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PRACTICAL SYNTHESIS OF (+)-ALLOISOLEUCINE

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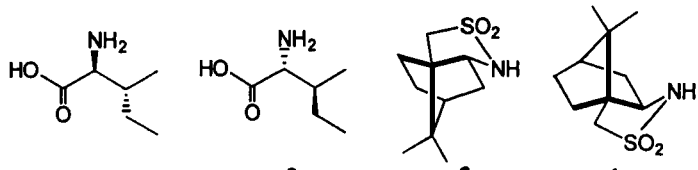
Abstract: Subsequent treatment of *N*-crotoyl-(1S,2R)-bornane-10,2-sultam with EtMgCl, recrystallization of the product and saponification, afforded R-(-)-3-methylpenthanoic acid which was used for acylation of (1R,2S)-bornane-10,2-sultam. The product was converted into *N*-[(2S,3R)-2-amino-3-methylpentanoyl]-(1R,2S)-bornane-10,2-sultam by hydroxyamination with 1-chloro-1-nitrosocyclohexane, followed by reduction of the hydroxylamine grouping. Saponification of the sultam imide provided (+)-alloisoleucine.

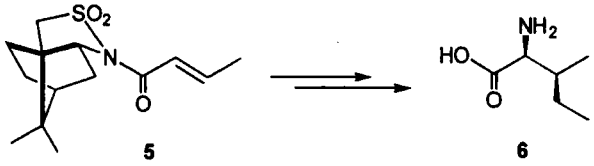
(+)-Alloisoleucine (**1**) is one of the diastereomers of natural isoleucine with reversed configuration at the β-carbon atom. Due to this feature, it is often used by the peptide chemists in SAR studies; incorporation of the amino acid **1** into a peptide chain may induce conformational changes which have been studied.[1] Amino acid **1** occurs as a component of some peptide antibiotics.[2] For the first time, both optically pure (+)- and (-)-alloisoleucines (**1**) and (**2**) have been obtained by resolution of racemates.[3,4] The stereocontrolled synthesis of **1** has

been accomplished by Oppolzer *et al.*[5] The synthesis employed a camphorosulfonic acid derivative as chiral auxiliary and consisted in conjugate addition of ethyl cuprate to the crotonyl fragment followed by bromination and nucleophilic substitution of the bromine atom by the azide anion. Subsequent papers from the same research group have reported syntheses of several α-amino acids including those having two stereogenic centers.[6-8] As chiral auxiliary (1S, 2R)- and (1R,2S)-bornane-10,2-sultams (**3**) and (**4**)[9,10] have been used.



1 **2** **3** **4**

The practical usefullness of bornane-10,2-sultams as chiral auxiliaries have been demonstrated in a variety of reactions.[10-12] The Oppolzer's[6] synthesis of (2S,3S)-isoleucine (**6**) consisted of conjugate addition of ethyl magnesium chloride to *N*-crotoyl-sultam (**5**) followed by hydroxyamination of the resulting salt of *N*-acylsultam with 1-chloro-1-nitroso-cyclohexane (**7**)[9] and reduction of the hydroxyamino grouping (Scheme 1).

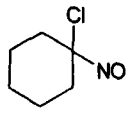


5 **6**

Scheme 1

Very recently a synthesis of **2** from (S)-2-methyl-1- butanol has been reported.[13] Oppolzer's[6] synthesis of **6** prompted us to adopt his methodology for the preparation of (2S,3R)-(+)-alloisoleucine (**1**). We therefore employed compound

8, derived from sultam **3**, and (E)-2-pentenoic acid assuming that conjugate addition of methylmagnesium chloride in the first step should produce the (3R) configuration whereas subsequent amination should produce the desired amino acid **1**.



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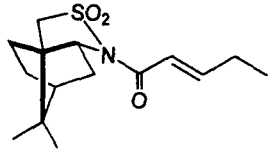
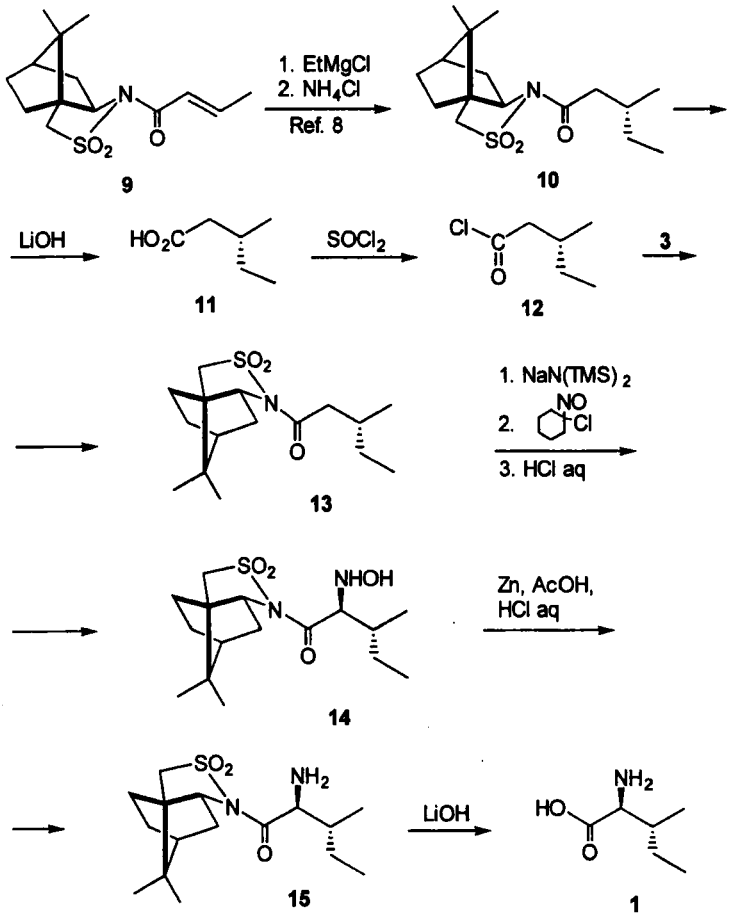


8

Unfortunately, methylmagnesium chloride, a harder nucleophile than the ethyl homolog, prefers 1,2-addition over the 1,4-one[8]; consequently the addition led to liberation of the sultam **3**. We decided therefore to prepare **1** in a two-step synthesis. At first, crotonosultam **9** was treated with ethylmagnesium chloride according to the Oppolzer's[8] procedure to afford compound **10** which was purified by recrystallization and subsequently it was saponified yielding (3R)-3-methyl-pentanoic acid (**11**). The acid **11** has been synthesized in the past several times;[14] **11** was converted into acid chloride **12** which was used to prepare acylsultam **13**. Amination of **13** with **7**[7,9] gave hydroxylamine **14** which after reduction afforded **15**. Recrystallization of **15** yielded the optically pure (2S,3R) diastereomer **16**. Saponification of **16** led to the formation of (2S,3R)-(+)-alloisoleucine **1**. The overall yield of **1** was about 9.0%. The failure of the 1,4-addition of methylmagnesium chloride to the acylsultam **9** made the synthesis more laborious. It should be noted, however, that crotoylsultam **9** used as the starting material of the synthesis is significantly less expensive than sultam **8**.



Scheme 2

EXPERIMENTAL

Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were obtained with a FT-1600 Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recordeed using a Bruker AM 500 spectrometer at 500 MHz. Mass spectra were obtained with an AMD 604 spectrometer. Column chromatography was performed on E. Merck Kieselgel (230 - 400 mesh).

N-[3(R)-Methylpentanoyl]-(1S,2R)-bornane-2,10-sultam (10).[8]

Ethylmagnesium chloride [2N in THF; 62.5 ml (125 mmol)] was added at - 78°C dropwise to a stirred solution of compound **9** (14.0 g, 50 mmol) in anhydrous THF (600 ml). Stirring was continued for 3 h while the temperature was maintained. Subsequently the temperature was allowed to rise to -60° and saturated aqueous NH_4Cl (60 ml) was slowly added. The mixture was filtered and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, filtered, evaporated, and purified by chromatography using AcOEt : Hexane 1 : 4 as en eluent. Crystallization from hexane afforded **10** (11.4 g, 73%), mp 72-73°C; $[\alpha]_D$ -84.9 (CH_2Cl_2, c = 1). IR ($CHCl_3$): ν = 1694 cm^{-1}. ^1H NMR ($CDCl_3$), selected signals: δ = 0.89 (t, 1H, J = 6.7 Hz, CH_3), 0.94 (d, 1H, J = 6.7 Hz, CH_3), 0.97, 1.15 (2s, 6H, $2CH_3$), 2.43 (dd, 1H, J_1 = 7.6, J_2 = 15.8 Hz, CH_AH_B), 2.76 (dd, 1H, J_1 = 6.1, J_2 = 15.8 Hz, CH_AH_B), 3.42, 3.50 (2d, 2H, J = 13.7 Hz, CH_2), 3.88 (t, 1H, CHN). Anal. Calcd for $C_{16}H_{27}NO_3S$ (313.5): C, 61.30; H, 8.68; N, 4.46. Found: 61.1; H, 8.8; N, 4.3.

(R)-(-)-3-Methylpentanoic acid (11). Saponification of **10** was performed using LiOH under standard conditions, 73%, $[\alpha]_D$ -8.4 (c 1, CH_2Cl_2); Ref. 14a, $[\alpha]_D$ -6.42 ($CHCl_3$, c = 4.03). ^1H NMR ($CDCl_3$): δ = 0.91 (t, 3H, J = 7.3 Hz, CH_3), 0.97 d, 3H, J = 6.7 Hz, CH_3), 1.10-1.52 (m, 2H, CH_2), 1.90 (m, 1H, CH), 2.15 (dd, 1H, J_1 = 8.0, J_2 = 14.0 Hz, CH_AH_B) 2.36 (dd, 1H, J_1 = 6.1, J_2 = 14.0 Hz, CH_AH_B).

(R)-(-)-3-Methylpentanoic acid chloride (12) was obtained under standard conditions using $SOCl_2$. The Product was purified by distillation, 83%, bp 137-141°C.

N-[(3R)-3-Methylpentanoyl]-(1R,2S)-bornane-2,10-sultam (13). Acylation of sultam (1R,2S)-bornane-2,10-sultam (**3**) was performed in the presence of NaH to afford **13** in 82% yield; mp. 76-78°; $[\alpha]_D^{20}$ +71.8 (CH_2Cl_2, c = 1). IR ($CHCl_3$): ν = 1694 cm^{-1}. ^1H NMR ($CDCl_3$) selected signals: δ = 0.89 (t, 3H, J = 7.4 Hz, CH_3). 0.93 (d, 3H, J = 6.7 Hz, CH_3), 0.91, 1.16 (2s, 6H, $2CH_3$), 2.60 (d, 2H, CH_2), 3.42, 3.51 (2d, 2H, J = 13.9 Hz, CH_2), 3.88 (t, 1H, CHN). Anal. Calcd for $C_{16}H_{27}NO_3S$ (313.5): C, 61.30; H, 8.68; N, 4.46. Found: C, 61.1; H, 8.8; N, 4.3.

N-[(2S,3R)-2-(N-hydroxyamino)-3-methylpentanoyl]-(1R,2S)-bornane-2,10-sultam (14). 1M Solution of $NaN(TMS)_2$ (44 ml, 44 mmol) was added to a stirred solution of **13** (12.5 g, 40 mmol) in dry THF (500 ml) at -78 °C. Stirring and temperature were maintained for 1 h. Subsequently, 1N solution of freshly distilled 1-chloro-1-nitrosocyclohexane (44 ml, 44 mmol) in THF was added dropwise and the stirring was continued for 1 h at -78 °C. Subsequently, 1N HCl aq. (140 ml) was added dropwise and the temperature was allowed to rise to room temperature. Solvents were evaporated under vacuo and the residue was partitioned between 1N HCl aq. and hexane. The aqueous layer was alkalized with solid sodium hydrogen carbonate and extracted with CH_2Cl_2. The extract was dried, evaporated and purified by chromatography to afford **14** (11.0 g, 80%), mp 144-145°C; $[\alpha]_D$ +88.0° (CH_2Cl_2, c = 1). IR ($CHCl_3$): ν = 3584, 3287, 1687 cm^{-1}. ^1H NMR ($CDCl_3$), selected signals: δ = 0.92 (t, 3H, J = 7.4 Hz, CH_3), 0.95 (d, 3H, J = 7.0 Hz, CH_3), 0.97, 1.19 (2s, 6H, $2CH_3$), 3.43, 3.53 (2d, 2H, J = 13.5 Hz, CH_2), 3.94 (dd, 1H, J_1 = 5.1, J_2 = 7.7 Hz, CHN), 4.06 (d, 1H, J = 6.5 Hz, CH).

Anal. Calcd for $C_{18}H_{28}N_2O_4S$ (368.5): C, 55.78; H, 8.19; N, 8.13. Found: C, 55.5; H, 8.2; N, 8.2.

N-[(2S,3R)-2-amino-3-methylpentanoyl]-(1R,2S)-bornane-2,10-sultam (15). A mixture of **14** (6.9 g, 20 mmol) and zinc powder (52 g) in 1N HCl aq. (120 ml) and acetic acid (60 ml) was stirred for 2 days at 0°C. Subsequntly the mixture was filtered, evaporated, and treated with saturated aqueous sodium hydrogen carbonate and CH_2Cl_2. The organic layer was dried, evaporated, and purified by chromatography to give **15** (5.0 g, 77%), mp 141-142°C $[\alpha]_D$ +127.1 (CH_2Cl_2, c = 1). IR ($CHCl_3$): ν = 3564, 3384, 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$), selected signals: δ = 0.91 (t, 3H, J = 7.3 Hz, CH_3), 0.99 (d, 3H, J = 6.5 Hz, CH_3), 0.97, 1.17 (2s, 6H, $2CH_3$), 3.44, 3.52 (2d, 2H, J = 13.8 Hz, CH_2), 3.71 (d, 1H, J = 6.9 Hz, CH), 3.90 (dd, 1H, J_1 = 5.2, J_2 = 7.6 Hz, CHN). Anal. Calcd for $C_{16}H_{28}N_2O_3S$ (352.5): C, 58.50; H, 8.59; N, 8.52. Found: C, 57.9; H, 8.7; N, 8.5.

(2S,3R)-(+)-Alloisoleucine (1). Saponification of **15** was performed using LiOH under standard conditions[6], 92%; $[\alpha]_D$ +16.3 (H_2O, c = 1) lit. Ref.3, $[\alpha]_D$ +14.0 (H_2O, c = 2); Ref.4, $[\alpha]_D$ +15.7 (H_2O, c = 1).

REFERENCES

(1) Di Blasio, B.; Saviano, M.; Del Duca, V.; De Simone, G.; Rossi, F.; Pedone, C.; Benedetti, E. and Lorenzi, G.P. *Biopolymers* **1995**, *36*, 401.

(2) Gurusiddaiah, S. and Graham, S.O. *Antimicrob. Agents Chemother.* **1980**, *17*, 980.

(3) Abderhalden, E. and Zeisset, W. *Z. Physiol. Chem.* **1931**, *195*, 121.

(4) Huffman, W.A.H. and Ingersold, A.W. *J. Am. Chem. Soc.* **1951**, *73*, 3369.

(5) Oppolzer, W.; Pedrosa, R. and Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831.

(6) Oppolzer, W. and Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991.

(7) Oppolzer, W.; Tamura, O. and Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965.

(8) Oppolzer, W.; Poli, G.; Kingma, A.J.; Starkemann, Ch. and Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201.

(9) Müller, E.; Metzger, H. and Fries, D. *Chem. Ber.* **1954**, *87*, 1449.

(10) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

(11) Kim, B.H. and Curran, D.P. *Tetrahedron* **1993**, *49*, 293.

(12) Chapuis, Ch.; Saint Laumer, J.-Y. and Marty, M. *Helv. Chim. Acta* **1997**, *80*, 146; Raczko, J.; Achmatowicz, M.; Jeżewski, A.; Chapuis, Ch.; Urbańczyk-Lipkowska, Z. and Jurczak, J. *Helv. Chim. Acta* **1998**, *81*, 1264; Kiegiel, J., Chapuis, Ch.; Urbańczyk-Lipkowska, Z. and Jurczak, J. *Helv. Chim. Acta* **1998**, *81*, 1672; Achmatowicz, M.; Chapuis, Ch.; Rzepecki, P. and Jurczak, J. *Helv. Chim. Acta* **1999**, *82*, 182.

(13) Portonovo, P.; Liang, B. and Joullie, M.M. *Tetrahedron: Asymmetry* **1999**, *10*, 1451.

(14) a) Mori, K.; Kuwahara, S. and Ueda, H. *Tetrahedron* **1983**, *39*, 2439; b) Helmchen, G. and Wenger, G. *Tetrahedron Lett.* **1985**, *26*, 6051; c) Oppolzer, W.; Mills, R.J. and Reglier, M. *Tetrahedron Lett.* **1986**, *27*, 183.

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