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Asymmetric synthesis of a phosphonic analogue of (−)-*allo*-norcoronamic acid

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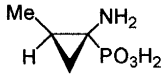
Abstract

(−)-(1*R*,2*R*)-1-Amino-2-methylcyclopropanephosphonic acid was synthesized in an enantiomerically pure form starting from the cyclic sulfate of (+)-(*S*)-1,2-propanediol and dimethyl *t*-butoxycarbonylmethylphosphonate.

Keywords: asymmetric synthesis; cyclic sulfates; amino phosphonic acid; cyclopropane.

In recent years, considerable interest has been focused on the synthesis of 1-aminocyclopropanecarboxylic acids (ACC derivatives) owing to their use as mechanistic probes and enzymes inhibitors as well as their incorporation in strained peptides.[1] α-Aminophosphonic acids, the phosphonic analogues of α-aminocarboxylic acids, are also important compounds presenting interesting biological activities by themselves or as components of peptidomimetics.[2] In connection with our ongoing program related to enantiopure cyclopropane derivatives,[3] and as part of a project directed to the preparation of novel conformationally restricted non-proteinogenic amino acids, we were interested in the synthesis of a phosphonic analogue of (−)-(1*S*,2*R*)-*allo*-norcoronamic acid.[4,5]



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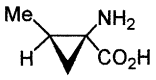

(-)-Allo-norcoronamic acid

The synthesis of (−)-(1*R*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid **1** was carried out starting from the sulfate **2**. This compound was obtained from (+)-(*S*)-1,2-propanediol by the one pot procedure reported by Sharpless and Gao in a 95% overall yield.[6] Treatment of **2** with dimethyl *t*-butoxy-carbonylmethylphosphonate in the presence of NaH afforded a 97:3 diastereomeric mixture of cyclopropanes **4** (Scheme 1).[7] The enantiomeric excess (>99%) was determined by ^{31}P NMR.[8]

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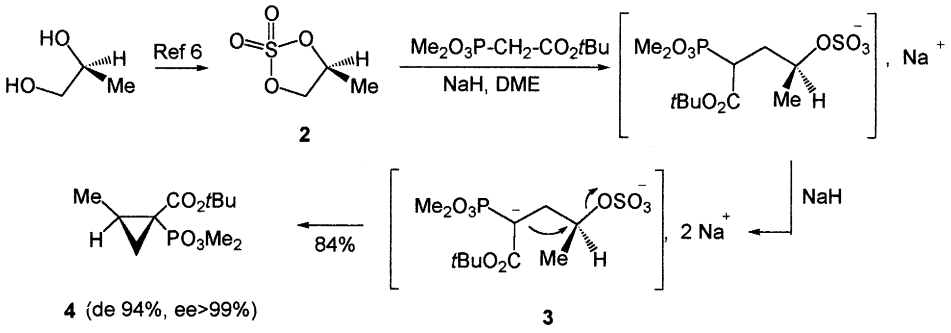


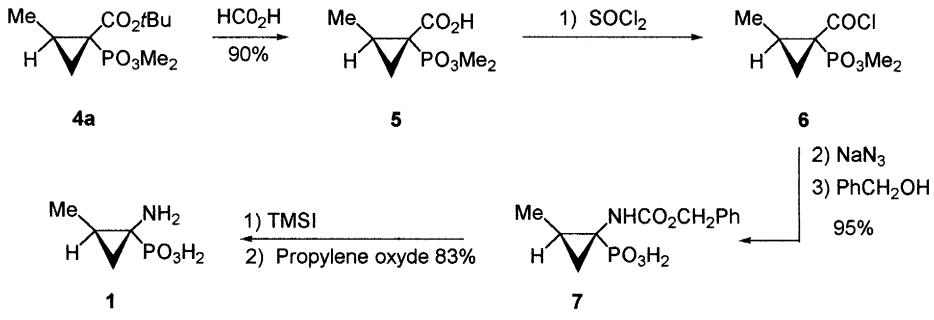
Scheme 1.

This high asymmetric induction is attributed to an efficient control of the configuration of the new created stereogenic center in the intramolecular cyclization step. This transformation occurred with total inversion and the difference of steric hindrance between the *t*-butyl ester and the phosphonate groups entailed the major formation of the (1*R*,2*R*)-isomer, therefore presenting the most sterically favored interaction with the methyl substituent of the initial sulfate.

Favored transition state Disfavored transition state

Chromatography on silica gel afforded the pure enantiomer (1*R*,2*R*)-**4** in a 84% yield. Assignment of the stereochemistry was based on the $^{3}J_{P-H}$ coupling constants between the cyclopropanic proton α to the methyl group and the phosphorus atom. The observed value ($^{3}J_{P-H}$=12.8 Hz) is consistent with the values reported in the literature for the *cis* configuration.[5]

The hydrolysis of the ester **4** with formic acid at room temperature for three hours gave the acid **5** which was converted to the acyl chloride **6**. Curtius rearrangement of the corresponding azide and subsequent addition of benzyl alcohol afforded the *N*-protected amino ester **7**. Treatment by trimethylsilyliodide in dichloromethane and addition of propylene oxyde in ethanol, yielded the crystalline and enantiomerically pure (−)-(1*R*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid **1** (Scheme 2).[9] The stereochemistry of this compound was unambiguously established by X-ray crystal analysis.[10]



Scheme 2.

In conclusion, we have developed a novel and practical method for the preparation of (−)-(1*R*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid by addition of dimethyl *t*-butoxycarbonylmethylphosphonate to a 1,2-cyclic sulfate. Numerous enantiomerically pure 1,2-diols, the precursors of these versatile bis-alkylating agents, are readily available. This approach should therefore constitute an efficient route for the synthesis of a wide range of aminocyclopropane phosphonic acids.

Acknowledgements

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7. (−)-(1*R*,2*R*) *t*-Butyl-1-dimethylphosphono-2-methylcyclopropanecarboxylic ester **4**. A 250 mL three-necked round-bottomed flask equipped with reflux condenser, $CaCl_2$ drying tube, nitrogen inlet and rubber septum was charged with NaH (60 mmol, 2.4 g of a 60% dispersion in mineral oil) and dry DME (100 mL). Cyclic sulfate **2** (30 mmol, 4.14 g) and dimethyl *t*-butoxycarbonylmethylphosphonate (20 mmol, 5.28 g) in dry DME (20 mL) were added in one portion by a syringe. The resulting mixture was stirred at 25°C for 16 h. The reaction mixture was cooled, poured in saturated NH_4Cl and chloroform (90 mL) was added. The two phases were separated, the aqueous layer extracted with chloroform (90 mL), the organic layer dried over $MgSO_4$, and the solvents evaporated. The crude phosphonate **4** was purified by chromatography (silica gel, EtOAc). Yield 3.59 g (84%). $[\alpha]_D^{20}$ −23 (c 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, *J*=6.2 Hz, 3H), 1.15–1.25 (m, 1H), 1.27–1.50 (m, 10H), 1.55–1.80 (m, 1H), 3.65–3.75 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.2, 18.1, 20.3, 24.2 (d, *J*=188 Hz), 52.6, 81.6, 166.4. ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.9. HRMS *m/z* found 264.112, calcd for $C_{11}H_{21}O_5P$ (M^+) 264.1126.
8. The determination of the enantiomeric excess of **4** was carried out as follows. Acidic hydrolysis of **4** gave quantitatively the corresponding cyclopropylcarboxylic acids, which were reacted with 1.2 equivalent of *s*-brucine in chloroform. The ^{31}P NMR spectrum of the crude product displayed two signals at 30.62 and 31.86 ppm in a 3:97 ratio. The ^{31}P NMR spectrum of a diastereomeric mixture of cyclopropanes **4**, obtained from the racemic sulfate **2**, displayed four signals at 30.50, 30.61, 31.78, and 31.85 ppm in a 1.5, 1.5, 48.5, 48.5 ratio. These results were not dependent on the reaction time of salt formation, that excludes a kinetic resolution.
9. Compound **1**: mp 245°C (decomp.). $[\alpha]_D^{20}$ −46.4 (C 0.2, H_2O). ^{1}H NMR (300 MHz, D_2O), δ 0.80 (q, J_{H-H}=6.5 Hz, J_{P-H}=6.5 Hz, 1H), 1.21 (d, *J*=6.5 Hz, 3H), 1.28 (ddd, J_{H-H}=6.5 and 9.5 Hz, J_{P-H}=12.3 Hz, 1H), 1.40–1.55 (m, 1H). ^{13}C NMR (75.5 MHz, D_2O) δ 13.4, 17.3, 18.5, 34.7 (d, J_{P-C}=192 Hz). ^{31}P NMR (121 MHz, D_2O) δ 16.93.
10. Crystal data for **1**. $C_4H_{10}NO_4P$; MW=167.10. Monoclinic, $P2_1$, *a*=6.522 (6), *b*=6.161 (4), *c*=9.983 (3) Å, β=99.97, V=395.1 (5) Å^3, *Z*=2, D_X=1.405 g cm^{-3}, λ (MoKα)=0.71073 Å, μ=3.10 cm^{-1}, T=294 K, F(000)=176, R=0.105 for 1836 reflections.