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On the Synthesis of (*S*)-α-Methylaspartic Acid by Diastereoselective Alkylation of a Chiral 2-Cyanopropanoate.

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Abstract: A novel and efficient procedure for the synthesis of optically pure α-methylaspartic acid, based on the diastereoselective alkylation of (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanopropanoate with α-halocarbonyl compounds, is described. © 1997 Elsevier Science Ltd.

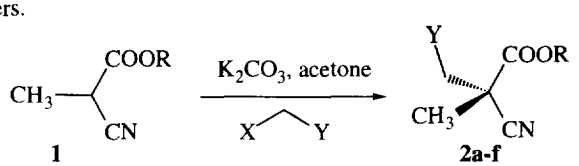
Conformationally constrained amino acid surrogates can be used to reduce the conformational space available to peptidomimetics.[1] The modified peptide may provide useful information on its bioactive conformation, and incorporation of the constrained amino acid residue may result in beneficial physiological effects such as optimisation of peptide-receptor binding and resistance to peptidases.[2] In the study of conformationally constrained amino acids, α-methyl derivatives have received special attention[3] due to their considerable scientific and medicinal significance. In particular, α-methylaspartic acid is of great interest owing to its ability to competitively inhibit aspartate amino transferase.[4]

L-Aspartic acid is widely used in medicines, as a chiral intermediate in drug synthesis and as a food additive. Recently, aspartame, a dipeptide comprising of L-aspartic acid and L-phenylalanine methyl ester, was commercialised as a low calorie synthetic sweetener. Moreover, aspartate is known[5] to be an excitatory amino acid (EAA) and α-methylaspartic acid may be an effective EAA antagonist. On the other hand, both L- and D-aspartic acid are important intermediates for the synthesis of many useful drugs.[6]

(*R*)- or (*S*)-2-methylaspartic acids have been prepared by asymmetric alkylation methods using suitable chiral precursors such as imidazolidinones,[7] oxazolidinones[8] or hexahydropyrroloindoles.[9] More recently, Obrecht *et al.*[10] have applied their resolution procedure to obtain (*R*)- or (*S*)-2-methylaspartic acids in enantiomerically pure form.

As a part of an ongoing program, our research group has developed a stereoselective route to α-alkyl amino acids from easily accessible (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanoesters. The underlying principle of our methodology is the highly diastereoselective alkylation of these chiral 2-cyanoesters by neutralisation of the enolate with a reactive electrophile.[11] We have recently observed that the alkylation reaction can be conveniently performed using potassium carbonate as a base and with only 2 equivalents of the electrophile to obtain amino acid precursors.[12] We report here the extension of this methodology to the stereoselective synthesis of α-methylaspartic acid using α-halocarbonyl compounds as reactive electrophiles.

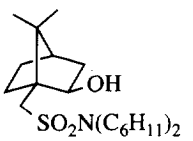
Scheme 1 shows our general strategy for the synthesis of α-methylaspartic acid. The starting material is (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanopropanoate, which is easily obtained by esterification of 2-cyanopropanoic acid with (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isoborneol according to a previously described procedure.[13] Firstly we attempted to alkylate **1** with α-haloesters. In these cases the reactions, performed with potassium carbonate as base and methyl, *tert*-butyl and benzyl bromoacetate as electrophiles, proceeded in nearly quantitative yields and with quite good stereoselectivities. In each case the C_2S diastereoisomer was the major compound.[14] Alkylation of methyl 2-cyanopropanoate with a chiral 2-bromoacetate as the electrophile afforded the corresponding alkylation product **2d** as an almost equimolecular mixture of diastereoisomers.



2a R = R*, Y = $COOCH_3$, **2b** R = R*, Y = $COOC(CH_3)_3$

2c R = R*, Y = $COOCH_2C_6H_5$, **2d** R = CH_3, Y = COOR*

2e R = R*, Y = CN, **2f** R = R*, Y = CO-N

R*OH = 

Scheme 1

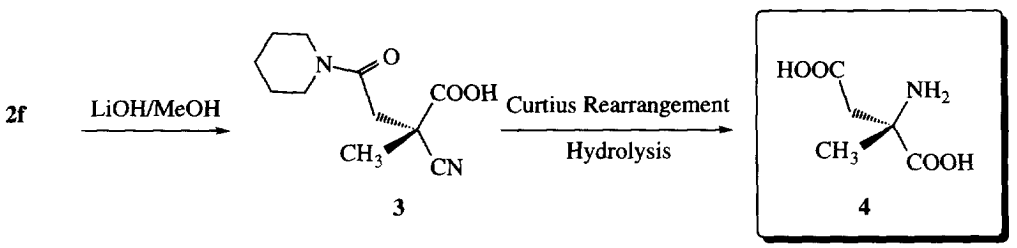
When iodoacetonitrile was used we obtained an inseparable mixture of compounds. *N*-(bromoacetyl)piperidine was found to be the best alkylating agent and the corresponding alkylation product was obtained in nearly quantitative yield with a very high diastereoselectivity. Moreover, both diastereoisomers of compound **2f** can be easily separated by flash chromatography (silica gel) using ether/hexane 95/5 as the eluent and the major compound was isolated in 90 % yield from the diastereomeric mixture. In contrast, isolation of the major compound from mixtures **2a-2c** proved extremely difficult in all cases and a diastereomerically pure sample of compound **2b** was obtained only after several crystallisations.

Table 1. Yields obtained in the alkylation of compound **1**.

Entry	Alkylating agent	Compound	Yield %	(d.r.)[a]
1	$BrCH_2CO_2CH_3$	**2a**	≈ 100	75/25
2	$BrCH_2CO_2C(CH_3)_3$	**2b**	≈ 100	80/20
3	$BrCH_2CO_2CH_2C_6H_5$	**2c**	≈ 100	82/18
4[b]	$BrCH_2CO_2R^*$	**2d**	80	45/55
5	ICH_2CN	**2e**	traces	-
6	$BrCH_2CO$-N	**2f**	≈ 100	92/8

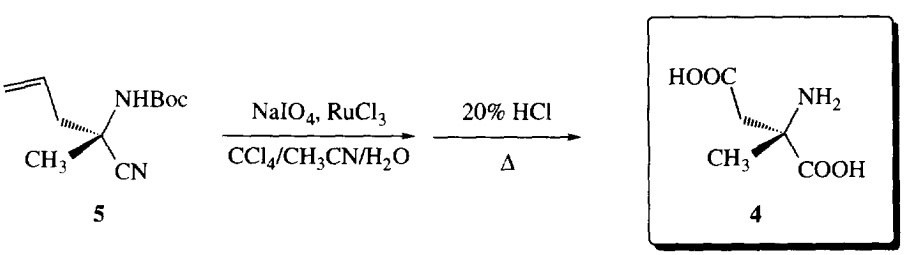
[a] Determined from the crude reaction mixture by integration of the ^1H NMR (300 MHz) absorptions of the methine protons (each diastereoisomer gives separate signals). [b] Alkylation with (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-bromoacetate was performed on methyl 2-cyanopropanoate.

Compound **2f** also has an advantage in that it is also more convenient to perform the selective hydrolysis of the chiral ester group as it possess two different functional groups (ester and amide). Selective hydrolysis of the ester group can easily be performed by treatment with a 1N solution of lithium hydroxide in methanol at room temperature. Under these conditions we obtained carboxylic acid **3** in 75 % yield after 4 days (Scheme 2).



Scheme 2

For the final step in the synthesis of α-methylaspartic acid we attempted the Curtius rearrangement of compound **3** under a variety of reaction conditions. In the synthesis of the acyl azide, the mixed anhydride obtained by treatment of compound **3** with isopropyl chloroformate was trapped *in situ* with sodium azide. This route was necessary as all attempts to obtain the corresponding acid chloride by treatment of **3** with thionyl chloride, phosphorous pentachloride or oxalyl chloride were unsuccessful. The acylazide obtained was submitted to Curtius rearrangement, without being isolated, by heating in a mixture of toluene/methanol. The resulting urethane was hydrolysed first in an acidic medium, to generate the amino acid moiety, and subsequently in a basic medium to liberate the β-carboxylic function. The overall yield for the reaction sequence was 87 %. We also tested the use of the one-pot procedure developed by Yamada *et al.*[15] and used diphenylphosphoryl azide in the presence of a base in order to obtain the intermediate acylazide. The reaction appeared to be dependent on the nature of the amine used and we obtained the best results using diisopropylethylamine as the base. The crude acylazide was heated in an acidic medium and then submitted to basic hydrolysis to afford α-methylaspartic acid in 83 % overall yield.



Scheme 3

An interesting alternative for the synthesis of α-methylaspartic acid is the oxidation of the allylic side chain of (2*S*)-2-*tert*-butoxycarbonylamino-2-methyl-4-pentenonitrile, which can be synthesised in enantiomerically pure form.[12] In effect, treatment of compound **5** with an excess of sodium periodate in the presence of ruthenium trichloride led to the conversion of the allylic side chain into a carboxylic acid group. Subsequent acid hydrolysis of the nitrile with 20 % hydrochloric acid afforded (*S*)-α-methylaspartic acid hydrochloride in 80% overall yield for the two steps (Scheme 3).

In conclusion, our methodology for the synthesis of α,α-dialkylamino acids based on the diastereoselective alkylation of chiral 2-cyano esters can be successfully applied to the synthesis of α-methylaspartic acid by simply using (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanopropanoate as the starting material and α-halocarbonyl compounds or allylbromide as the electrophile.

EXPERIMENTAL

***Apparatus*:** Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian Unity-300 or a Bruker ARX-300 spectrometer in deuterochloroform or deuterated water using the residual solvent signal as the internal standard; chemical shifts (δ) are given in parts per million and the coupling constants (*J*) in Hertz. Elemental analyses were performed using a Perkin-Elmer 2400 analyser. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25 °C.

***Chemicals*:** Methyl, *tert*-butyl and benzyl bromoacetate and iodoacetonitrile were purchased from the Aldrich Chemical Co. and used as received. (1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoyl-2-bromoacetate and *N*-(bromoacetyl)piperidine were obtained by treatment of bromoacetylbromide with (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isoborneol and piperidine respectively according to standard procedures. (1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl-2-cyanopropanoate[12] **1** and (2*S*)-2-*tert*-butoxycarbonylamino-2-methyl-4-pentenonitrile[11] **5** were obtained according to literature procedures. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulfuric acid/ethanol (2/1/100). Flash column chromatography was performed using silica-gel (Kiesegel 60).

General procedure for the enolate alkylation of compound 1

Potassium carbonate (690 mg, 5 mmol) was added to a well stirred solution of the corresponding (2*RS*) (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-cyanopropanoate **1** (478 mg, 1 mmol) and the corresponding alkylating agent (2 mmol) in dry acetone (15 ml). The resulting mixture was stirred at room temperature for 48 h, filtered and the solid residue washed with ether. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ether, washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding alkylated compound **2a-f** as a mixture of diastereoisomers (see table 1). When *N*-bromoacetylpiperidine was used as the alkylating agent, the major compound **2f** was isolated in 90 % yield from the diastereomeric mixture by flash chromatography (eluent ether/hexane 95/5) as a white solid.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-methyl-3-methoxycarbonyl propanoate 2a

From the (75/25) diastereomeric mixture, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.15 (s, 3H), 1.68 (s, 3H), 1.00-2.05 (m, 27H), 2.62 (d, 1H, J = 13.5 Hz), 2.67 (d, 1H, J = 17.3 Hz), 3.09 (d, 1H, J = 17.3 Hz), 3.20-3.36 (m, 2H), 3.44 (d, 1H, 13.5 Hz), 3.70 (s, 3H), 4.88 (dd, 1H, J = 7.4 Hz, J = 3.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 20.2, 23.3, 25.0, 26.1, 26.2, 26.9, 30.5, 32.2, 33.0, 38.4, 40.2, 41.8, 44.2, 49.3, 52.1, 53.6, 57.3, 81.1, 119.3, 167.6, 169.1; Anal. Calcd. for $C_{29}H_{46}N_2O_4S$: C, 63.24; H, 8.42; N, 5.09; S, 5.82. Found: C, 63.03; H, 8.15; N, 5.33; S, 6.07.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-methyl-3-*tert*-butoxycarbonylpropanoate 2b

From the (80/20) diastereomeric mixture, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.14 (s, 3H), 1.41 (s, 9H), 1.65 (s, 3H), 1.00-2.05 (m, 27H), 2.61 (d, 1H, J = 13.5 Hz), 2.64 (d, 1H, J = 16.8 Hz), 2.97 (d, 1H, J = 16.8 Hz), 3.18-3.40 (m, 2H), 3.43 (d, 1H, 13.5 Hz), 4.87 (dd, 1H, J = 7.5 Hz, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 20.4, 23.7, 25.2, 26.3, 26.4, 27.1, 28.0, 30.7, 32.3, 33.3, 38.4, 40.6, 43.3, 44.4, 49.5, 53.8, 57.2, 81.1, 82.1, 119.7, 167.8, 168.1; Anal. Calcd. for $C_{32}H_{52}N_2O_6S$: C, 64.83; H, 8.84; N, 4.73; S, 5.41. Found: C, 64.75; H, 8.91; N, 4.59; S, 5.29.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-methyl-3-benzyloxycarbonylpropanoate 2c

From the (82/18) diastereomeric mixture, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.13 (s, 3H), 1.69 (s, 3H), 1.00-2.05 (m, 27H), 2.61 (d, 1H, J = 13.2 Hz), 2.64 (d, 1H, J = 17.4 Hz), 3.14 (d, 1H, J = 17.4 Hz), 3.20-3.36 (m, 2H), 3.43 (d, 1H, 13.2 Hz), 4.87 (dd, 1H, J = 7.2 Hz, J = 3.3 Hz), 5.10 (d, 1H, J = 12.3 Hz), 5.16 (d, 1H, J = 12.3 Hz), 7.30-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 20.4, 23.8, 25.2, 26.3, 26.4, 27.1, 30.7, 32.4, 33.2, 38.6, 40.4, 42.2, 44.4, 49.5, 49.6, 53.8, 57.5, 67.4, 81.4, 119.7, 128.1, 128.5, 128.6, 135.0, 167.7, 168.8; Anal. Calcd. for $C_{35}H_{50}N_2O_6S$: C, 67.06; H, 8.04; N, 4.47; S, 5.12. Found: C, 66.91; H, 7.89; N, 4.25; S, 5.28.

(2*S*)-(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-methyl-3-(1-piperidylcarbonyl)propanoate 2f

Mp 160 °C ; $[\alpha]_D^{20}$ = - 67.2 (c = 1 in $CHCl_3$); IR (Nujol) 2246, 1737, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 3H), 1.23 (s, 3H), 1.71 (s, 3H), 1.00-2.05 (m, 33H), 2.64 (d, 1H, J = 13.4 Hz), 2.78 (d, 1H, J = 16.4 Hz), 3.06 (d, 1H, J = 16.4 Hz), 3.22-3.36 (m, 2H), 3.38-3.46 (m, 2H), 3.49 (d, 1H, 13.4 Hz), 3.55-3.64 (m, 2H), 4.85 (dd, 1H, J = 7.6 Hz, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0, 20.5, 23.9, 24.3, 25.2, 25.3, 26.2, 26.3, 26.4, 27.2, 30.6, 32.4, 33.2, 38.4, 40.8, 42.3, 42.8, 44.4, 46.3, 49.4, 49.5, 53.8, 57.5, 80.9, 120.4, 165.8, 168.4; Anal. Calcd. for $C_{33}H_{53}N_3O_5S$: C, 65.64; H, 8.85; N, 6.96; S, 5.31. Found: C, 65.82; H, 8.71; N, 7.04; S, 5.18.

(2*S*)- 2-cyano-2-methyl-3-(1-piperidylcarbonyl)propanoic acid 3

(1*S*,2*R*,4*R*)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-methyl-3-(1-piperidylcarbonyl)propanoate **2f** (603 mg, 1 mmol) was added to a 1N solution of LiOH in methanol (15 ml) and the reaction mixture was stirred at room temperature for 4 days. The resulting solution was partitioned between ether and water and the aqueous layer was extracted with ether (3 x 20 ml) in order to remove and recover the chiral auxiliary. The aqueous layer was then acidified with 20% hydrochloric acid and extracted with methylene chloride (3 x 20 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford (2*S*)- 2-cyano-2-methyl-3-(1-piperidylcarbonyl) propanoic acid **3** as a white solid in 75% yield.

Mp 127 °C ; $[\alpha]_D^{20}$ = - 39.8 (c = 1 in methanol); IR (Nujol) 2271, 1750, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40-1.60 (m, 6H), 1.58 (s, 3H), 2.72 (d, 1H, J = 16.5 Hz), 2.95 (d, 1H, J = 16.5 Hz), 3.22-3.30 (m, 2H), 3.35-3.54 (m, 2H), 4.68 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 24.1, 25.2, 26.0, 41.2, 42.6, 46.2, 120.8, 165.9, 171.0; Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.92; H, 7.19; N, 12.49. Found: C, 60.08; H, 7.03; N, 12.62.

(2*S*)-α-Methylaspartic acid 4

Method A. *N*-Methylmorpholine (56 mg, 0.55 mg) and isopropyl chloroformate (67 mg, 0.55 mmol) were added successively to a solution of (2*S*)- 2-cyano-2-methyl-3-(1-piperidylcarbonyl) propanoic acid **3** (112 mg, 0.5 mmol) in THF (10 ml) at -30 °C and the reaction was stirred for 30 min. The resulting mixture was allowed to warm to room temperature and a solution of sodium azide (65 mg, 1 mmol) in water (1 ml) was added. The resulting mixture was stirred for an additional 30 min and extracted with ether (3 x 20 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* without heating. The crude carbonylazide was dissolved in toluene/methanol 2:1 (15 ml) and the resulting solution was heated under reflux for 8 h. The solvents were removed *in vacuo* to afford the crude urethane which was hydrolysed without purification by addition of 20 % hydrochloric acid solution (40 ml) and heating under reflux conditions for 24 h. The solution was concentrated *in vacuo*, diluted with water (15 ml) and concentrated *in vacuo* once again. The residue was partitioned between ether and water and the aqueous layer was extracted with ether (3 x 20 ml). 10% aqueous sodium hydroxide solution was added to the aqueous layer and the basic solution was extracted with methylene chloride (3 x 20 ml). The resulting aqueous solution was heated at 110 °C with stirring for 4 h and then acidified with 5% hydrochloric acid. The reaction mixture was evaporated to dryness *in vacuo* to give the crude amino acid salt which was purified by elution with 2N aqueous ammonia through a cation exchange resin column (Dowex 50W x 8, H^+). 128 mg (87%) of (2*S*)-α-methylaspartic acid **4** was obtained as a white solid.

Method B. Diisopropylethylamine (143 mg, 1.1 mmol) and diphenylphosphoryl azide (303 mg, 1.1 mmol) were added successively to a solution of (2*S*)- 2-cyano-2-methyl-3-(1-piperidylcarbonyl)propanoic acid **3** (224 mg, 1 mmol) in dry toluene (10 ml) and the reaction was stirred for 6 h under reflux . When the reaction was complete the solvent was evaporated *in vacuo* to afford the crude isocyanate which was hydrolysed without purification by heating under reflux with 20 % aqueous hydrochloric acid (40 ml) for 24 h. The solution was concentrated *in vacuo*, diluted with water (15 ml) and concentrated *in vacuo* once again. The residue was partitioned between ether and water and the aqueous layer was extracted with ether (3 x 20 ml). Aqueous sodium hydroxide (10%) was added to the aqueous layer and the basic solution was extracted with methylene chloride (3 x 20 ml). The resulting aqueous solution was heated at 110 °C with stirring for 4 h and then acidified with 5% aqueous hydrochloric acid. The reaction mixture was evaporated to dryness *in vacuo* to give the crude amino acid salt which was purified by elution with 2N aqueous ammonia through a cation exchange resin column (Dowex 50W x 8, H^+). 122 mg (83%) of (2*S*)-α-methylaspartic acid **4** was obtained as a white solid.

Method C. Small portions of $NaIO_4$ (877 mg, 4.1 mmol) were added to a stirred solution of (2*S*)-2-*tert*-butoxycarbonylamino-2-methyl-4-pentenonitrile **5** (210 mg, 1 mmol) in a mixture of acetonitrile-carbon tetrachloride-water (2:2:3) (20 ml). On completion of the addition, the mixture was vigorously stirred for 5 min and was treated with $RuCl_3 \cdot H_2O$ (10 mg, 0.044 mmol). The mixture was stirred for a further 3 h and saturated aqueous sodium bicarbonate solution was added until the pH was 8-9. The aqueous solution was washed with dichloromethane (3 x 10 ml) and the resulting aqueous layer was then carefully acidified with 20% aqueous hydrochloric acid and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* . The resulting crude (3*S*)-3-*tert*-butoxycarbonylamino-3-cyanobutanoic acid was hydrolysed by stirring with 20% aqueous hydrochloric acid (40 ml) for 24 h under reflux . The reaction mixture was washed with ether and the aqueous layer evaporated to dryness *in vacuo* to give 117 mg (80 %) of the amino acid hydrochloride from which the free amino acid was be isolated by ion exchange chromatography (Dowex 50W x 8,H^+) as a white solid.

Physical and spectroscopic data of the hydrochloride: M.p. > 300 °C; $[\alpha]^{25}_D$ = + 31 (c, 0.5 in methanol), lit[9] $[\alpha]^{25}_D$ = + 33.5 (c, 1.5 in methanol); ^{1}H NMR (D_2O, 300 MHz): δ 1.30 (s, 3H), 2.40 (d, 1H, J = 7.2 Hz), 2.67 (d, 1H, J = 7.2 Hz); ^{13}C NMR (D_2O, 75 MHz): δ 20.7, 40.8, 57.6, 175.5, 176.2.

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