185. A Practical Synthesis of (2*S*,3*R*)-3-Amino-2-methylpentanoic Acid from L-Aspartic Acid

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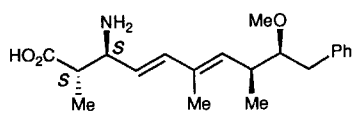
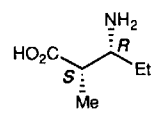
L-Aspartic acid by successive *N*-tosylation, anhydride formation, and reduction was converted into (3*S*)-3-(tosylamino)butano-4-lactone (**4**). Electrophilic methylation of **4**, subsequent iodo-esterification and nucleophilic methylation, followed by saponification and deprotection, gave (2*S*,3*R*)-3-amino-2-methylpentanoic acid (**2**) with an ee of > 99% in seven steps and in an overall yield of 34%.

Introduction. – β-Amino-α-methyl acids are the crucial components of many biologically active cyclic peptides of marine origin. Representative examples are nodularin and microcystin, notorious for their hepatotoxicity [1], majusculamide C [2], 57-normajusculamide C [3], and dolastatins 11 and 12 [4] which are appreciated for their antifungal and antineoplastic activity. The first two compounds incorporate (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (**1**) into their structures, while the last four all contain (2*S*,3*R*)-3-amino-2-methylpentanoic acid (**2**) [5]. Despite their apparent structural simplicity, the synthesis of such α-substituted β-amino acids in an enantiomerically pure state constitutes a challenge and has stimulated different approaches [6] including the α-alkylation of β-amino esters and their equivalents [7]. Two recent methods used for synthesizing **1** and **2** illustrate different solutions to the common problem of assembling the diastereoisomeric C(2),C(3) element. The innate chirality of 3-[(benzyloxycarbonyl)amino]butano-4-lactone was carried through to **1** by α-methylation, equilibration, hydrolysis, and chain extension [8]. On the other hand, the external chirality of a lithium amide was transferred by conjugate addition to (*E*)-2-methylpent-2-enoate, thereby yielding **2** after deprotection was effected [9].



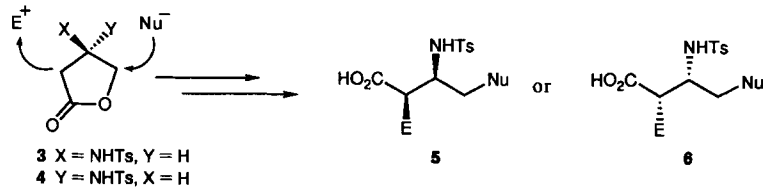
1



2

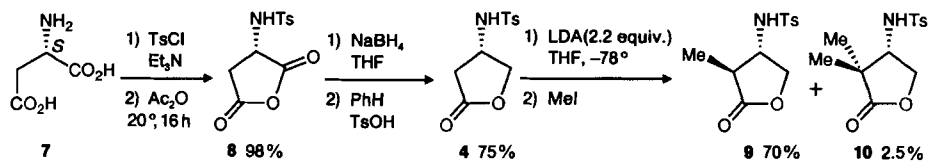
We now describe a concise and practical means of synthesizing **2** which exploits 3-(tosylamino)butano-4-lactone (**3** or **4**) as a versatile building block for constructing 2,4-disubstituted 3-amino acids (*Scheme 1*). We have already shown that an electrophile (E^+), as exemplified by hydroxylation, can be introduced at the α-position in **3** or **4** with *trans*-orientation so that the products, obtained after ring opening and attachment of a nucleophile (Nu^-) at the γ-position, are the *'syn'* derivatives **5** or **6**, respectively [10–12]. In an analogous fashion, sequential double methylation of **4** is expected to produce **2**.

Scheme 1



Results and Discussion. – For the present purposes, the required chirality was provided by L-aspartic acid (**7**; *Scheme 2*). Protection of **7** as the *N*-tosyl derivative and submission to excess Ac_2O for 16 h at 20° gave optically pure *N*-tosylaspartic anhydride **8** in 98% yield. If heating was used to accelerate closure, racemization occurred [13]. Selective reduction of **8** with $NaBH_4$ in THF for 2 h at 20°, followed by solution in benzene containing a drop of toluene-4-sulfonic acid (TsOH), furnished (3*S*)-3-(tosylamino)butano-4-lactone (**4**) in 75% yield. Similar regioselective reduction was previously observed with 2-substituted derivatives of succinic anhydride [14] [15b].

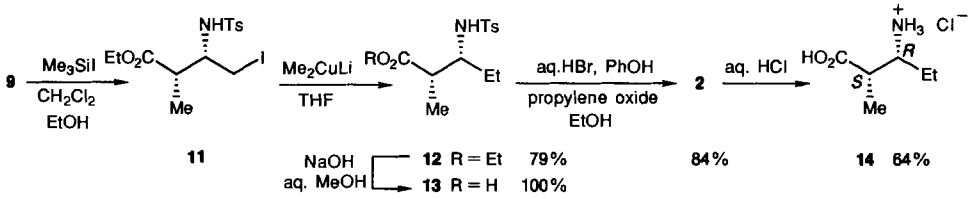
Scheme 2



Next, **4** was successively treated with lithium diisopropylamide (LDA) and MeI at −78° with subsequent warming to −60°. The (2*S*,3*S*)-2-methyl-3-(tosylamino)butano-4-lactone (**9**) was obtained in 70% yield. Monomethylation was highly diastereoselective and evidently entirely controlled by the bulk of the amino substituent, as no trace of the corresponding monomethylated *cis*-isomer was detected. Nonetheless, the dimethyl derivative **10** was also formed, but in negligible amounts, even though the reaction of **4** was incomplete. It is worth noting here that our choice of the tosyl group for protection was originally dictated by its ability to survive the subsequent step of iodo-esterification (*vide infra*). However, a further advantage, as attested by the present result, is its unequivocal diastereocontrol on the course of electrophilic reactions. In contrast, the previously reported monomethylation of the corresponding 3-[(benzyloxycarbonyl)-amino]butano-4-lactone displayed diminished diastereoselectivity by giving a 4:1 ratio of the *trans*- and *cis*-isomers [8] [15]. The *cis*-isomer may have arisen by the competing operation of a complex-induced proximity effect which is characteristic of the carbamate group [16].

The lactones **9** and **10** were easily separated from **4** by chromatography. Opening of **9** was accomplished by reaction with Me_3SiI in CH_2Cl_2 and a little EtOH at 0° under N_2 (*Scheme 3*). Under these conditions, the silyl ester was formed first and immediately underwent ethanolysis *in situ*, leaving the *N*-tosyl group intact [17]. The resulting iodo ethyl ester **11** was directly submitted to the next step without purification. Nucleophilic substitution in **11** with lithium dimethylcuprate in THF at −20° proceeded smoothly to give ethyl (2*S*,3*R*)-2-methyl-3-(tosylamino)pentanoate (**12**) in 79% yield for the two

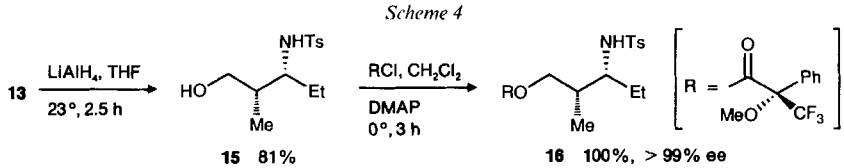
Scheme 3



steps. Saponification with NaOH in $MeOH/H_2O$ afforded the tosylamino acid **13**, which by reductive deprotection with aqueous HBr solution and phenol followed by the addition of propylene oxide (methyloxirane) delivered the free β-amino acid **2** in 84% yield.

Finally, **2** was dissolved in conc. aqueous HCl solution and evaporated, whereupon the hydrochloride **14** was obtained as a colorless solid, spectroscopically identical in every respect with the natural and previously synthesized materials [2] [5]. However, as a more rigorous check, the optical integrity of **13** was verified by its reduction with $LiAlH_4$ in THF to the primary alcohol **15** in 81% yield (*Scheme 4*). Conversion to *Mosher*'s ester **16** with (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 was effected in quantitative yield. Inspection of the ^{1}H-NMR spectrum at 400 MHz revealed the presence of a single diastereoisomer, consonant with an ee of > 99%.

Scheme 4



Conclusion. – Although two chromatographic separations are necessary, the present procedure is straightforward and provides enantiomerically pure product **2** in seven operationally simple steps from L-aspartic acid (**7**) in a yield of 34%. Consequently, it should find general application for the preparation of other '*syn*'-α-alkylated β-amino acids and *cis*-3,4-disubstituted β-lactams [18].

Experimental Part

General. Flash chromatography (FC): *SDS* 230–400 mesh silica gel. Thin-layer chromatography (TLC): *Merck* silica gel $60F_{254}$ plastic sheets, layer thickness 0.2 mm, visualization by UV or anisaldehyde. M.p.: *Büchi-SMP-20* melting-point apparatus; uncorrected. Optical rotation: *Perkin-Elmer-241* polarimeter. IR: *Perkin-Elmer 1600* series FTIR; absorptions in cm^{-1}. NMR: *Bruker AMX-400*; in $CDCl_3$; chemical shifts δ in ppm downfield from $SiMe_4$, coupling constants J in Hz; $SiMe_4$ (^{1}H; δ 0) or $CDCl_3$ (^{13}C; δ 77.09) as internal reference. MS: intensities in % rel. to base peak; *Finnigan GC/MS-4023*; electron impact, 70 eV. Elemental analyses were performed by Dr. *H.J. Eder*, Microanalytical Service, Department of Pharmaceutical Chemistry, University of Geneva.

(S)-N-Tosylaspartic Anhydride (**8**). A soln. of (*S*)-*N*-tosylaspartic acid (8.26 g, 28.8 mmol) was stirred in Ac_2O (21 ml) for 16 h. After removal of the solvent under high vacuum without heating, **8** was obtained as a crystalline mass (7.58 g, 98%). Alternatively, the concentrated product was triturated with Et_2O (40 ml) and the resultant crystalline suspension chilled, filtered by suction, washed with Et_2O, and dried to give **8** (6.22 g, 80%) as white crystals. M.p. 137–138°. $[\alpha]_D^{20} = +7.20$ (c = 1.0, $CHCl_3$). NMR: in accord with the literature values [19].

(3S)-3-(Tosylamino)butano-4-lactone (= *(S)-4,5-Dihydro-4-(tosylamino)furan-2(3H)-one*; **4**). A soln. of **8** (5.36 g, 19.9 mmol) was added dropwise to a suspension of $NaBH_4$ (0.79 g) in THF (32.5 ml) at 0° under N_2. After leaving for 2 h at 0° and 1 h at r.t., 1.0M aq. HCl (5 ml) was carefully added and the pH adjusted to 1.0. The THF was then removed under reduced pressure and the residue thoroughly extracted with AcOEt. Evaporation of the dried AcOEt extracts gave an oil (5.35 g). The oil was dissolved in benzene (50 ml) containing TsOH (20.5 mg) and the soln. heated under reflux in a *Dean-Stark* H_2O separator for 6 h. The crude material was filtered through a short plug of silica gel, the filtrate evaporated and the residue recrystallized from CH_2Cl_2/hexane: **4**, white crystals (3.83 g, 75%) in two crops. M.p. 112–113°, $[\alpha]_D^{20} = -15.7$ ($c = 1.0$, EtOH). NMR: in accord with the literature values [18].

(2S,3S)-2-Methyl-3-(tosylamino)butano-4-lactone (= *(3S,4S)-4,5-Dihydro-3-methyl-4-(tosylamino)furan-2(3H)-one*; **9**). To a soln. of $(i\text{-}Pr)_2NH$ (0.64 ml) in dry THF (10 ml) at 0° under N_2 was added 1.5M MeLi in Et_2O (3 ml). After stirring for 10 min, the soln. was cooled to −78°, and a soln. of **4** (0.511 g, 2 mmol) in dry THF (3 ml) was added over 1 min. The resulting yellow soln. was stirred for 60 min and then MeI (0.5 ml) added. The soln. was gradually warmed from −78 to −60° over 60 min and quenched by adding sat. aq. NH_4Cl soln. (2 ml). After warming to r.t., the mixture was partitioned between 1.0M aq. HCl (20 ml) and CH_2Cl_2 (3 × 20 ml); the combined org. phases were washed with 5% $Na_2S_2O_3$ soln., dried (Na_2SO_4), and evaporated. The resulting crystalline mass (0.590 g) was subjected to FC (40 × 2 cm, hexane/AcOEt 6:4): **10** (13.7 mg, 2.5%), then **9** (0.37 g, 70%), and finally **4** (61 mg, 12%).

9: Colorlesss crystals. M.p. 103–105°. $[\alpha]_D^{20} = -18.8$ ($c = 0.865$, $CHCl_3$). IR: 1786 (C=O). ^{1}H-NMR: 7.77 (*d*, $J = 8.4$, 2 H); 7.35 (*d*, $J = 8.4$, 2 H); 5.42 (*d*, $J = 7.7$, 1 H); 4.33 (*dd*, $J = 9.6$, 7.4, 1 H); 3.87 (*dd*, $J = 9.6$, 8.1, 1 H); 3.68 (*m*, 1 H); 2.46 (*s*, 3 H); 2.41 (*m*, 1 H); 1.12 (*d*, $J = 7.4$, 3 H). ^{13}C-NMR: 176.1, 144.5, 136.8, 129.8, 127.0, 70.4, 56.4, 40.4, 21.6, 12.7. MS: 269 (12, M^+), 213 (34), 155 (30), 147 (10), 139 (11), 120 (15), 91 (100). HR-MS: 269.0739 ($C_{12}H_{15}NSO_4^+$, calc. 269.0722).

10: Colorless crystals. M.p. 102–104°. ^{1}H-NMR: 7.77 (*d*, $J = 8.1$, 2 H); 7.34 (*d*, $J = 8.1$, 2 H); 5.40 (*d*, $J = 8.4$, 1 H); 4.21 (*m*, 1 H); 3.79 (*m*, 2 H); 2.46 (*s*, 3 H); 1.11 (*s*, 6 H). ^{13}C-NMR: 179.2, 144.4, 137.1, 129.9, 127.1, 68.6, 58.3, 41.3, 22.7, 21.6, 18.1.

(2S,3S)-Ethyl 4-Iodo-2-methyl-3-(tosylamino)butanoate (**11**). To a soln. of **9** (0.733 g, 2.72 mmol) in dry CH_2Cl_2 (10 ml) at 0° under N_2 was sequentially added Me_3SiI (1.1 ml) and abs. EtOH (0.8 ml). The mixture was stirred at r.t. for 6 h when further aliquots of abs. EtOH (0.8 ml) and Me_3SiI (1.1 ml) were added. After stirring at r.t. for a further 12 h, EtOH (3 ml) was added; 30 min later, the mixture was partitioned between H_2O and CH_2Cl_2 (4 × 20 ml), the combined org. phases were washed with 5% aq. $Na_2S_2O_3$ soln., dried (Na_2SO_4), and evaporated; white solid (1.082 g, 94%). An anal. sample of **11** was obtained by FC (23 × 2 cm, hexane/AcOEt 6:4): colorless crystals. M.p. 124–125°. $[\alpha]_D^{20} = +16.8$ ($c = 0.525$, EtOH). IR: 1707 (C=O). ^{1}H-NMR: 7.77 (*d*, $J = 8.4$, 2 H); 7.32 (*d*, $J = 8.4$, 2 H); 4.90 (*d*, $J = 9.2$, 1 H); 4.07 (*dq*, $J = 7.4$, 3.7, 1 H); 4.02 (*dq*, $J = 7.4$, 3.7, 1 H); 3.34–3.28 (*m*, 2 H); 3.05 (*dd*, $J = 10.3$, 4.4, 1 H); 2.75 (*quint.*, $J = 7.4$, 1 H); 2.43 (*s*, 3 H); 1.21 (*t*, $J = 7.2$, 3 H); 1.15 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR: 173.6, 143.8, 137.5, 129.7, 127.2, 61.0, 54.9, 43.9, 21.5, 14.0, 13.5, 10.7. MS: 426 (4), 408 (1), 380 (1), 324 (27), 298 (14), 284 (10), 155 (61), 91 (100). Anal. calc. for $C_{14}H_{20}INO_4S$: C 39.54, H 4.74, N 3.29; found: C 39.66, H 4.74, N 3.31.

(2S,3R)-Ethyl 2-Methyl-3-(tosylamino)pentanoate (**12**). To a suspension of CuI (2.33 g, 12.2. mmol) in dry THF (25 ml), stirred at −78° under N_2, was added 1.5M MeLi in Et_2O (15.27 ml, 22.9 mmol). The resulting suspension was briefly warmed to 0° to dissolve solids and then recooled to −78°. Next, the flask was immersed in an EtOH bath at −30°, and a soln. of crude **11** (1.074 g, 2.53 mmol) in dry THF (25 ml) was added to the clear brown soln. The soln. was stirred at −20° for 5 h at which time sat. aq. NH_4Cl soln. was added cautiously. After warming to r.t., H_2O (40 ml) was added, the mixture acidified, then neutralized with aq. $NaHCO_3$ soln., filtered by suction, and extracted with AcOEt (4 × 15 ml). The combined org. phase was dried (Na_2SO_4) and evaporated and the crude oil (0.917 g) purified by FC (31 × 2 cm, hexane/AcOEt 1:1): **12** (0.67 g, 84%). Colorless crystals. M.p. 48–50°. $[\alpha]_D^{20} = +29.5$ ($c = 1.32$, EtOH). IR: 1731 (C=O). ^{1}H-NMR: 7.76 (*d*, $J = 8.4$, 2 H); 7.29 (*d*, $J = 8.4$, 2 H); 5.05 (*d*, $J = 9.9$, 1 H); 4.05 (*m*, 2 H); 3.31 (*sept.*, $J = 4.4$, 1 H); 2.48 (*ddd*, $J = 14.5$, 7.1, 4.6, 1 H); 2.42 (*s*, 3 H); 1.49 (*m*, 1 H); 1.31 (*m*, 1 H); 1.23 (*t*, $J = 7.2$, 3 H); 1.05 (*d*, $J = 7.4$, 3 H); 0.79 (*t*, $J = 7.3$, 3 H). ^{13}C-NMR: 173.9, 143.2, 138.4, 129.5, 126.9, 60.7, 57.7, 43.1, 24.5, 21.5, 14.1, 13.3, 10.4. MS: 313 (2), 284 (24), 238 (12), 212 (89), 155 (76), 91 (100), 65 (20). HR-MS: 313.1329 ($C_{15}H_{23}NSO_4^+$, 313.1347).

(2S,3R)-3-Amino-2-methylpentanoic Acid Hydrochloride (**14**). To a soln. of **12** (0.23 g, 0.74 mmol) in MeOH (3.70 ml) at r.t. was added 1.5M aq. NaOH (4 ml). The stirred soln. was immersed in a H_2O bath at 60° until TLC analysis indicated complete hydrolysis (30 min). The soln. was acidified with conc. aq. HCl soln. and partitioned between sat. aq. NaCl soln. and Et_2O (4 × 15 ml). The combined Et_2O extracts were dried (Na_2SO_4) and evaporated: **13** (0.21 g). Phenol (26 mg) and HBr (2 ml, 48% aq.) were added to **13** (23.8 mg), and the soln. was

heated under reflux for 1.5 h under N_2. After cooling to r.t., the resulting soln. was partitioned between H_2O (5 ml) and AcOEt (2 × 5 ml) and the aq. phase evaporated to give an orange semi-solid (13 mg). This solid was dissolved in methyloxirane (1 ml) and EtOH (5 ml) and the resulting soln. heated under reflux for 60 min. Evaporation gave the free amino acid **2** as a white solid (8.4 mg, 84%). The solid was dissolved in conc. aq. HCl soln. (2 ml) and extracted with AcOEt (2 ml). Concentration of the aq. phase yielded **14** (8.2 mg, 64%) as a solid film, the spectroscopic properties of which were identical to those reported for the natural [2] and previously synthesized [5] material.

(2S,3R)-2-Methyl-3-(tosylamino)pentanol (**15**). To a suspension of $LiAlH_4$ (50 mg) in THF (1 ml) at r.t. was added a soln. of **13** (56.6 mg, 0.198 mmol) in THF (2.5 ml). After 2.5 h, H_2O (6 drops) was carefully added and the suspension stirred until it turned white; next, the latter was diluted with CH_2Cl_2 (20 ml) and filtered. The concentrated filtrate was subjected to FC (AcOEt/hexane 6:4): **15** (43.5 mg, 81%). Colorless film. ^{1}H-NMR: 7.76 (*d*, *J* = 8.4, 2 H); 7.31 (*d*, *J* = 8.4, 2 H); 4.71 (*d*, *J* = 9.5, 1 H); 3.62 (*dd*, *J* = 11.6, 10.3, 1 H); 3.46 (*dd*, *J* = 11.6, 4.8, 1 H); 3.39 (*m*, 1 H); 2.43 (*s*, 3 H); 1.85 (*m*, 1 H); 1.4–1.3 (*m*, 1 H); 1.25–1.15 (*m*, 1 H); 0.70 (*d*, *J* = 7.0, 3 H); 0.60 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR: 143.4, 138.1, 129.6, 127.0, 64.4, 55.5, 37.8, 25.6, 21.5, 10.7, 9.8.

Mosher's *Ester* **16**. To a soln. of **15** (17 mg) in dry CH_2Cl_2 (1 ml) at 0° under N_2 was added (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (35 µl) and DMAP (23 mg). The mixture was stirred for 3 h at 0° and evaporated, the residue partitioned between 2M HCl (20 ml) and AcOEt (20 ml), and the AcOEt phase washed successively with aq. $NaHCO_3$ soln. (20 ml) and H_2O (20 ml), dried (Na_2SO_4), and evaporated: **16** (31 mg). Colorless film. ^{1}H-NMR: 7.61 (*d*, *J* = 8.4, 2 H); 7.45 (*m*, 2 H); 7.35 (*m*, 3 H); 7.18 (*d*, *J* = 8.4, 2 H); 4.28 (*d*, *J* = 8.8, 1 H); 4.11 (*dd*, *J* = 11.1, 8.3, 1 H); 4.05 (*dd*, *J* = 11.1, 5.7, 1 H); 3.49 (*s*, 3 H); 3.12 (*m*, 1 H); 2.34 (*s*, 3 H); 1.92 (*m*, 1 H); 1.28 (*m*, 1 H); 1.00 (*m*, 1 H); 0.74 (*d*, *J* = 7.4, 3 H); 0.55 (*t*, *J* = 7.4, 3 H).

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