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Unusually Large Reactivity Differences in the Transformation of Cyclopropane Lactones to 1-Aminocyclopropane-1-phosphonic Acids and Their Carboxylic Acid Analogues

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ABSTRACT: *Starting from a cyclopropane lactone* **5**, *the synthesis of a 1-aminocyclopropane-1-phosphonic acid derivative* **11** *is described. The considerable differences in the reactivity of the lactone ring opening in the case of a cyclopropane lactone substituted by a phosphonic acid ester* **5** *and their carboxylic acid ester analogue* **2** *toward ammonia or amines have been compared and interpreted by using the map of electrostatic potentials.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:90–96, 2001

INTRODUCTION

In the last decade, aminocyclopropanecarboxylates (ACCs) and their phosphonic acid analogues, aminocyclopropanephosphonates (ACPs) have attracted special attention because of their biological activity. Many articles have been published on the synthesis of ACC [1–4] and on the preparation of ACP [5–7]. In 1993, we published an article on the synthesis, starting from malonic acid allyl esters, of cyclopropane carboxylic lactones that are useful intermediates in the preparation of ACC [8] (Scheme 1).

We thought that the same type of synthetic sequence might supply the corresponding ACPs, starting from phosphonoacetic allyl esters (Scheme 2). As described earlier [9], the synthetic steps for obtaining cyclopropane phosphonic acid lactones had been almost completely fulfilled, with only one exception: in the single-electron transfer (SET)-induced radical type processes, it is not the five-membered radical intermediate ($R^{1}\cdot$) that was formed, but rather the radical $R^{2}\cdot$ by an endo six process that was detected in the electron spin resonance (ESR) tube. Calculations were carried out to explain these findings, and we found that it is not the thermodynamic but rather the kinetic preferences that prevail to afford the 5-exo product $R^{1}\cdot$ in the ring closure reaction of **1** and the 6-endo product $R^{2}\cdot$ in the reaction of **4** [10].

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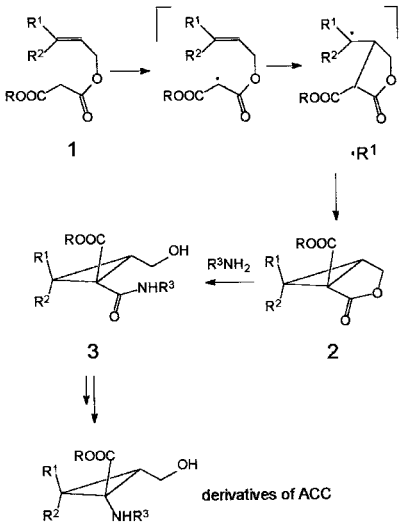


SCHEME 1

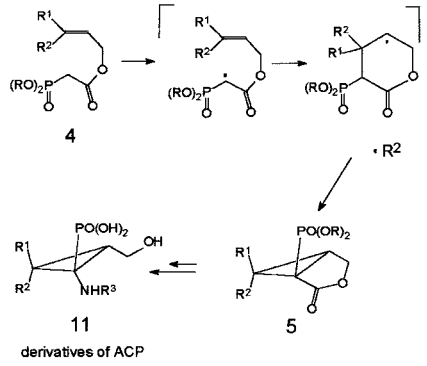
In this article, the ammonolysis of the lactones **5**, the subsequent Hofmann degradations, and the dealkylations are reported to give the ACP. Large differences in the reactivities of the lactones **5** in the ammonolysis process have been observed as compared to the reactions of the carboxylic counterpart **2**.

These differences, at least in the first sight, seem to be difficult to rationalize, but, by means of the maps of electrostatic potentials (MEP), the problem has been solved successfully. The details of these calculations and the explanations are included in the article.

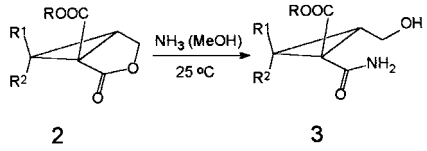
RESULTS AND DISCUSSION

In Scheme 3, the data of Koskinen and Munoz [4] for the nucleophilic ring opening reactions of the lactone groups in **2** by ammonia are shown. Smooth reactions took place with saturated methanolic ammonia at room temperature resulting in the formation of the carboxylic amides in excellent yields. The lactone moiety in the phosphonic acid ester analogues **5** behaved quite differently; no reaction could be observed with **5a** using the same conditions, methanolic ammonia, in the presence or in the absence of 4-dimethylaminopyridine (DMAP) as a catalyst, even after a prolonged reaction time (Scheme 4).

Under forced conditions, in liquid ammonia in a sealed tube at elevated temperature and for a long reaction time, the lactone ring still remained intact but a crystalline product could be isolated, which proved to be the P–O monodealkylated product **6**.

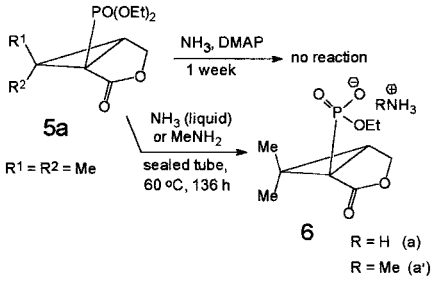


SCHEME 2



	R1	R2	R	Time of reaction
(a)	H	H	*t*-Bu	6 h
(b)	Me	H	*t*-Bu	8 h
(c)	Me	Me	*t*-Bu	7 days
(d)	Ph	H	*t*-Bu	8 h

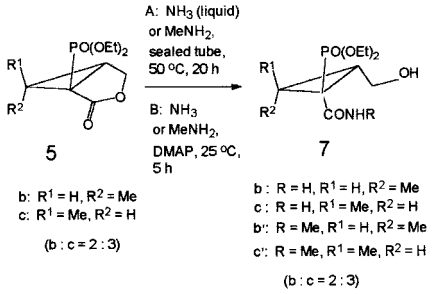
SCHEME 3



SCHEME 4

The same result was obtained in the reaction of **5a** with methylamine or with benzylamine; no lactone ring opening occurred.

The outcome of the reaction of the monomethyl derivatives **5b** and **5c** or **5b** + **5c** mixture [11] with ammonia changed; under the conditions used for the lactone ring opening in **2** with ammonia, nothing happened, but, under forced conditions, with use of liquid ammonia in a sealed tube and for a longer period of time (20 hours), the ring in **5b** (endo-methyl) and **5c** (exo-methyl) opened to give a mixture of **7b** and **7c** with the same isomeric ratio as found in the starting lactones (Scheme 5). However, in the presence of the catalyst (4-dimethylaminopyr-



SCHEME 5

idine), the duration of the ring opening reaction was shortened to 5 hours, giving a mixture of **7b** and **7c** or **7b′** and **7c′**, respectively.

The complete unreactivity of the lactone ring in the dimethyl derivative **5a**, as compared to that of the carboxylic acid ester analogue **2c**, and the diminished reactivity of the same moiety in the monomethyl derivatives **5b** or **5c**, as compared to that of the ester analogue **2b**, still remained to be rationalized.

An explanation is proposed by us using the maps of the electrostatic potentials (MEP) calculated for all of the compounds in question.

Figure 1 shows the MEP for the dimethylcyclopropane carboxylic ester lactone **2c** and its analogue **5a**. One can see that the nucleophile (NH_3, CH_3NH_2) can attack the lactone carbonyl group in **2c** without any hindrance from the exo-side because the negatively charged potential cloud is far from this side. The endo attack is hindered because of the presence of an endo-methyl group. Regarding the phosphonic acid analogue **5a**, we can observe a much larger negatively charged potential cloud covering the region of the lactone carbonyl carbon atom even at the exo-side, making the nucleophile attack impossible from this direction, whereas the endo-side is hindered by the endo-methyl group, resulting in a complete unreactivity of the lactone moiety in **5a**.

Figure 2 shows the MEPs for the two monomethyl derivatives **5c** and **5b**. As it can be seen, the nucleophilic attack at the lactone carbonyl in **5c** from the exo-direction is strongly hindered by the phosphonic ester substituent that is forced to that position so as to minimize the steric interference between the exo methyl group and the ethoxy substituent in the phosphonic group. However, some reactivity in **5c** still remains because the endo-side is open for the reagent.

Figure 2 also shows that in the endo monomethyl lactone **5b** the endo-side is obviously hindered, but the exo-side is free for the attack because the P=O bond can rotate to reach the highest possible distance from the reaction center because its rotation is not prevented by a methyl group.

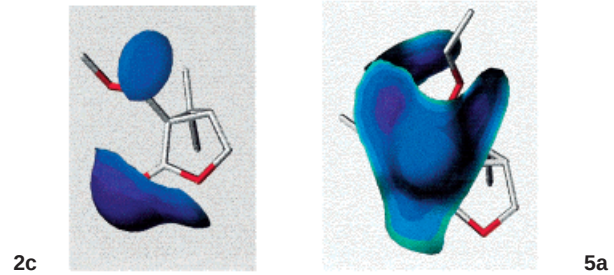


FIGURE 1 MEP for the dimethylcyclopropane carboxylic ester lactone **2c** and its phosphonic acid ester analogue **5a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com].

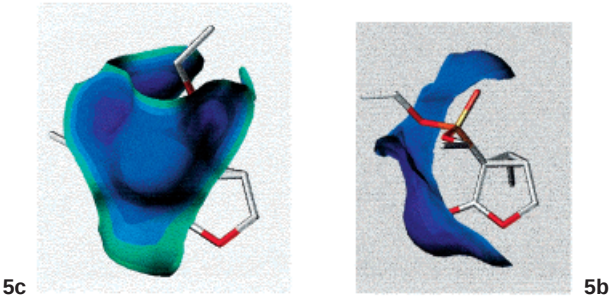


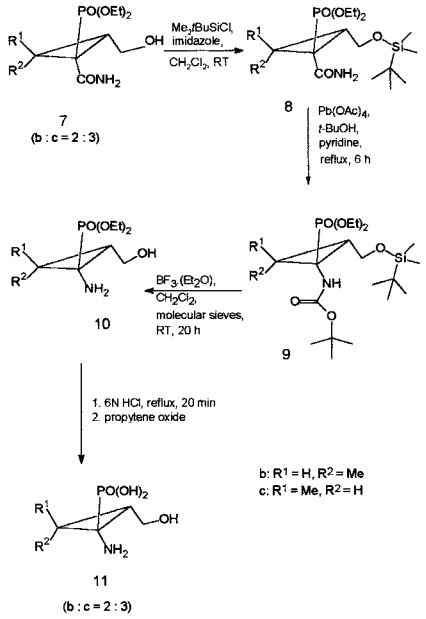
FIGURE 2 MEP for the monomethyl cyclopropanephosphonic ester lactone isomers **5c** and **5b**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com].

To obtain the phosphonic acid analogue **11** (ACP) of the aminocyclopropane carboxylic acid (ACC) the alcoholic OH group in **7** was protected by formation of a dimethyl *tert*-butylsilyl ether, and then a Hofmann rearrangement was performed by the action of lead tetraacetate in the presence of *tert*-butanol [12], resulting in the formation of the *tert*-butoxycarbonyl (BOC) protected aminocyclopropane phosphonate **9**. For the removal of the BOC group from **9**, the BF_3 etherate reagent proved to be the best [13], removing, at the same time, the silyloxy group from the alcoholic moiety to give **10** (Scheme 6).

Finally, the free 1-aminocyclopropane-1-phosphonic acid derivative **11** was obtained as a 2:3 mixture of **11** using standard acidic hydrolysis followed a propylene oxide treatment to remove the HCl contamination of the mixtures.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer FT-IR instrument. ^{1}H NMR and ^{13}C NMR spectra were taken by a Brucker WM-250 spectrometer, ^{31}P NMR spectra by a Brucker DRX-500 using tetramethylsi-



SCHEME 6

lane (^{1}H, ^{13}C) as internal standard and 85% H_3PO_4 (^{31}P) as external standard, all in $CDCl_3$ solution except as otherwise cited. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates with the eluent shown. Column chromatography was carried out on Merck Kieselgel 60 (60–200 mesh), with the same eluent. Mass spectra were obtained by use of a VG Quatro LC-MS Spectrometer (Fisons). Elemental analyses were performed on a Perkin Elmer 240 and Fisions EA 1108 automatic analyzer.

Minimum-energy conformations of **2c, 5a, 5b**, and **5c** were obtained by a systematic conformational analysis technique using the MM2 force field [14] within the SPARTAN package [15]. Minimum energy conformers were re-optimized by AM1 semiempirical calculations [16]. Electrostatic potential maps (MEP) were calculated from the AM1 wavefunction by use of SPARTAN. Isopotential representation of MEP maps (-10 kcal/mol) were calculated for the corresponding minimum energy conformation and displayed by the graphical interface of the SPARTAN package.

Ring Opening Experiments of Lactones **5**

*Diethyl 1α-Carboxamido-2α(and β)methyl-3α-hydroxymethyl-1-cyclopropyl phosphonate (***7b** *and* **7c***). Method A:* Lactone (**5b** and **5c**) (15 mmol, 3.3 g) and liquid ammonia (15 mL) was heated in a sealed tube at 60°C for 48 hours. After the sealed tube had been opened, the ammonia was allowed to evaporate, and the residue was submitted to column chromatography (eluent: toluene/methanol 8:2) to result in 2.03 g (yield 51%) **7b** and **7c** as 2:3 isomeric mixture (by NMR). Anal. calcd. for $C_{10}H_{20}NO_5P$: C, 45.28; H, 7.60. Found: C, 45.22; H, 7.55; MS *m/z* (%) 264: (M + 1, 2), 234 (100), 195 (44), 178 (28), IR (neat): ν = 3362 (vs, NH_2), 1668 (vs, CO), 1226 (vs, PO), 1021 (vs, POC), 974 (s, POEt) cm^{-1}; **7b** ^{1}H-NMR 1.19 (d, 3H, J_{HH} = 6.5 Hz, 2α-CH_3), 1.35 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.38 (t, 3H, J_{HH} = 6.8 Hz, CH_2CH_3), 1.65–1.80 (m 1H, 2β-H), 1.90–2.10 (m, 1H, 3β-H), 3.30–4.00 (m, 2H, 3α-CH_2), 4.15–4.32 (m, 4H, CH_2CH_3), 6.14 (b, 2H, NH_2), ^{13}C NMR 10.0 ($2\alpha CH_3$), 13.3 (C1), 16.7 (CH_2CH_3), 21.5 (C2, J_{PC} = 35 Hz), 29.4 (C3, J_{PC} = 71 Hz), 58.7 (CH_2CH_3), 61.5 ($3CH_2$), 169.1 (CO), ^{31}P NMR 26.4; **7c** ^{1}H NMR 1.35 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.38 (t, 3H, J_{HH} = 6.8 Hz, CH_2CH_3) 1.38 (d, 3H, J_{HH} = 7.0 Hz, 2β-CH_3), 1.82–1.87 (m 1H, 2α-H), 1.90–2.10 (m, 1H, 2β-H), 3.30–4.00 (m, 2H, 3α-CH_2), 4.15–4.32 (m, 4H, CH_2CH_3), 6.14 (b, 2H, NH_2), ^{13}C NMR 9.9 ($2\beta CH_3$), 13.3 (C1), 16.7 (CH_2CH_3), 21.5 (C2, J_{PC} = 35 Hz), 29.4 (C3, J_{PC} = 71 Hz), 58.7 (CH_2CH_3), 61.5 ($3CH_2$), 169.1 (CO), ^{31}P NMR 26.0.

Method B: A methanolic solution (85 mL) of the lactone **5b** and **5c** (30 mmol, 6.6 g) and 4-dimethylaminopyridine (1.5 mmol, 0.18 g) was saturated with dry ammonia gas. The solution was allowed to stand at room temperature, and the reaction was monitored by TLC. After consumption of the starting lactone (72 hours), the solvent and the remaining ammonia were evaporated under reduced pressure, and the residual oil was purified by column chromatography (eluent: toluene/methanol 8:2) to result in 6.5 g (yield 82%) **7b** and **7c** as a 2:3 isomeric mixture.

*Diethyl 1α-N-methylcarboxamido-2α(and β)methyl-3α-hydroxymethyl-1-cyclopropyl phosphonate (***7b′** *and* **7c′***). Method A:* A mixture of the lactone (**5b** and **5c**) (10 mmol, 2.48 g) and the absolute ethanolic solution of methylamine (24 mmol, 3 mL, 8M) was heated in a sealed tube at 70°C for 24 hours. After the sealed tube had been opened, the solvent and the unreacted methylamine were evaporated, and the remaining oil was purified by column chromatography (eluent: toluene/methanol 8:2) to result in 1.34 g (yield 48.0%) **7b′** and **7c′** as 2:3 isomeric mixture (by NMR). Anal calcd. for $C_{11}H_{22}NO_5P$: C, 47.31; H, 7.94; N, 5.02; P, 11.09. Found: C, 47.22; H, 8.00; N, 5.00; P, 11.21; MS *m/z* (%) 278: (M^+, 1.8), 248 (97), 236 (55), 209 (100), IR (neat): ν = 3376 (vs, NH_2), 1647 (vs, CO), 1228 (vs, PO), 1024 (vs, POC), 971 (s, POEt) cm^{-1}; **7b′** ^{1}H NMR 1.08 (d, 3H, J_{HH} = 7.5 Hz, CH_2CH_3), 1.23 (t, 3H, J_{HH} = 6.4 Hz, CH_2CH_3), 1.24 (t, 3H, J_{HH} = 7.0 Hz, 2α-CH_3) 1.70–1.80 (m 1H, 2β-H), 1.90–2.10 (m, 1H, 3β-H), 2.80 (d, 3H, J = 4.6 Hz, NCH_3), 3.41–4.00 (m, 2H, 3α-CH_2), 4.10–4.22 (m, 4H,

CH_2CH_3), 7.83 (b, 1H, NH), ^{31}P NMR 26.4; **7c′** ^{1}H NMR 1.23 (t, 3H, J_{HH} = 6.4 Hz, CH_2CH_3), 1.24 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3) 1.38 (d, 3H, J_{HH} = 7.5 Hz, 2β-CH_3), 1.70–1.80 (m 1H, 2α-H), 1.90–2.10 (m, 1H, 3β-H), 2.80 (d, 3H, J = 4.6 Hz, NCH_3), 3.41–4.00 (m, 2H, 3α-CH_2), 4.10–4.22 (m, 4H, CH_2CH_3), 7.83 (b, 1H, NH), ^{31}P NMR 26.0.

Method B: To the absolute ethanolic solution of methylamine (24 mmol, 3 mL, 8M), the lactones (**5b** and **5c**) (10 mmol, 2.48 g) and 4-dimethylaminopyridine (1 mmol, 0.12 g) were added, and the mixture was allowed to stand at room temperature for 72 hours. After evaporation of the volatile materials, the residue was purified by column chromatography (eluent: toluene/methanol 8:2) to result in 2.17 g (yield 77.7%) **7b′** and **7c′** as an exo/endo 3:2 isomeric mixture.

*6,6-Dimethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid ethyl ester ammonium salt (**6a**).* A mixture of the lactone **5a** (10 mmol, 2.62 g) and liquid ammonia (20 mL) was kept in a sealed tube at 60°C for 5 days. After the sealed tube had been opened, the remaining ammonia was evaporated, and then the residual oil was treated with 10 mL of methanol/diethyl ether 1:1 mixture to give 1.83 g (yield 73%) of a white crystalline product. **6a** m.p.: 188–191°C. Anal calcd. for $C_9H_{14}O_5P^*NH_4$: C, 43.03; H, 7.22; N, 5.58. Found: C, 42.95; H, 7.15; N, 5.50; MS *m/z* (%): 235 (80), 252 (M + 1, 100), 280 (M + 2 + NH_3, 28), IR ($CHCl_3$): ν = 3196 (vs, NH), 1755 (vs, CO), 1167 (vs, PO), 995 (vs, POC), 949 (s, POEt) cm^{-1}, ^{1}H NMR 1.17 (s, 3H, 6endo-CH_3), 1.24 (t, 3H, J_{HH} = 7.1 Hz, CH_2CH_3), 1.29 (t, 3H, J_{HH} = 7.2 Hz, CH_2CH_3), 1.48 (s, 3H, 6exo-CH_3), 2.45 (dd, 1H, J_{HH} = 6.0 Hz, J_{PH} = 10.0 Hz, 5-H), 3.90 (m, 4H, CH_2CH_3), 4.05–4.43 (m, 2H, C(4)H_2) 8.10 (b, 4H, NH_4), ^{31}P NMR 10.5.

*6,6-Dimethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid ethyl ester methylammonium salt (**6a′**).* A mixture of the lactone **5a** (10 mmol, 2.62 g) and the absolute ethanolic solution of methylamine (24 mmol, 3 mL, 8M) was heated in a sealed tube at 70°C for 40 hours. After the sealed tube had been opened, the solvent and the unreacted methylamine were evaporated. The residual oil was treated with 6 cm^3 of acetone to give 1.78 g (yield: 67.1%) of white crystals **6a′** m.p.: 152–155°C. Anal calcd. for $C_9H_{14}O_5P^*CH_3NH_3$: C, 45.28; H, 7.60; N, 5.28. Found: C, 45.15; H, 7.50; N, 5.20; MS *m/z* (%). 265: (M^+, 18), 252 (100), 235 (83), 32 (30), IR (KBr): ν = 2988 (vs, NH), 1751 (vs, CO), 1203 (vs, PO), 1053 (vs, POC), 949 (s, POEt) cm^{-1}, ^{1}H NMR 1.23 (s, 3H, 6endo-CH_3), 1.30 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.54 (s, 3H, 6exo-CH_3), 2.55 (s, 3H, NCH_3), 4.04 (dq, 2H, J_{HH} = 6.9 Hz, J_{PH} = 7.9 Hz, CH_2CH_3), 4.13 (dd, 1H, J_{AB} = 9.7 Hz, J_{HH} = 2.4 Hz, C(4)H_A), 4.45 (dd, 1H, J_{AB} = 9.7 Hz, J_{HH} = 5.4, C(4)H_B), 8.41 (b, 3H, NH_3), ^{13}C NMR 16.7 (CH_2CH_3), J_{PC} = 6 Hz), 21.7 (6αCH_3), 21.8 (C6), 24.7 (6βCH_3), 28.1 (C5, J_{PC} = 2 Hz), 35.8 (NCH_3), 36.1 (C1), 60.5 (CH_2CH_3), 65.5 (C4), 174.9 (C2), ^{31}P NMR 11.1.

Protection by Silylation

*Diethyl 1α-carboxamido-2α(and β)methyl-3α-(tert-butyldimethysilyloxy)methylcyclopropyl phosphonate (**8b** and **8c**).* The alcohol (**7b** and **7c**) (20 mmol, 5.3g) was dissolved in dry dichloromethane (200 mL), and *tert*-butyldimethylchlorosilane (22 mmol, 3.32 g) and imidazole (22 mmol, 0.18 g) were added. The mixture was stirred at room temperature for 48 hours under an argon atmosphere. The solution was washed with saturated aqueous sodium bicarbonate (2 × 100 mL) and brine 100 mL. The organic phase was dried with magnesium sulfate, filtered, and concentrated. The residue (7.36 g, yield 97.0%) can be purified by column chromatography (eluent: toluene-methanol 9:1), but can also be used for the next step without purification. Anal. calcd. for $C_{16}H_{34}NO_5PSi$: C, 50.64; H, 9.03; N, 3.69; P, 8.16. Found: C, 50.50; H, 8.95; N, 3.75; P, 8.10; IR (neat): ν = 3388 (vs, NH), 1661 (vs, CO), 1252 (vs, PO), 1033 (vs, POC), 969 (s, POEt) 837 (s, OSiMe) cm^{-1}; **8b** ^{1}H NMR 0.11 (s, 6H, $SiCH_3$), 0.84 (s, 9H, $C(CH_3)_3$), 1.20 (d, 3H, J_{HH} = 7.0 Hz, 2α-CH_3), 1.36 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.37 (t, 3H, J_{HH} = 6.5 Hz, CH_2CH_3), 1.60–1.64 (m 1H, 2β-H), 2.00–2.10 (m, 1H, 3β-H), 3.72–4.10 (m, 2H, 3α-CH_2), 4.15–4.33 (m, 4H, CH_2CH_3), 5.52–5.70 (m, 2H, NH_2), ^{31}P NMR 24.4; **8c** ^{1}H NMR 0.11 (s, 6H, $SiCH_3$), 0.84 (s, 9H, $C(CH_3)_3$), 1.36 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.37 (t, 3H, J_{HH} = 6.5 Hz, CH_2CH_3), 1.38 (d, 3H, J_{HH} = 6.5 Hz, 2β-CH_3), 1.75–1.98 (m 1H, 2α-H), 2.00–2.10 (m, 1H, 3β-H), 3.72–4.10 (m, 2H, 3α-CH_2), 4.15–4.33 (m, 4H, CH_2CH_3), 5.52–5.70 (m, 2H, NH_2), ^{31}P NMR 25.4.

Hofmann Degradation

*Diethyl 1α-tert-butoxycarbonylamido-2α(and β) methyl-3α-(tert-butyldimethylsilyloxy)-methylcyclopropyl phosphonate (**9b** and **9c**).* A mixture of the protected amide (**8b** and **8c**) (20 mmol, 7.58 g) and lead tetraacetate (30 mmol, 13.23 g) in anhydrous *tert*-butanol (180 mL) was heated rapidly to reflux and held there for 1.5 hours. After the reaction mixture had been allowed to cool, it was poured into toluene and washed twice with saturated potassium bicarbonate (2 × 200 mL), and once with brine (200

mL). The organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The residue (7.59 g, yield: 84.1%, **9b** and **9c** isomeric mixture) can be purified by column chromatography (eluent: toluene-methanol 9:1), but it is pure enough for the next step without purification. Anal. calcd. for $C_{20}H_{42}NO_6PSi$: C, 53.19; H, 9.37; N, 3.10; P, 6.86. Found: C, 53.08; H, 9.40; N, 3.00; P, 6.86; IR (neat): ν = 1726 (vs, CO), 1251 (vs, PO), 1028 (vs, POC), 970 (s, POEt) cm^{-1}; **9b** ^{1}H NMR 0.07 (s, 6H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.16 (d, 3H, J_{HH} = 6.1 Hz, 2α-CH_3) 1.32 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.36 (t, 3H, J_{HH} = 7.7 Hz, CH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 1.50–1.58 (m, 1H, 2β-H), 1.75–1.90 (m, 1H, 3β-H), 3.30–3.80 (m, 2H, 3β-CH_2), 4.00–4.25 (m, 4H, CH_2CH_3), 5.07 (b 1H, NH), ^{31}P NMR 25.6; **9c** ^{1}H NMR 0.07 (s, 6H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.32 (t, 3H, J_{HH} = 7.0 Hz, CH_2CH_3), 1.36 (t, 3H, J_{HH} = 7.7 Hz, CH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 1.48 (d, 3H J_{HH} = 6.3 Hz, 2β-CH_3), 1.50–1.58 (m, 1H, 2α-H), 1.75–1.90 (m, 1H, 3β-H), 3.30–3.80 (m, 2H, 3α-CH_2), 4.00–4.25 (m, 4H, CH_2CH_3), 5.07 (b, 1H, NH), ^{31}P NMR 24.5.

Deprotection

*1α-Amino-2α(and β)methyl-3α-hydroxymethyl-1-cyclopropylphosphonic acid diethyl ester (***10b** *and* **10c***).* To the vigorously stirred and ice cooled mixture of molecular sieves (4 Å) (8.5 g) and the N-BOC aminophosphonic acid ester (**9b** and **9c**) (10 mmol, 4.15 g) and dry dichloromethane (180 mL), borontrifluoride diethyletherate (50 mmol, 6.2 cm^3) in dichloromethane (60 mL) was added dropwise (30 minutes). Then, the reaction mixture was warmed to room temperature and allowed to stir under nitrogen for 2 days. The molecular sieves were removed by filtration and washed several times with dichloromethane. The filtrate was washed with saturated sodium bicarbonate (25 mL). The aqueous layer was extracted three times with dichloromethane. The combined organic fractions were dried over sodium sulfate and concentrated in vacuo. The remaining oil was purified by column chromatography (eluent: toluene-methanol 8:2) resulting in 1.5 g (yield 63.3%) of product **10b** and **10c** in a 2:3 isomeric mixture (by NMR). Anal. calcd. for $C_9H_{20}NO_4P$: C, 45.57; H, 8.50; N, 5.90; P, 13.06. Found: C, 45.45; H, 8.35; N, 5.90; P, 13.00; IR (neat): ν = 3385 (vs, NH), 1217 (vs, PO), 1024 (vs, POC), 967 (s, POEt) cm^{-1}; **10b** ^{1}H NMR 1.12 (d, 3H, J_{HH} = 6.4 Hz, 2α-CH_3), 1.34 (d, 3H, J_{HH} = 12.3 Hz, CH_2CH_3), 1.35 (d, 3H, J_{HH} = 12.3 Hz, CH_2CH_3), 1.40–1.48 (m, 1H, 2β-H), 1.50–1.65 (m, 1H, 3β-H), 2.52 (b, 2H, NH_2), 3.76–4.05 (m, 2H, 3α-CH_2), 4.13 (dq, 4H, J_{PH} = 9.5 Hz, CH_2CH_3), ^{13}C NMR 6.2 (C2), 16.5 (CH_2CH_3, J = 3.5 Hz), 18.9 (2α-CH_3), 23.3 (C3), 56.8 (C1), 59.3 (3α-CH_2), 62.1 and 62.2 (CH_2CH_3, J = 7 Hz), ^{31}P NMR 28.5; **10c** ^{1}H NMR 1.34 (d, 3H, J_{HH} = 12.3 Hz, CH_2CH_3), 1.35 (d, 3H, J_{HH} = 12.3 Hz, CH_2CH_3), 1.28–1.38 (m, 3H, 2β-CH_3), 1.29–1.38 (m, 1H, 2α-H), 1.40–1.48 (m, 1H, 3β-H), 2.52 (b, 2H, NH_2), 3.76–4.05 (m, 2H, 3α-CH_2), 4.13 (dq, 4H, J_{PH} = 9.5 Hz, CH_2CH_3), ^{13}C NMR 6.2 (C2), 13.2 (2β-CH_3), 16.5 (CH_2CH_3, J = 3.5 Hz), 23.3 (C3), 56.8 (CH_2CH_3), 59.3 (3α-CH_2), 61.8 and 62.0 (CH_2CH_3, J = 7 Hz), ^{31}P NMR 26.7.

Acidic Hydrolysis

*1α-Amino-2α(and β)methyl-3α-hydroxymethyl-1-cyclopropylphosphonic acid (***11b** *and* **11c***).* Phosphonic acid ester (**10b** and **10c**) (5 mmol, 1.18 g) was refluxed in 6N hydrochloric acid (70 mL) for 30 minutes. The mixture was concentrated at reduced pressure, and the residue was dissolved in a mixture of absolute ethanol (20 mL) and propylene oxide (1 mL) and was allowed to stand for several days. After evaporation of the volatile materials, the product was crystallized by adding a 5:1 mixture of ethanol:diethyl ether, and filtering off the solid to yield 0.74 g (yield 82.0%) white crystals (**11b** and **11c**). m.p.: 248°C. Anal. calcd. for $C_5H_{12}NO_4P$: C, 33.16; H, 6.68; N, 7.73; P, 17.10. Found: C, 33.10; H, 6.58; N, 7.90; P, 17.00; IR (KBr): ν = 3405 (vs, NH_2), 1215 (vs, PO) cm^{-1}; **11b** ^{1}H NMR (D_2O) 1.22 (d, 3H, J_{HH} = 7.1 Hz, 2α-CH_3), 1.28–1.35 (m, 1H, 2β-H), 1.50–1.60 (m, 1H, 3β-H), 3.65–4.00 (m, 2H, 3α-CH_2), 6.10 (b 2H, NH_2), ^{13}C NMR (D_2O) 12.7 (C2), 16.5 (2α-CH_3), 21.4 (C3), 58.6 (C1), 61.8 (3α-CH_2), ^{31}P NMR (D_2O) 14.5; **11c** ^{1}H NMR (D_2O) 1.25 (d, 3H, J_{HH} = 9.9 Hz, 2β-CH_3), 1.36–1.45 (m, 1H, 2α-H), 1.50–1.60 (m, 1H, 3β-H), 3.65–4.00 (m, 2H, 3α-CH_2), 6.10 (b 2H, NH_2), ^{13}C NMR (D_2O) 12.7 (C2), 16.0 (2β-CH_3), 21.4 (C3), 58.6 (C1), 61.8 (3α-CH_2), ^{31}P NMR (D_2O) 12.2.

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