.4 Hz, 3H, -HC-C*H*$_3$), 1.49–1.82 (m, 4H, -C*H*$_2$-C*H*$_2$), 1.97 (t, J=2.6 Hz, 1H, CC*H*), 2.22–2.27 (td, J=6.8, 2.6 Hz, 2H, -C*H*$_2$-CC), 2.79 (m, 1H, *H*C-CH$_3$), 3.24 (m, J=6.6, 2.1 Hz, 1H, N-C*H*-), 6.19 (broad s, 1H, N*H*); ^{13}C-NMR: δ 13.5 (CH_3), 18.6 (CH_2), 25.5 (CH_2), 34.2 (CH_2), 51.8 (CH), 56.8 (CH), 69.5 (CH), 83.9 (C), 171.9 (CO); IR: (cm^{-1}), 833, 1052, 1198, 1264, 1380, 1453, 1745, 2863, 2933, 3289. HRMS: calculated for $C_9H_{14}NO$ (M+1) 152.1075, found 152.1075.

*(3R,4R)-3-Methyl-4-(4′-pentynyl)-azetidin-2-one (3R,4R)-**11***

β-Lactam (3*R*,4*R*)-**11** was prepared following the same procedure described above for the enantiomeric β-lactam (3*S*,4*S*)-**11**. Thus, a solution of ammonium cerium (IV) nitrate (918 mg, 1.65 mmol) in water (15 mL) was added dropwise to a cooled (−15°C) solution of the β-lactam (3*R*,4*R*)-**10** (142 mg, 0.55 mmol) in acetonitrile (5 mL). After work-up and purification, β-lactam (3*R*,4*R*)-**11** was obtained as a yellowish oil (68 mg, 82% yield). $[\alpha]_D$=+13.1 (c 1.2 $CHCl_3$). Spectral data are identical to those obtained for the enantiomeric β-lactam.

*(2S,3S)-Methyl-3-amino-2-methyl-7-octynoate (2S,3S)-**12***

Hydrogen chloride was bubbled into a solution of the β-lactam (3*S*,4*S*)-**11** (11 mg, 0.07 mmol) in anhydrous methanol (1 mL). The resulting solution was stirred at room temperature for 30 min. The reaction was poured in 5% $NaHCO_3$ (10 mL) and the resulting mixture was extracted with EtOAc (3×20 mL). The organic phase was dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure yielding the β-amino ester (2*S*,3*S*)-**12** as an unstable yellowish oil (12 mg, 93% yield); $[\alpha]_D$=+8.3 (c 0.5 $CHCl_3$); ^{1}H-NMR: δ 1.16 (d, J=7.0 Hz, 3H, -HC-C*H*$_3$), 1.22–1.75 (m, 6H, -C*H*$_2$-C*H*$_2$-, N*H*$_2$), 1.94 (t, J=2.5 Hz, 1H, -CC*H*), 2.17–2.23 (m, 2H, -C*H*$_2$CCH), 2.44 (m, 1H, *H*C-CH$_3$), 2.87 (broad s, 1H, *H*CNH$_2$), 3.68 (s, 3H, C*H*$_3$O); ^{13}C-NMR: δ 14.6 (CH_3), 18.7 (CH_2), 25.3 (CH_2), 34.2 (CH_2), 46.5 (CH), 51.9 (CH_3), 54.0 (CH), 69.0 (CH), 84.5 (C), 176.3 (CO); IR: cm^{-1}, 804, 1093, 1178, 1189, 1368, 1457, 1597, 1726, 2135, 2855, 2937, 3285, 3365. HRMS: calculated for $C_{10}H_{17}NO_2$ 183.1259, found 183.1262.

*(2R,3R)-Methyl-3-amino-2-methyl-7-octynoate (2R,3R)-**12***

β-Amino ester (2*R*,3*R*)-**12** was prepared following the same procedure described above for enantiomeric (2*S*,3*S*)-**12**. Thus, hydrogen chloride was bubbled into a solution of the β-lactam (3*R*,4*R*)-**11** (8 mg, 0.05 mmol) in anhydrous methanol (1 mL). After work-up β-amino ester (2*R*,3*R*)-**12** was obtained as an unstable yellowish oil (9 mg, 92%); $[\alpha]_D$=−6.0 (c 0.4 $CHCl_3$). Spectral data are identical to those obtained for enantiomeric β-amino ester.

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References

1. Presented at the Eighth International Symposium on Marine Natural Products held at Santa Cruz de Tenerife, Canary Islands (Spain), September 1995.
2. For examples of natural products containing β-amino acids see: (a) Taxol: Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327. (b) Jasplakinolide: Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797–2800. Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.;

Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123–4. (c) Microginin: Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501.(d) Majusculamide C: Carter, D. C.; Moore, R. E.; Mynderse, J. S.; Niemczura, W. P.; Todd, J. S. *J. Org. Chem.* **1984**, *49*, 236. (e) Cispentacin: Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749. Iwamoto, T.; Tsujii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H. *J. Antibiot.*, **1990**, *43*, 1. (f) 57-Normajusculamide C: Mynderse, J. S.; Hunt, A. H.; Moore, R.E. *J. Nat. Prod.* **1988**, *51*, 1299.

3. Wang, W.-B.; Roskamp, E. J. *J. Am. Chem. Soc.* **1993**, *115*, 9417–9420 and references cited therein.
4. Xie, J.; Soleilhac, J.; Schimdt, C.; Peyroux, J.; Roques, B. P.; Fournie-Zaluski, M. *J. Med. Chem.* **1989**, *2*, 1497. Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.
5. For recent reviews on enantioselective synthesis of β-amino acids see:(a) Cole, D. C. *Tetrahedron*, **1994**, *50*, 9517–9582; (b) Juaristi, E.; Quintana, D.; Escalante, J.; *Aldrichimica Acta*, **1994**, *27*, 3–11. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117–128; (d) Juaristi, E. (ed*) Enantioselective Synthesis of β-Amino Acids*; VCH: New York, 1996. (e) For a review of the synthesis of the C-13 side chain of taxol see: Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemporary Organic Synthesis* **1994**, *1*, 47.
6. (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1129–1139. Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1141–1147. Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry*, **1995**, *6*, 165. Burke, A. J.; Davies, S. G.; Hedgecock, C. J. R. *Synlett*, **1996**, 621. (b) Jefford, C. W.; McNulty, J. *Helv. Chim. Acta* **1994**, *77*, 2142. Jefford, C. W.; Wang, J. B.; Lu, Z.-H. *Tetrahedron Lett.* **1993**, *34*, 7557–7560. Jefford, C. W.; Lu, Z.-H.; Wang, J. B. *Pure & Appl. Chem.* **1994**, 2075. (c) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396. Juaristi, E.; Escalante, J. *J. Org. Chem.* **1993**, *58*, 2282. (d) Koskinen, A. M. P.; Karvinen, E. K.; Siirila, J. P. *J. Chem. Soc., Chem. Commun.* **1994**, 21. (e) Falborg, L.; Jorgensen, K.A. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2823–2826. (f) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1996**, *7*, 243. (g) Warmerdam, E. G. J. C.; van Rijn, R. D.; Brussee, J.; Kruse, C. G.; van der Gen, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1723. (h) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529.
7. Rodríguez, J.; Fernández, R.; Quiñoá, E.; Riguera, R.; Debitus, C.; Bouchet, P. *Tetrahedron Lett.* **1994**, *35*, 9239–9242.
8. Fernández, R.; Rodríguez, J.; Quiñoá, E.; Riguera, R.; Muñoz, L.; Fernández-Suárez, M.; Debitus, C. *J. Am. Chem. Soc.* **1996**, *118*, 11635–11643.
9. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
10. Carballo, R.; Fernández-Suárez, M.; Muñoz, L.; Riguera, R.; Maichle-Mössmer, C. submitted to *Acta Cryst.* A list of structure factors, anisotropic displacement parameters, H-atom coordinates and the complete geometry have been deposited with the IUCr (Reference: SX1016). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
11. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
12. Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426–1430.
13. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
14. (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980. (c) Hughes, D. L. *Organic Reactions*, **1992**, *42*, 335.
15. Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1994**, *59*, 906–913. For a similar well-established methodology see Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
16. Mukaiyama, T.; Ueki, M.; Maruyama, H.; Matsueda, R. *J. Am. Chem. Soc.* **1968**, 90, 4490. Ibid, **1969**, *91*, 1554.

17. Kronenthal, D. R.; Han, C. Y.; Taylor, M. H. *J. Org. Chem.* **1982**, *47*, 2765–2768.
18. For a similar reactivity see, for instance, Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129–1135.

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