Pergamon

Tetrahedron Letters 43 (2002) 4633–4636

TETRAHEDRON LETTERS

An efficient asymmetric synthesis of azetidine 2-phosphonic acids

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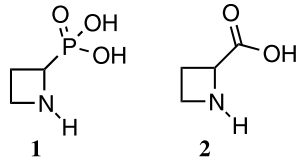
Received 11 April 2002; revised 2 May 2002; accepted 7 May 2002

Abstract—Substituted azetidinic 2-phosphonates were prepared in diastereoisomerically and enantiomerically pure form, starting from readily available β-amino alcohols. This synthesis involved a three-step sequence: (i) *N*-alkylation of the starting amino alcohol with a methylene phosphonate moiety, (ii) chlorination of the alcohol, and (iii) stereoselective 4-*exo*-*tet* ring closure through an intramolecular alkylation of the lithiated aminophosphonate.

α-Aminophosphonic acids are considered as mimics of the corresponding α-aminocarboxylic acid.[1] This resemblance explains the large range of biological activities displayed by the members of this class of compounds and the applications they have found in agriculture and medicine.[2] Consequently, development of efficient methodologies for the asymmetric synthesis of α-aminophosphonic acids is an active area of research and many methods are now available that provide acyclic α-aminophosphonic acids,[3] as well as phosphonic surrogates of proline[4] and pipecolic acid derivatives[5] in enantiomerically pure form. However, to our knowledge, the asymmetric synthesis of 4-membered azetidinic α-phosphonic acids has not been reported so far. Nevertheless, it is interesting to note that a synthesis of racemic **1**, the phosphonic analogue of azetidine 2-carboxylic acid **2** was published very recently.[6]



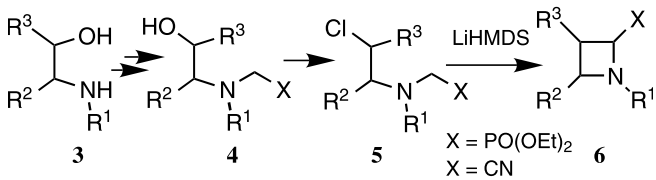
1 **2**

We describe in this Letter a straightforward preparation of enantiomerically pure azetidinic 2-phosphonic acids starting from readily available β-amino alcohols. The key step of this synthesis is based on a 4-*exo*-*tet* anionic alkylation of a lithiated α-aminophosphonate (**5**: X = $PO(OEt)_2$, Scheme 1); this strategy was successfully developed in our group for the preparation of 2-cyano azetidines (**6**, X = CN in Scheme 1).[7]

The required starting aminophosphonates **4** were prepared via a two-step sequence involving: (i) oxazolidine-formation in the presence of formaldehyde, and (ii) acid-catalysed ring opening of the oxazolidine followed by nucleophilic addition of triethyl phosphite.[8] Using this sequence, aminophosphonates **9**, **12**, **15** and **18** were prepared in good overall yields from, (*S*)-*N*-benzyl phenylglycinol **7**, (*S*)-*N*-benzyl phenylalaninol **10**, (1*R*,2*S*)-ephedrine **13** and (1*R*,2*R*)-*pseudo*ephedrine **16**, respectively (Scheme 2).

Chlorination of these amino phosphonates alcohols was effected by treatment with thionyl chloride in refluxing dichloromethane. As previously reported in the case of related amino nitriles,[7] compound **9** having a benzylic amine gave rearranged chloride **19** in good yield. On the other hand, ephedrin family-derived phosphonates **15** and **18** gave chlorides **20** and **21**. These compounds were produced with total retention of configuration at the hydroxylated stereocenter (Scheme 3). This was proved indirectly through determination of the relative configuration of the azetidines resulting from the cyclisation of these chlorides (vide infra).

As a matter of fact, this high stereoselectivity can be explained by the participation of the amine in the



3 **4** **5** **6**

Scheme 1.

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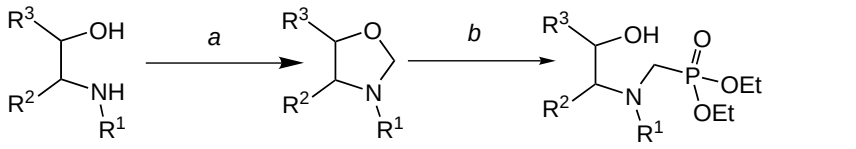
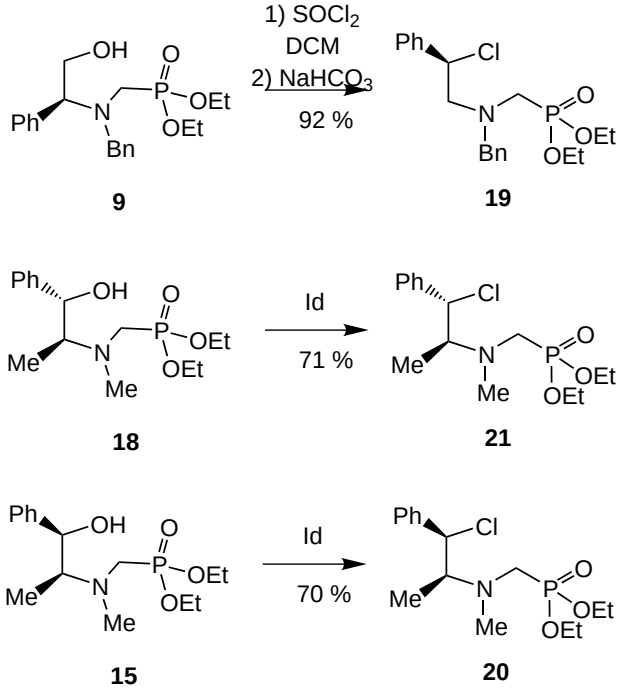
PII: S0040-4039(02)00868-7



R_1= Bn; R_2=Ph ; R_3=H	**7**	**8**	**9**	68
R_1= Bn; R_2=Bn ; R_3=H	**10**	**11**	**12**	68
R_1= Me; R_2=Me ; R_3=Ph	**13**	**14**	**15**	74
R_1= Me; R_2=Me ; R_3=Ph	**16**	**17**	**18**	78

Scheme 2. *Reagents and conditions*: (a) formaldehyde, toluene, reflux; (b) diethylphosphite, citric acid, EtOH, reflux.



Scheme 3.

substitution process through an aziridinium ion and the configuration in compound **19** (although not proven unequivocally) was attributed on the basis of this behaviour

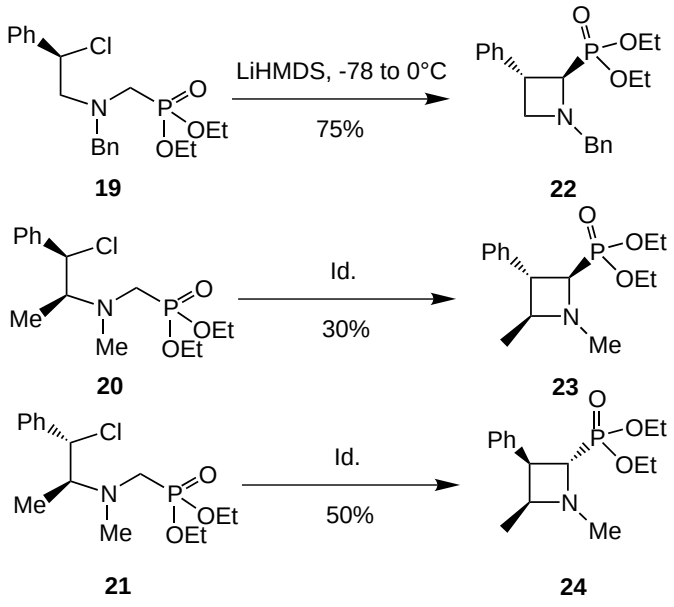
On the other hand, chlorination of amino phosphonate **12** derived from phenylalaninol was disappointing since in this case, an unseparable mixture of two compounds that could not be separated and characterized was obtained. This result is in contrast with the chlorination of the related amino nitrile[7] that cleanly gave the corresponding primary chloride.

The ring closure of chlorides **19**–**21** was next achieved by treatment with LiHMDS in THF at −78 to 0°C. In all cases, only the 1,3-*trans* isomer **22**–**24** could be isolated in this reaction, but the yield was highly dependent on the substitution pattern of the substrate (Scheme 4).

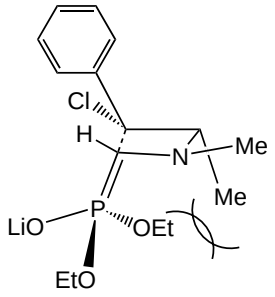
An S_N2 mechanism is probably operating during this ring closure. The relative configurations in the azetidines were assigned on the basis of NMR studies. For example, H_2, in compound **23** appears as a doublet of doublet at 3.23 ppm, with $^2J_{H2-H3}=8.6$ Hz and $^2J_{H2-P}=6.2$ Hz. The former coupling constant is in agreement with a *trans* relationship between the subtituents at C_2 and C_3, as checked after AM_1 minimisation of the conformation of **23**. Particularly relevant is the long range $^4J_{C-P}$ coupling constant of 5.9 Hz between the methyl substituent at C_4 and phosphorous atom in compound **23**. This coupling does not appear in diasteroisomer **24** and this observation set up unambiguously a *cis* relationship between the C_2 and C_4 substituents (W pattern between carbon and phosphorous) in **23**.[9] The yield of this reaction seems to be influenced by the steric demand in the transition state: phosphonate anions are known to have a sp^2 structure with a tetrahedral phosphorous,[10] the important size of the tetrahedral lithiated phosphorous moiety induces a severe steric interaction with the *cis* substituent of the azetidine ring in formation. This can explain the low yield obtained with substrate **20**, in which an interaction between the lithiated phosphoenolate and the C_4 methyl substituent is operating during the ring closure (Scheme 5).

The bulkiness of the lithiated phosphoenolate compared to an ester enolate and hence its beneficial effect with regard to 2,3-*trans* stereoselectivity during the ring closure is also put in light in the experiment described in Scheme 6. Indeed, when chloro ester **26**, prepared through alkylation of (*S*)-*N*-benzyl phenylglycinol **7** with ethyl bromoacetate followed by treatment with thionyl chloride, is deprotonated with LiHMDS in the presence of HMPA, the intramolecular alkylation now gives a mixture of *cis* and *trans* 2-carboethoxy azetidines **27** and **28** (de: 36%). Clearly, the steric interaction between the sp^2 ester enolate and the α phenyl substituent is less severe in this case.

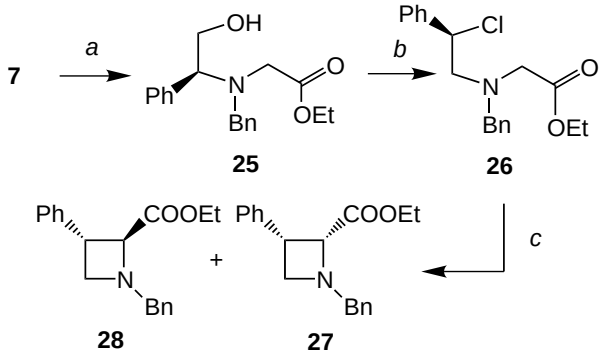
The enantiomeric purity of compound **22** had to be checked, since the rearrangement occurring during the transformation **9**→**19** might have proceeded with some extent of racemisation. To this end, *ent*-**22** was prepared from (*R*)-*N*-benzyl phenylglycinol *ent*-**9**. Examination of the ^{31}P NMR spectra of a mixture of enantiomers **22** in the presence of (*S*)-α-(trifluoromethyl)benzyl alcohol[11] showed an efficient separation of the ^{31}P signals for each enantiomers. This method allowed an accurate determination of the enan-



Scheme 4.



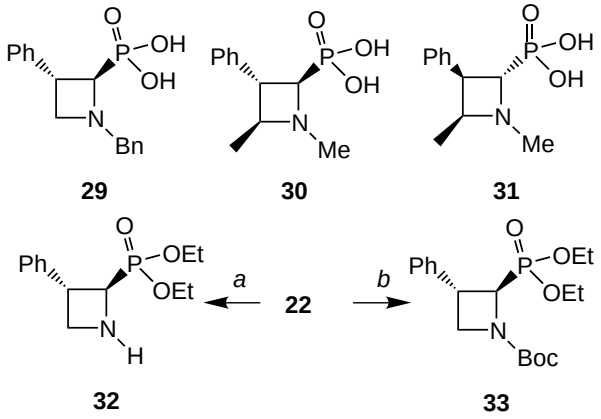
Scheme 5.



Scheme 6. *Reagents and conditions*: (a) ethyl bromoacetate, $NaHCO_3$, NaI, DMF, 86%; (b) $SOCl_2$, DCM, 58%; (c) LiHMDS, THF/HMPA, −78°C, 48%.

tiomeric excesses of **22** and *ent*-**22** and these compounds proved to be enantiomerically pure, within the precision of NMR (300 MHz).

Further chemical transformations of azetidinic phosphonate esters **22**–**24** were also studied. Hydrolysis of the phosphonate moiety was effected by treatment with bromotrimethylsilane in acetonitrile,[6] followed by purification by ion-exchange chromatography (Dowex 1X2), to give phosphonic acids **29**–**31** in, respectively, 86, 82 and 80% yields. Alternatively, aminophosphonate **22** could be *N*-debenzylated by hydrogenolysis to give amine **32**. When this hydrogenolysis was conducted in the presence of $(Boc)_2O$, *N*-Boc protected azetidine **33** was obtained (Scheme 7).



Scheme 7. *Reagents and conditions*: (a) EtOH, HCl, cat. $Pd(OH)_2$, H_2, 40%. (b) $(Boc)_2O$, AcOEt, H_2, cat. Pd/C, 60%.

In conclusion, we have reported the first asymmetric synthesis of azetidinic 2-phosphonic acids and derivatives[12] starting from readily available β-amino alcohols. Further studies are in progress in our group in order to delineate the scope of this cyclisation with other phosphorous-containing moieties.

Acknowledgements

The authors wish to thank Professor J. C. Cherton and Dr. M. J. Pouet for their help in the determination of enantiomeric purity of compound **22**.

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12. All new compounds gave ^{1}H, ^{13}C and ^{31}P NMR data in accordance with their structure. Selective data: Compound **15**: R_f: 0.2 (diethyl ether/petroleum ether), $[\alpha]_D^{20}$ +48 (*c* 0.5, $CHCl_3$). IR (film) 3380, 3063, 2991, 2925, 2873, 2786, 1496, 1455, 1214 (P=O), 1158 (P–O–C). ^{1}H NMR (250 MHz, $CDCl_3$): 0.8 (d, 3H, $J=6.8$ Hz), 1.19 and 1.20 (2 t, 6H, $J=7.1$ Hz), 2.35 (s, 3H), 2.72–2.81 (m, 1H), 2.73 (dd, 1H, $J=9.8$ and 15.8 Hz), 2.98 (dd, 1H, $J=11$ and 15.8 Hz), 3.90–4.02 (m, 4H), 4.16 (bs, 1H), 4.77 (d, 1H, $J=3.8$ Hz), 7.10–7.27 (m, 5H); ^{13}C NMR: 8.3, 16.3 (d, $J=5.7$ Hz), 41.8, 49.5 (d, $J=167.3$ Hz), 61.9 (t, $J=7.4$ Hz), 65.4 (d, $J=12$ Hz), 74.3, 125.9, 126.6, 127.7, 142.9; ^{31}P NMR (Ref: H_3PO_4): 27.9; anal. calcd for $C_{15}H_{26}NO_4P$: C, 57.13; H, 8.31; N, 4.44. Found: C, 57.42; H, 8.69; N, 4.07. Compound **19**: R_f: 0.5 (diethyl ether), $[\alpha]_D^{20}$ −33.5 (*c* 2.5, $CHCl_3$). IR (film) 3063, 3032, 2980, 2919, 2843, 1674, 1598, 1230 (P=O), 1050 (P–O–C), 728. ^{1}H NMR (250 MHz, $CDCl_3$): 1.17 and 1.19 (2 t, 6H, $J=7.1$ Hz), 2.86 (d, 2H, $J=9.6$ Hz), 3.21 (dd, 1H, $J=1.2$ and 13.3 Hz), 3.80 (dd, $J=1.5$ and 13.6 Hz), 3.85–4.04 (m, 4H), 4.92 (t, 1H, $J=7.1$ Hz), 7.11–7.26 (m, 10H); ^{13}C NMR: 16.5 (d, $J=6.3$ Hz), 49.4 (d, $J=154.7$ Hz), 60.2 (d, $J=3.9$ Hz), 61.1, 61.7 (t, $J=3.9$ Hz), 62.8 (d, $J=3.9$ Hz), 127.3, 127.6, 128.2, 128.4, 129.0, 138.2, 140.1; Anal. Calcd for $C_{20}H_{27}ClNO_3P$: C, 60.68; H, 6.87; N, 3.54. Found: C, 60.57; H, 6.98; N, 3.44. Compound **23**: R_f: 0.34 (ethyl acetate/ethanol: 98/2), $[\alpha]_D^{20}$ −62.9 (*c* 1.3, $CHCl_3$). IR (film) 3060, 3028, 2978, 1603, 1497, 1453, 1242 (P=O), 1026 (P–O–C);. ^{1}H NMR (250 MHz, $CDCl_3$): 0.74 (d, 3H, $J=6.5$ Hz), 1.20 (t, 3H, $J=7.1$ Hz), 1.25 (t, 3H, $J=7.1$ Hz), 2.35 (s, 3H), 3.86 (dd, 1H, $J=6.2$ and 5.8 Hz), 4.00–4.16 (m, 6H), 7.12–7.28 (m, 5H); ^{13}C NMR: 12.1, 16.7 (d, $J=5.9$ Hz), 37.3 (d, $J=5.9$ Hz), 41.3 (d, $J=3.9$ Hz), 61.7 (d, $J=5.9$), 62.2 (d, $J=5.9$ Hz), 62.5 (t, $J=135.9$ Hz), 63.6 (d, $J=45.3$ Hz), 126.7, 128.2, 128.3, 137.4; ^{31}P NMR (Ref: H_3PO_4): 26.2; anal. calcd for $C_{15}H_{24}NO_3P$: C, 60.59; H, 8.14; N, 4.71. Found: C, 60.43; H, 8.31; N, 4.60. Compound **29**: R_f: 0.22 (ethanol/30% NH_4OH/H_2O: 30/10/3), Mp: 223–229°C; $[\alpha]_D^{20}$ −2.5 (*c* 0.6, 1 M NaOH). ^{1}H NMR (250 MHz, CD_3OD): 3.89–3.99 (m, 1H), 4.09–4.22 (m, 1H), 4.24–4.34 (m, 1H), 4.30 (d, 1H, $J=12.1$ Hz), 4.34–4.44 (m, 1H); 4.55 (d, 1H, $J=13.2$ Hz), 7.17–7.35 (m, 5H), 7.46–7.56 (m, 2H), 7.65–7.73 (m, 2H); ^{13}C NMR: 39.0, 56.2 (d, $J=11.8$ Hz), 58.3, 71.4 (d, $J=137.8$ Hz), 128.0, 128.4, 129.7, 130.3, 130.7, 130.9, 140.1. HRMS: (MH^+) calcd 304.1103. Obs. 304.1107.