Asymmetric synthesis of (1S,2R)-1-amino-2-methylcyclopropanephosphonic acid, a phosphonic analog of (−)-norcoronamic acid. Influence of stereochemistry on regioselectivity in sulfoxide/metal exchange

Wanda H. Midura*, Aneta Rzewnicka

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Heteroorganic Chemistry, 90-363 Lodz Sienkiewicza 112, Poland

Fax +48(42)6847126; e-mail whmidura@cbmm.lodz.pl

Supporting Information

Cyclopropanation of cyano-1-diethylphosphonoacrylate

A round-bottomed flask equipped with a magnetic stirrer bar was charged with 1 mmol (0.20 g) of cyano-1-diethylphosphonoacrylate and 1 mmol (0.3 g) of (S)-dimethyl sulfoxonium-(p-tolylsulfinyl) methyl tetrafluoroborate in 10 mL of CH₂Cl₂. To this suspension was added 0.7 g of K₂CO₃ and the mixture was stirred vigorously overnight. Filtration and evaporation of the solvent afforded a crude residue in 93% yield. The major diastereomer was separated by column chromatography on silica (hexane/acetone 2:1)

(+)-(1R,2S,3S) Diethyl 1-cyano-2-p-tolylsulfinyl cyclopropylphosphonate 6a

\[\text{Yield: 53%; yellowish oil; } [\alpha]_D^{20} = +57.8 \text{ (c 3.2, acetone); } ^{31}\text{P NMR (81 MHz, CDCl}_3) \delta: 14.7; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3) \delta: 1.16 \text{ (t, 3H, POCH}_2\text{CH}_3, J_{HH} = 7.1 \text{ Hz}), 1.36 \text{ (t, 3H POCH}_2\text{CH}_3, J_{HH} = 7.0 \text{ Hz}), 1.97 \text{ (ddd, 1H, CHH, } J_{HH} = 5.5, 8.3 \text{ Hz, } J_{PH} = 14.1 \text{ Hz}), 2.28 \text{ (m, 1H, CHH), 2.39 (s, 3H, C}_6\text{H}_4\text{CH}_3), 2.97 \text{ (ddd, 1H, CHH, } J_{HH} = 6.7, 8.3 \text{ Hz, } J_{PH} = 13.0 \text{ Hz CHS(O)), 3.63-3.82 (m, 1H, POCH}^\text{HCH}_3), 3.86-4.05 \text{ (m, 1H, POCH}^\text{HCH}_3), 4.10-4.25 \text{ (m, 2H, POCH}_2\text{CH}_3), 7.36 \text{ and 7.70 (AsB}_2, 4H, C}_6\text{H}_4\text{CH}_3); ^{13}\text{C NMR (125 MHz, CDCl}_3) \delta: 9.90 (C}_2\text{H}_2), 11.4 \text{ (d, } J_{CP} = 191.3 \text{ Hz), 16.1 (d, } J_{CP} = 6.0 \text{ Hz, CH}_3\text{CH}_2\text{OP}, 16.3 \text{ (d, } J_{CP} = 6.0 \text{ Hz, }
CH₃CH₂OP), 21.6 (C₆H₄CH₃), 44.2 (CHSO), 64.2 (d, JCP = 6.5 Hz, CH₃CH₂OP), 64.6 (d, JCP = 6.5 Hz, CH₃CH₂OP), 114.9 (CN), 124.4, 130.4, 139.8, 143.1; MS(Cl) m/z 342 (M+H)⁺; HR MS(EI) 341.0851 calcd for C₁₂H₂₀NO₄PS [M⁺]⁺ Found 341.0848

**Alkylation of 6a**

To a solution of 189 mg, 0.55 mmol of cyclopropyl sulfoxide 6a, LiHMDS (prepared by addition of 0.28 mL of 2.17 M solution of BuLi to 0.14 mL of HMDS) was added at −78 °C. The reaction was allowed to stir for 15 min. and MeI or (MeO)₂SO₂ (0.6 mmol) was then added at −78 °C, and the reaction was allowed to warm slowly to 0 °C. After quenching with NH₄Cl the water phase was extracted three times with CH₂Cl₂, and the combined organic phase were dried over MgSO₄, filtrated and evaporated. The crude product was purified by column chromatography (ethyl acetate/hexane 2:1).

(+)-(1R,2R,Ss)-Diethyl 1-cyano-2-p-tolylsulfinyl 2-methylcyclopropylphosphonate 7a

![Structural diagram of 7a](attachment:image)

Yield: 63 % (when (MeO)₂SO₂ was used); yellowish oil; [α]D²⁰ = + 52.5 (c, 0.9 acetone); ³¹P NMR (81 MHz, CDCl₃) δ: 13.8; ¹H NMR (500 MHz, CDCl₃) δ: 1.17 (t, 3H, (CH₃CH₂O)P, JHH = 7.0 Hz), 1.24 (s, 3H, CH₃), 1.27 (t, 3H, (CH₃CH₂O)P, JHH = 7.0 Hz), 2.06 (dd, 1H, JHH = 5.8 Hz, JPH = 14.0 Hz, CH₃cis), 2.40 (dd, 1H, JHH = 5.8 Hz, JPH = 8.9 Hz CH₂trans CHS(O)), 2.43 (s, 3H, C₆H₄CH₃), 3.96-3.99 (m, 1H, (CH₃CH₂O)P), 4.01-4.05 (m, 1H, (CH₃CH₂O)P), 4.23-4.27 (m, 2H, (CH₃CH₂O)P), 7.36 and 7.73 (A₂B₂, 4H, C₆H₄CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 9.1 (CH₃), 14.5 (d, JCP = 180.3 Hz), 16.1 ((CH₃CH₂O)P), 21.5 (C₆H₄CH₃), 25.6, 47.8 (CHSO), 63.7 (d, JCP = 6.5, (CH₂CH₂O)P), 46.4 (d, JCP = 6.1 Hz, (CH₂CH₂O)P), 116.6 (CN), 124.9, 129.8, 136.9, 142.4; HR MS(Cl) 356.10833 calcd for C₁₆H₂₄NO₄PS [M+H⁺]⁺ Found 356.108545

(+)-(1R,2S,Ss)-Diethyl 1-cyano-2-p-tolylsulfinyl 2-methylcyclopropylphosphonate 7b

![Structural diagram of 7b](attachment:image)

Yield: 28% % (when (MeO)₂SO₂ was used); yellowish oil; [α]D²⁰ = +22.1 (c, 0.7 acetone); ³¹P NMR (81 MHz, CDCl₃) δ: 14.0; ¹H NMR (500 MHz, CDCl₃) δ: 1.46 (t, 3H, (CH₃CH₂O)P,
\( J_{HH} = 7.0 \text{ Hz} \), 1.48 (t, 3H, (CH\(_3\)CH\(_2\)O)P, \( J_{HH} = 7.0 \text{ Hz} \)), 1.49 (s, 3H, CH\(_3\)), 1.66 (dd, 1H, \( J_{HH} = 6.1 \text{ Hz} \), \( J_{PH} = 7.7 \text{ Hz} \), CH\(_{trans}\)), 2.25 (dd, 1H, \( J_{HH} = 6.1 \text{ Hz} \), \( J_{PH} = 16.1 \text{ Hz} \) CH\(_{trans}\)), 2.43 (s, 3H, C\(_6\)H\(_5\)CH\(_3\)), 4.29-4.40 (m, 2H, (CH\(_3\)CH\(_2\)O)P), 4.41-4.44 (m, 2H, (CH\(_3\)CH\(_2\)O)P), 7.32 and 7.51 (A\(_2\)B, 4H, C\(_6\)H\(_5\)CH\(_3\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 11.9 (CH\(_3\)), 16.3 ((CH\(_3\)CH\(_2\)O)P), 20.0 (d, \( J_{CP} = 190.4 \text{ Hz} \)), 21.4 (C\(_6\)H\(_5\)CH\(_3\)), 24.1, 50.0 (CHSO), 64.2 (d, \( J_{CP} = 6.2 \text{ Hz} \), (CH\(_3\)CH\(_2\)O)P), 64.9 (d, \( J_{CP} = 6.5 \text{ Hz} \), (CH\(_3\)CH\(_2\)O)P), 116.5 (CN), 124.5, 129.9, 138.0, 142.2; HR MS(El) 355.100720 calcd for C\(_{16}\)H\(_{22}\)NPSO\(_4\) [M]+ Found 355.100500

**Sulfoxide/metal exchange – general**

To a stirred solution of cyclopropane 7 (0.159 mmol) in anhydrous THF (5.0 mL), \( \text{t-PrMgCl} \) (2.0 M in THF, 0.79 mmol, 0.084 mL), was added at \(-50 \text{ °C} \) and the mixture was stirred at this temperature for 1 h. The reaction was quenched by NH\(_4\)Cl, and extracted with chloroform (5 x 5 mL). The combined extracts were dried over anhydrous MgSO\(_4\), filtered, and concentrated. Purification was performed by plate chromatography (hexane/acetone 4:1).

\((+)-(1S,2R)-\text{Diethyl 1-cyano-2-methylcyclopropylphosphonate 8}\)

Yield: 63%; yellowish oil; \([\alpha]D\)\(^{20} = -14.3 \) (c 6.7, acetone); \(^{31}\)P NMR (81 MHz, CDCl\(_3\)) \( \delta \): 18.0

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 1.40 (t, 3H, (CH\(_3\)CH\(_2\)O)P, \( J_{HH} = 7.0 \text{ Hz} \)), 1.42 (t, 3H, CH\(_3\)CH\(_2\)O)P, \( J_{HH} = 7.0 \text{ Hz} \)), 1.44 (d, 3H, CH\(_3\)), 1.55 (ddd, 1H, \( J_{HH} = 4.8 \), \( J_{HH} = 7.1 \), \( J_{PH}=14.2 \text{ Hz} \), CH\(_{trans}\)), 1.70 (ddd, 1H, \( J_{HH} = 4.8 \), \( J_{HH} = 8.9 \), \( J_{PH}=7.3 \text{ Hz} \), CH\(_{trans}\)), 1.90 (m, CH\(_3\)CH\(_3\)), 4.24 (m, 4H, (CH\(_3\)CH\(_2\)O)P); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 8.6 (d, \( J_{CP}=198.8 \text{ Hz} \), C1), 13.0 (d, \( J_{CP}=3.4 \text{ Hz} \), \( J_{CP}=3.4 \text{ Hz} \)), 16.3 (d, \( J_{CP}=6.0 \text{ Hz} \), (CH\(_3\)CH\(_2\)O)P), 16.4 ((CH\(_3\)CH\(_2\)O)P), 21.9, 24.4, 63.3 (d, \( J_{CP}=6.5 \text{ Hz} \), (CH\(_3\)CH\(_2\)O)P), 63.6 (d, \( J_{CP}=6.0 \text{ Hz} \), (CH\(_3\)CH\(_2\)O)P), 119.9 (CN); HR MS (Cl) 218.09497 calcd for C\(_9\)H\(_{17}\)NPO\(_3\) [M+H]+ Found 218.094607.

\((+)-(1R,2R)-\text{Diethyl 2-cyano-1-methylcyclopropylphosphonate 9}\)

---

**Note:** The content of the text appears to be cut off or incomplete. The full context is not visible. Please review the full document for a complete understanding.
[α]D<sup>20</sup> = −38.8 (c, 0.25 acetone); <sup>31</sup>P NMR (81 MHz, CDCl<sub>3</sub>) δ 26.1; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 1.11 (ddd, 1H, J<sub>HH</sub> = 5.0, J<sub>HH</sub> = 5.5, J<sub>PH</sub> = 13.5 Hz), 1.39 (t, 3H, J<sub>HH</sub> = 7.0 Hz), 1.40 (t, 3H, J<sub>HH</sub> = 7.0 Hz), 1.47 (d, 3H J<sub>PH</sub> = 13.0 Hz, CH<sub>3</sub>-CP), 1.62 (ddd, 1H, J<sub>HH</sub> = 5.0, J<sub>HH</sub> = 9.0, J<sub>PH</sub> = 14.0 Hz), 2.04 (ddd, 1H, J<sub>HH</sub> = 5.5, J<sub>HH</sub> = 9.0, J<sub>PH</sub> = 14.3 Hz), 4.13 (m, 4H, POCH<sub>2</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 15.9 (CH<sub>2</sub>C), 16.4 (d, J<sub>CP</sub> = 5.7 Hz) 17.1 (d, J<sub>CP</sub> = 194.0 Hz, CP), 18.2, 29.7 (d, J<sub>CP</sub> = 2.9 Hz), 62.8 (d, J<sub>CP</sub> = 6.2 Hz, POCH<sub>2</sub>), 127.1 (C<sub>N</sub>); HR MS(FAB) 9217.0872 calcd for C<sub>9</sub>H<sub>16</sub>NPO<sub>3</sub>[M]<sup>+</sup> Found 217.086782.

**Conversion of nitrile 8**

To a solution of 8 (0.0227 g, 0.104 mmol) in MeOH (3 mL) H<sub>2</sub>O<sub>2</sub> (0.037g, 1.1 mmol, 0.033 mL) and K<sub>2</sub>CO<sub>3</sub> (0.079 g, 0.575 mmol) was added. The mixture was stirred at 70 °C for 24h. After then the mixture was dissolved with water (3 mL) and extracted with dichloromethane (5 x 5 mL). The combined extracts were dried over MgSO<sub>4</sub>. The solvent was evaporated

(−)-(1S,2R)-Diethyl 1-carbamoyl-2-methylcyclopropylphosphonate 10

Yield: 90%; colorless oil; [α]D<sup>20</sup> = −4.8 (c 4.8, acetone); <sup>31</sup>P NMR (81 MHz, CDCl<sub>3</sub>) δ: 27.0

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 1.32-1.37 (m, 6H, (CH<sub>3</sub>CH<sub>2</sub>O)P), 1.38-1.40 (m, 3H, CH<sub>3</sub>) 1.4-1.45 (m, 1H, CH<sub>2</sub>), 1.66-1.70 (m, 1H, CH<sub>2</sub>), 1.83-1.91 (m, 1H, CH-CH<sub>3</sub>), 4.13-4.21 (m, 4H, (CH<sub>3</sub>CH<sub>2</sub>O)P), 5.58 (br s, 1H, CONHH), 7.51 (br s, 1H, CONHH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 13.6, 16.3 (d, J<sub>CP</sub> = 6.3 Hz, (CH<sub>3</sub>CH<sub>2</sub>O)P), 16.4 ((CH<sub>3</sub>CH<sub>2</sub>O)P), 21.6, 23.6, 24.3 (d, J<sub>CP</sub> = 159.0 Hz), 62.5 ((CH<sub>3</sub>CH<sub>2</sub>O)P), 62.6 (d, J<sub>CP</sub> = 6.3 Hz, (CH<sub>3</sub>CH<sub>2</sub>O)P), 171.1 ((C(O)NH<sub>2</sub>); MS(Cl) m/z 236 (M+H)<sup>+</sup>

**Transformation of amide 10**

To a solution of amide (0.0052 g, 0.0239 mmol) in tert-butyl alcohol (4 mL), lead tetraacetate (0.0424 g, 0.0956 mmol) was added and the mixture was heated at reflux for 5 h. After cooling to room temperature, diethyl ether (2.5 mL) followed by NaHCO<sub>3</sub> (0.002 g, 0.0239
mmol) were added, and the mixture was stirred for 10 min at room temperature. The mixture was filtered through a short plug of silica gel and the filtrate evaporated.

tert-Butyl (−)-(1S,2R)-1-(diethoxyphosphoryl)-2-methylcyclopropylcarbamate 11

![Chemical structure](image)

Yield: 76%; colorless oil; $^{31}$P NMR (81 MHz, CDCl$_3$) δ: 25.4

$^1$H NMR (500 MHz, CDCl$_3$) δ: 1.29-1.36 (2 x t, 6H, $J_{HH} = 7.3$ Hz, POCH$_2$CH$_3$), 1.36-1.50 (m, 3H, CH$_2$, CH-CH$_3$), 1.40 (s, 3H, CH$_3$), 1.43 (s, 9H, C(O)C(CH$_3$)$_3$), 4.13-4.25 (m, 4H, POCH$_2$CH$_3$), 4.96 (s, 1H, NH)); MS(Cl) m/z 308 (M+H)$^+$

(+)-(1S,2R)-Amino-2-methylcyclopropylphosphonic acid 12

![Chemical structure](image)

A solution of N-Boc-protected cyclopropylamine 10 (0.0046 g) in 2 mL of 6 N HCl was heated at 100 °C for 24 h and then concentrated under vacuum. The residue was dissolved in absolute ethanol (0.5 mL) and then treated with propylene oxide (0.04 mL). After standing overnight at room temperature, the mixture was filtered to afford a white solid. $^{31}$P NMR (81 MHz, D$_2$O) δ: 13.6; $^1$H NMR (500 MHz, D$_2$O) δ: 0.85–0.88 (m, 2H, CH$_2$), 0.99-1.03 (m, 3H, CH$_3$), 1.13-1.16 (m, 1H); $^{13}$C NMR (125 MHz, D2O) δ: 12.9, 16.6, 18.0, 32.2 (d, $J_{CP} = 197$ Hz); MS(Cl) m/z 152 (M+H)$^+$
\[
\text{(EtO)}_2\text{C} = \text{CN} \quad 1H[31P] \\
\]

1H homodec@Me(1.43ppm)

1H[31P] + homodec@Me(1.43ppm)

\[
a. \text{rzewnica} = \text{arz202pp2/f1} = A-1H.stan
\]