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Direct observation of aziridinium ions in a 2-(*N*,*N*-dibenzylamino)- to 1-(*N*,*N*-dibenzylamino)phosphonate rearrangement

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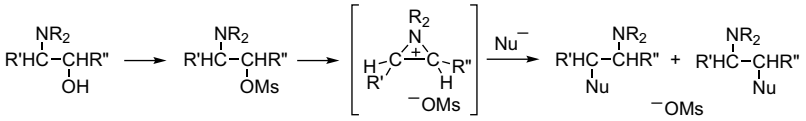
This paper is respectfully dedicated to Professor Maria Michalska

ABSTRACT

Aziridinium mesylates stable in the reaction medium for several hours to over a week were observed in a rearrangement of dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-mesyloxyethylphosphonates substituted at C2 with Bn, *i*-Pr and *t*-Bu to the respective 1-(*N*,*N*-dibenzylamino)-2-mesyloxyethylphosphonates. Rates of formation of these aziridinium mesylates and rates of their reactions with poorly nucleophilic mesylate anion were governed by steric and electronic factors. The conformation of (2*S*,3*S*)-1,1-dibenzyl-2-(*tert*-butyl)-3-(dimethoxyphosphoryl)aziridinium mesylate in solution was established based on ^{1}H and ^{13}C NMR spectroscopic studies including a NOESY experiment.

1. Introduction

It is well established that in reactions of amines substituted at the β-position with good leaving groups aziridinium ions are formed as reactive intermediates (neighbouring group participation).[1] For chiral compounds the ring closure leading to aziridinium ions and their further transformations require S_N2-like displacements. The involvement of aziridinium ions has also been supported by kinetic studies.[2–6] Numerous aziridinium salts, e.g., perchlorates,[3,5,7–19] tetrafluoroborates,[15,20–23] tetraphenylborate,[24] triflates,[3,24–29] mesylates[30,31] and even iodides[3,4,13,29] or bromides[30,31] have been isolated and characterised by ^{1}H,[3–5,7,8,13–19,23,25–28,30–37] ^{13}C[7,10,25–27,33] and ^{19}F[22] NMR spectroscopy, and for some crystal structures were obtained.[24,34,38,39] Most of them are fairly stable solids mostly due to the presence of non-nucleophilic or poorly nucleophilic counter ions. However, under standard conditions of mesylation of 2-aminoalcohols **1** the intermediate aziridinium mesylates **3** appeared too reactive and, to the best of our knowledge, they have never been detected in the presence of the respective mesylates **2** and/or products of the nucleophilic substitution **4a** and/or **4b** (Scheme 1). In this paper we wish to show that direct observation of fairly stable aziridinium ions is possible in a 2-(*N*,*N*-dibenzylamino)- to 1-(*N*,*N*-dibenzylamino)phosphonate rearrangement.[40]



Scheme 1.

2. Results and discussion

2.1. Stability of aziridinium mesylates

Dimethyl (1*R**,2*S**)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-2-phenylethylphosphonate (1*R**,2*S**)-**5a**[41] was treated with mesyl anhydride in the presence of triethylamine in toluene at 0 °C for 30 min. After washing ammonium salts with cold water, the toluene solution was concentrated at room temperature and the residue was monitored by ^{1}H and ^{31}P NMR spectroscopy as a chloroform-*d* solution. As judged from ^{31}P NMR spectra after 80 min the reaction mixture was composed of 1-*O*-mesylate (1*R**,2*S**)-**6a**[40] (88%) and 2-*O*-mesylate (1*S**,2*R**)-**8a**[40] (12%) (Scheme 2). The amount of 2-*O*-

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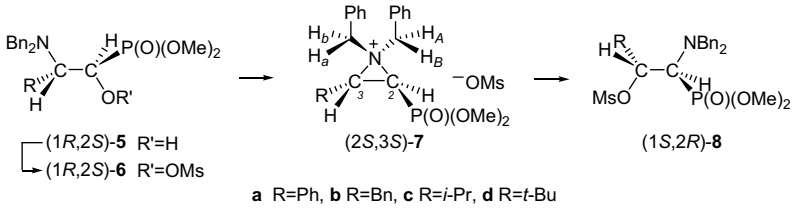


Scheme 2. A 1-*O*-mesylate (1*R*,2*S*)-**6a**–**d** to 2-*O*-mesylate (1*S*,2*R*)-**8a**–**d** rearrangement.

Table 1
The ^{31}P NMR monitoring of a 1-*O*-mesylate (1*R*,2*S*)-**6c** to 2-*O*-mesylate (1*S*,2*R*)-**8c** rearrangement

Compound	Reaction time [h]					
	1.25	1.83	2.83	3.83	4.83	24
(1*R*,2*S*)-**6b**	76%	52%	23%	12%	0%	0%
(2*S*,3*S*)-**7b**	9%	11%	7%	3%	1%	1%
(1*S*,2*R*)-**8b**	15%	37%	70%	85%	99%	99%

mesylate (1*S**,2*R**)-**8a** increased to 46.5, 64 and 73% after 140, 200 and 260 min, respectively. The rearrangement was practically complete after 24 h, since only traces of 1-*O*-mesylate (1*R**,2*S**)-**6a** could be detected in ^{1}H and ^{31}P NMR spectra. Detailed inspection of the ^{1}H NMR spectrum showed that the reaction mixture also contained some triethylammonium mesylate and toluene, which could not be completely removed during work-up. However, no other signals could be detected in the ^{1}H and ^{31}P NMR spectra.

When dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate (1*R*,2*S*)-**5b** (δ ^{31}P 27.34 ppm) was subjected to our standard mesylation procedure (vide supra), ^{1}H and ^{31}P NMR spectra recorded 75 min after addition of mesyl anhydride was complete clearly showed the formation of three species: 1-*O*-mesylate (1*R*,2*S*)-**6b** (δ ^{31}P 21.74 ppm), 2-*O*-mesylate (1*S*,2*R*)-**8b** (δ ^{31}P 26.18 ppm) and the aziridinium mesylate (2*S*,3*S*)-**7b** (δ ^{31}P 13.97 ppm) (Scheme 2). The progress of the reaction was monitored by ^{1}H and ^{31}P NMR spectroscopy (Table 1). The maximum concentration of the aziridinium mesylate (2*S*,3*S*)-**7b** (ca. 11%) was reached after ca. 2 h. The 1-*O*-mesylate (1*R*,2*S*)-**6b** to 2-*O*-mesylate (1*S*,2*R*)-**8b** transformation was complete in about 5 h leading to a 99:1 equilibrium mixture of 2-*O*-mesylate (1*S*,2*R*)-**8b** and the aziridinium mesylate (2*S*,3*S*)-**7b**, as concluded from the ^{1}H and ^{31}P NMR spectra taken 24 and 48 h after addition.

After 65 min the reaction mixture obtained by our standard mesylation of dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-methylbutylphosphonate (1*R*,2*S*)-**5c**[42] (δ ^{31}P 26.89 ppm) consisted of 2-*O*-mesylate (1*S*,2*R*)-**8c** (δ ^{31}P 29.59 ppm—35%) and the aziridinium mesylate (2*S*,3*S*)-**7c** (δ ^{31}P 14.56 ppm—65%) only. The amount of 2-*O*-mesylate (1*S*,2*R*)-**8c** grew up at the expense of the aziridinium mesylate (2*S*,3*S*)-**7c** to reach an 85:15 equilibrium mixture of (1*S*,2*R*)-**8c** and (2*S*,3*S*)-**7c** within 24 h. In order to detect 1-*O*-mesylate (1*R*,2*S*)-**6c** the mesylation was directly performed in the NMR tube. Thus, when a solution of phosphonate (1*R*,2*S*)-**5c** in chloroform-*d* was treated with mesyl anhydride in the presence of triethylamine and catalytic DMAP at room temperature, mesylation of the hydroxy group occurred immediately. In the ^{1}H NMR spectrum taken after 7 min doublets of C*H*$_3$CC*H*$_3$ at 0.98 and 1.23 ppm characteristic of (1*R*,2*S*)-**5c** completely disappeared, while two new sets of C*H*$_3$CC*H*$_3$ resonances at 0.89 and 1.09 ppm [(1*R*,2*S*)-**6c**—30%] and at 0.79 and 1.24 ppm [aziridinium mesylate (2*S*,3*S*)-**7c**—70%] emerged. In the ^{31}P NMR spectrum taken 3 min later the 1-*O*-mesylate (1*R*,2*S*)-**6c** (δ ^{31}P 23.04 ppm) to the aziridinium mesylate (2*S*,3*S*)-**7c** (δ ^{31}P 14.56 ppm) ratio changed to 12:88 but a signal of 2-*O*-mesylate (1*S*,2*R*)-**8c** was not yet present. The ^{1}H and ^{31}P NMR monitoring of the reaction mixture (Fig. 1) showed that the

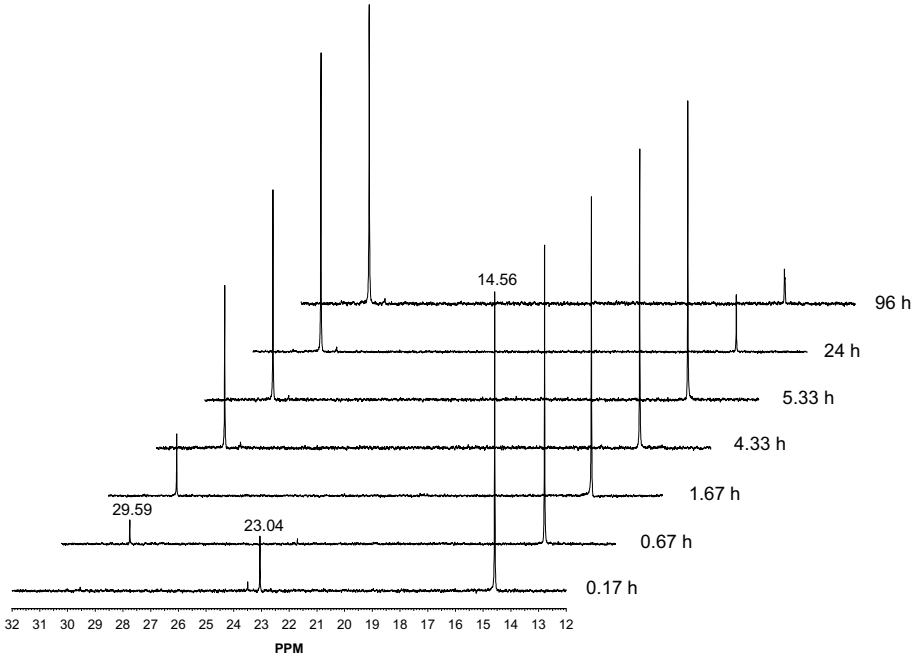


Figure 1. The ^{31}P NMR monitoring of a 1-*O*-mesylate (1*R*,2*S*)-**6c** to 2-*O*-mesylate (1*S*,2*R*)-**8c** rearrangement.

maximum concentration of the aziridinium mesylate (2*S*,3*S*)-**7c** (ca. 93%) was observed within 40 min and, as noticed above, an 84:16 equilibrium mixture of (1*S*,2*R*)-**8c** and (2*S*,3*S*)-**7c** was obtained after 24 h.

Taking into account the structural features of the aziridinium mesylates **7b** and **7c** we hypothesised that their stability may depend on the bulkiness of substituents R in the starting 1-*O*-mesylates **6**. To test this assumption dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3,3-dimethylbutylphosphonate (1*R*,2*S*)-**5d** was synthesised (vide infra). While application of our standard procedure of mesylation in toluene (followed by an aqueous wash-up) to phosphonate (1*R*,2*S*)-**5d** led to the formation of complex mixture containing traces of the aziridinium mesylate (2*S*,3*S*)-**7d** due to its poor solubility in the reaction medium, the direct mesylation of phosphonate (1*R*,2*S*)-**5d** in a chloroform-*d* solution performed in the NMR tube was successful. Within 15 min the amount of the aziridinium mesylate (2*S*,3*S*)-**7d** reached 95%, and the 1-*O*-mesylate (1*R*,2*S*)-**6d** was the second phosphonate found in the reaction mixture. The maximum quantity (99%) of (2*S*,3*S*)-**7d** was noticed after ca. 1 h, but now 2-*O*-mesylate (1*S*,2*R*)-**8d** was detected as the other phosphonate present. The transformation of the aziridinium mesylate (2*S*,3*S*)-**7d** into the 2-*O*-mesylate (1*S*,2*R*)-**8d** was slow and, unfortunately, decomposition products were produced on prolonged (1 week) observation. Thus, after 24 h almost 51% of the 2-*O*-mesylate, 44% of the aziridinium mesylate and 5% of an unidentified phosphonate (δ^{31}P 10.9 ppm) were found in the reaction mixture. The amount of 2-*O*-mesylate (1*S*,2*R*)-**8d** reached 80% after 6 days at room temperature, but due to the formation of several unidentified phosphonates we were unable to establish the equilibrium ratio of the aziridinium mesylate (2*S*,3*S*)-**7d** to 2-*O*-mesylate (1*S*,2*R*)-**8d**.

2.2. Structure of aziridinium mesylates

To prove that the aziridinium mesylates (2*S*,3*S*)-**7b**–**d** have been formed, their ^{1}H and ^{13}C NMR spectroscopic data were compared with those of the starting phosphonates (1*R*,2*S*)-**5b**–**d**, their mesylates (1*R*,2*S*)-**6b**–**d** and the respective 2-*O*-mesylates (1*S*,2*R*)-**8b**–**d**. It appeared that spectral patterns for *H*–C–C(P)–*H*, H_2C–N–CH_2 and aromatic protons are identical for the aziridinium mesylates (2*S*,3*S*)-**7b**–**d**, the only difference being the separation of the multiplets. Since the best separation was observed in the ^{1}H NMR spectrum of (2*S*,3*S*)-**7c**, we will limit our considerations to this case. After mesylation of HO–C1 in phosphonate (1*R*,2*S*)-**5c** the signal of *H*–C1 was significantly shifted downfield from 4.10 ppm in the starting material to 5.50 ppm in the 1-*O*-mesylate (1*R*,2*S*)-**6c** due to the inductive effect of the methylsulfonyloxy group. Further downfield shift is expected, when this group is replaced by the positively charged ammonium residue. However, this effect is partially compensated by the well recognised tendency for all protons connected to three-membered rings to be shifted upfield and for this reason *H*–C1 in the aziridinium mesylate (2*S*,3*S*)-**7c** resonates at 5.60 ppm, still demonstrating the close vicinity of a very strong electron-withdrawing group. In the 2-*O*-mesylate (1*S*,2*R*)-**8c** *H*–C1 resonates at 3.28 ppm in agreement with previous observations for the structurally related 1-(*N*,*N*-dibenzyl)alkylphosphonates.[40] A small downfield shift ($\Delta\delta$=0.14 ppm) observed for *H*–C2 in the mesylate (1*R*,2*S*)-**6c** (δ 2.96 ppm) in comparison with phosphonate (1*R*,2*S*)-**5c** reflects the presence of the mesyloxy group at C1. As expected, in the aziridinium mesylate (2*S*,3*S*)-**7c** *H*–C2 is further shifted downfield (to 3.42 ppm) to accommodate two already mentioned factors. In the acyclic mesylate (1*S*,2*R*)-**8c** *H*–C2 resonates in low field (δ=4.80 ppm) clearly showing only the contribution from the electronegative mesyloxy group.

The most diagnostic feature found in the ^{13}C NMR spectra of the aziridinium mesylates (2*S*,3*S*)-**7b**–**d** is the large upfield shift of *C*–P to the 47–49 ppm region proving the incorporation of this atom into a three-membered ring and a significant increase in the one-bond C–P coupling to 173–178 Hz, when compared with the same parameters of the 1-*O*-mesylate (1*R*,2*S*)-**6b** (δ_{C-P} 74.43 ppm, $^1J_{C-P}$= 160.3 Hz).

Stereoheterotopic relationships have been successfully applied in many cases to solve structural problems in organic chemistry.[43] As expected, diastereotopicity of the H_a and H_b protons in the H_aCH_b–N–H_aCH_b fragments in phosphonate (1*R*,2*S*)-**5c**, its mesylate (1*R*,2*S*)-**6c** and the 2-*O*-mesylate (1*S*,2*R*)-**8c** was demonstrated by the observation of two different chemical shifts for these protons. However, in the aziridinium mesylate (2*S*,3*S*)-**7c** protons in the CH_2–N^+–CH_2 fragment become heterotopic and for this reason they are expected to resonate at four different fields. This was found to be the case in the ^{1}H NMR spectrum of the aziridinium mesylate (2*S*,3*S*)-**7c**. Furthermore, due to the inductive effect of the positively charged N atom, signals of the heterotopic CH_2–N^+–CH_2 protons in (2*S*,3*S*)-**7c** are significantly ($\Delta\delta$=0.4–1.2 ppm) shifted downfield in comparison to those in CH_2–N–CH_2 fragments in (1*R*,2*S*)-**5c**, (1*R*,2*S*)-**6c** and (1*S*,2*R*)-**8c**. Another argument for the intermediacy of aziridinium ion came from the ^{13}C NMR spectra, in which for heterotopic carbons of the *C*–N^+–*C* moiety two resonances were observed for all aziridinium mesylates (2*S*,3*S*)-**7b**–**d**. Furthermore, eight well-separated resonances for heterotopic carbons of two phenyl groups were found in the ^{13}C NMR spectra of the aziridinium mesylates (2*S*,3*S*)-**7c**–**d**.

Because the aziridinium mesylate (2*S*,3*S*)-**7d** appeared to be the most abundant in the reaction mixtures obtained after mesylation of hydroxyphosphonates (1*R*,2*S*)-**5a**–**d** and the slowest in decay, it was subjected to detailed ^{1}H NMR studies including a NOESY spectrum at 700 MHz in order to gather information on spatial arrangement of two phenyl groups. To identify H_R–C_S–H_S and C_6H_5–C_S–N resonances NOESY correlations of *H*–CP (δ 5.26 ppm) were first investigated. Besides the expected interactions with $(CH_3)_3$C (δ 1.12 ppm), the other important findings include the observation of NOESY signals with a doublet at δ 7.66 ppm (*ortho* protons) and with a doublet at δ 4.74 ppm but the appropriate signal was not found for a doublet of doublets at δ 4.40 ppm (H_2C_S–N). Furthermore, since a doublet at δ 4.74 ppm correlates with a doublet at δ 7.66 ppm (weak) and with $(CH_3)_3$C (strong), while a doublet of doublets at δ 4.40 ppm correlates also with a doublet at δ 7.66 ppm (strong) and with $(CH_3)_3$C (medium), one can conclude that H_R–C_S–N resonates at δ 4.74 ppm and H_S–C_S–N appears at δ 4.40 ppm. This assignment is further supported by the observation of a four-bond H–P coupling, since the required W-arrangement of coupled nuclei can only be achieved within the H_S–C_SNC–P moiety. It is very important to notice lack of a NOESY correlation signal between resonances of *ortho* protons in C_6H_5–C_S–N and $(CH_3)_3$C. Taking into account all these observations we suggest that the phenyl ring connected to C_S–N is located as far away as possible from the *tert*-butyl group (Fig. 2).

Identification of H_R–C_R–H_S and C_6H_5–C_R–N resonances was also accomplished by analysis of NOESY correlations. Thus, a doublet at δ 7.35 ppm comes from the *ortho* protons of C_6H_5–C_R–N, because they correlate with $(CH_3)_3$C (δ 1.12 ppm), *H*–CCP (δ 3.57 ppm) and both H_2C_R–N (δ 4.46 and 4.39 ppm) but a doublet of doublets at

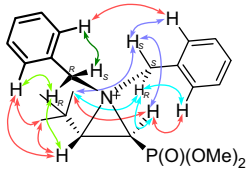
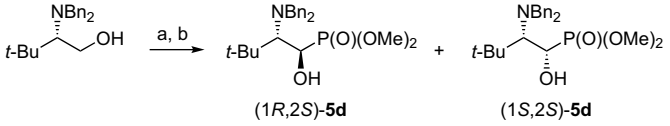


Figure 2. The most important NOESY correlations observed for (2*S*,3*S*)-**7d**.

δ 3.57 ppm (*H*–CCP) gave a NOESY correlation with a doublet at δ 4.46 only. This observation allows us to assign chemical shifts of δ 4.46 and 4.39 ppm to H_R–C_R and H_S–C_R, respectively. Under these circumstances one can suggest that the phenyl ring connected to C_R–N is located as far away as possible from the diethoxyphosphoryl group (Fig. 2). Two phenyl rings are not that far away in space, because both *ortho* protons (δ 7.66 and 7.35 ppm) display a weak NOESY correlation. Downfield shifts of the *ortho* and also *meta* protons of C_6H_5–C_S–N (δ 7.66 and 7.51 ppm) as well as of H_R–C_S–N (δ 4.74 ppm) in comparison with the respective resonances of the *ortho* protons in C_6H_5–C_R–N (δ 7.35 ppm) and of H_S–C_S–N (δ 4.40 ppm) as well as H_R–C_R–H_S (δ 4.46 and 4.39 ppm) can be attributed to deshielding effect of the P═O group.

2.3. Synthesis of starting materials

Dimethyl (1*R**,2*S**)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-2-phenylethylphosphonate (1*R**,2*S**)-**5a** and dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-methylbutylphosphonate (1*R*,2*S*)-**5c** were obtained as described in the literature.[41,42] To synthesise dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-phenylpropylphosphonates (1*R*,2*S*)-**5b** the procedure already described[42] for the diethyl ester was applied to give a 85:15 mixture of (1*R*,2*S*)- and (1*S*,2*S*)-**5b**, from which the major phosphonate was isolated chromatographically followed by repeated crystallisation of appropriate fractions. In a similar fashion phosphonylation of *N*,*N*-dibenzyl-L-*tert*-leucinal[44] (Scheme 3) led to the formation of an 83:17 mixture of dimethyl (1*R*,2*S*)- and (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3,3-dimethylbutylphosphonate (1*R*,2*S*)- and (1*S*,2*S*)-**5d**. The required phosphonate (1*R*,2*S*)-**5d** was then separated by column chromatography.



(1*R*,2*S*)-**5d** (1*S*,2*S*)-**5d**

Scheme 3. Reagents and conditions: (a) Swern oxidation; (b) $(MeO)_2P(O)H$, NEt_3.

3. Conclusions

Aziridinium mesylates observable for several hours to over a week were detected in a 2-(*N*,*N*-dibenzylamino)- to 1-(*N*,*N*-dibenzylamino)phosphonate rearrangement, which was studied on 2-substituted (R═Ph, Bn, *i*-Pr, *t*-Bu) 2-(*N*,*N*-dibenzylamino)-1-mesyloxyethylphosphonates **6a**–**d**. The rates of formation of the respective aziridinium mesylates **7a**–**d** and their reactions with poorly nucleophilic mesylate anion were governed by steric and electronic factors. Thus, the aziridinium mesylate **7a** was not observed because nucleophilic substitutions at benzylic carbon are much faster than those at non-activated carbon atoms.

In this case the rate of formation of the aziridinium mesylate is the rate-determining step in a two-step consecutive reactions, which can be followed (ca. 10 h) at room temperature by the ^{31}P NMR spectroscopy as a decay in the concentration of the 1-*O*-mesylate **6a**.

When the bulkiness of the substituents attached to *C*–C–P is being increased (Bn, *i*-Pr, *t*-Bu) two phenomena have been noticed. Transformation of the 1-*O*-mesylates **6b**–**d** into the respective aziridinium mesylates **7b**–**d** is significantly accelerated, and nucleophilic ring opening by the mesylate anion is dramatically slowed down. Although the decrease in concentration of the 1-*O*-mesylate **6b** (R═Bn) can still be monitored by the ^{31}P NMR spectroscopy (ca. 5 h), the presence of the 1-*O*-mesylate **6d** (R═*t*-Bu) can only be detected by ^{31}P NMR in the first 15 min of the experiment. The relief in intramolecular interactions of very bulky groups (*N*,*N*-dibenzylamino with benzyl, isopropyl or *tert*-butyl) during the formation of the aziridinium mesylates **7b**–**d** seems to be responsible for the observed acceleration. Our NMR spectroscopic studies (vide supra) on the structure of the aziridinium mesylates **7b**–**d** fully support this conclusion.

The ring opening of the aziridinium mesylates **7b**–**d** with the mesylate anion is purely governed by steric factors. Substitution at the secondary centre flanked by the benzyl group is fairly fast (ca. 5 h), and the reaction at the secondary carbon substituted with isopropyl is rather slow (ca. 1 day), but when *tert*-butyl is attached to the secondary centre (neopentyl-like position) the substitution is extremely slow (incomplete in one week).

4. Experimental

4.1. General

^1H NMR spectra were taken in $CDCl_3$ on the following spectrometers: Bruker Avance II Plus (700 MHz) and Varian Mercury-300 with TMS as an internal standard. ^{13}C and ^{31}P NMR spectra were recorded for $CDCl_3$ solutions on Bruker Avance II Plus (700 MHz) spectrometer at 176.2 and 283.5 MHz, or a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. $^1H\{^{31}P\}$ NMR, ^1H–^1H COSY and NOESY experiments were applied to support spectral assignments. The spectral data of the 1-*O*-mesylates **6b**–**d**, the aziridinium mesylates **7b**–**d** and the 2-*O*-mesylates **8b**–**d** were extracted from ^1H, ^{13}C and ^{31}P NMR spectra of the reaction mixtures. For this reason in some cases it was not possible to collect a complete set of data due to too low concentration of very reactive compounds or superimposition of multiplets.

IR spectra were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on Perkin–Elmer PE 2400 CHNS analyser. Polarimetric measurements were conducted on an Optical Activity PolAAr 3001 apparatus.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}.

4.2. Dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate (1*R*,2*S*)-5b

A mixture of a crude (*S*)-*N*,*N*-dibenzylphenylalaninal [obtained after Swern oxidation of (*S*)-*N*,*N*-dibenzylphenylalaninol (2.32 g, 7.00 mmol)], dimethyl phosphite (0.900 mL, 7.00 mmol) and triethylamine (0.097 mL, 0.70 mmol) was left at room temperature for 20 h. The residue was twice chromatographed on a silica gel column; first with chloroform–methanol (100:1, v/v) and later with ethyl acetate–hexanes (2:1, v/v). The appropriate fractions were combined to give phosphonate (1*R*,2*S*)-**5b** (0.730 g, 24%) as an amorphous solid, which was recrystallised from ethyl acetate to afford (1*R*,2*S*)-**5b** (0.280 g, 9%) as small white needles. Mp 135–135 °C. $[\alpha]_D^{20}$ +32.0 (*c* 0.9, $CHCl_3$). IR (KBr) ν=3426, 3244, 2950, 1452, 1220, 1037, 835, 748, 691 cm^{-1}. ^1H NMR ($CDCl_3$) δ=7.29–7.06 (m, 15H), 4.38 (ddd, J_{H1-P}=9.6 Hz, J_{H1-HO}=7.8 Hz, J_{H1-H2}=1.8 Hz, 1H, *H*CP), 3.92 (br s, 1H, OH), 3.86 (d, *J*=14.1 Hz, 2H, Ph*H*CHN), 3.73 and 3.69 (2×d, *J*=10.5 Hz, 6H, CH_3OPOCH_3), 3.59 (d, *J*=14.1 Hz, 2H, PhHC*H*N), 3.34 (dddd, J_{H2-P}=14.9 Hz, J_{H2-H3b}=J_{H2-H3a}=7.1 Hz, J_{H2-H1}=1.8 Hz, 1H, *H*CCP), 3.09 (d, $J_{H3a,b-H2}$=7.1 Hz, 2H, PhH_aCH_bCCP). ^{13}C NMR ($CDCl_3$) δ=140.08, 139.46, 129.76, 128.86, 128.17, 128.14, 126.89, 126.01, 66.03 (d, *J*=154.0 Hz, C1), 60.13 (d, *J*=5.7 Hz, C2), 54.51 (s, $PhCH_2N$), 53.71 and 53.13 (2×d, *J*=7.3 Hz, CH_3OPOCH_3), 32.34 (s, C3). ^{31}P NMR ($CDCl_3$) δ=27.34. Anal. Calcd for

$C_{25}H_{30}NO_4P$: C, 68.32; H, 6.88; N, 3.19. Found: C, 68.09; H, 6.93; N, 3.33.

4.3. Dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3,3-dimethylbutylphosphonate (1*R*,2*S*)-5d

A mixture of a crude (*S*)-*N*,*N*-dibenzyl-L-*tert*-leucinal [obtained after Swern oxidation of (*S*)-*N*,*N*-dibenzyl-L-*tert*-leucinol[45] (0.530 g, 1.78 mmol)], dimethyl phosphite (0.163 mL, 1.78 mmol) and triethylamine (0.073 mL, 0.53 mmol) was left at room temperature for 60 h. The residue was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v), the appropriate fractions were collected and recrystallised from chloroform–diethyl ether to give phosphonate (1*R*,2*S*)-**5d** (0.327 g, 45%) as colourless needles. Mp 133–134 °C. $[\alpha]_D^{20}$ −27.8 (*c* 1.0, $CHCl_3$). IR (KBr) ν=3232, 2956, 1494, 1453, 1222, 1058, 1017, 745, 701 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.40–7.20 (m, 10H), 4.56 (dd, $^2J_{H-P}$=17.7 Hz, J_{H1-HO}=7.2 Hz, 1H, *H*CP), 4.30–3.75 (vbr s, 2H, Ph*H*CHN), 3.86 and 3.81 (2×d, *J*=10.2 Hz, 6H, CH_3OPOCH_3), 3.45 (br d, *J*=13.0 Hz, 2H, PhHC*H*N), 2.94 (d, $^3J_{H2-P}$=12.6 Hz, 1H, *H*CCP), 2.45 (dd, J_{P-HO}=8.1 Hz, J_{H1-HO}=7.2 Hz, 1H, HO), 1.00 [s, 9H, (CH_3)$_3$C]. ^{13}C NMR ($CDCl_3$) δ=139.67 (br s), 129.48 (br s), 128.16, 127.02, 68.43 (d, $^1J_{CP}$=150.9 Hz, C1), 64.81 (d, *J*=6.0 Hz, C2) 56.96 (br s, PhCH_2N), 53.56 and 53.37 (2×d, *J*=7.5 Hz, CH_3OPOCH_3), 36.99 (C3), 29.56. ^{31}P NMR ($CDCl_3$) δ=28.28. Anal. Calcd for $C_{22}H_{32}NO_4P$: C, 65.17; H, 7.95; N, 3.45. Found: C, 65.34; H, 7.87; N, 3.45.

4.4. Mesylation of 1-hydroxyphosphonates (general procedures)

4.4.1. In a toluene solution

To a solution of 1-hydroxyphosphonate **5b**, **5c** or **5d** (0.051 mmol) in toluene (1 mL) triethylamine (0.036 mL, 0.255 mmol) was added followed by mesyl anhydride (0.027 g, 0.153 mmol) at 0 °C. The reaction mixture was stirred at 0–5 °C for 30 min, diluted with toluene (5 mL) and washed with cold water (2×5 mL). The organic phase was dried over $MgSO_4$. All volatiles were removed in vacuo at room temperature, the residue was dissolved in $CDCl_3$ (0.7 mL) and the solution was immediately analysed by ^1H, ^{31}P and ^{13}C NMR spectroscopy.

4.4.2. NMR tube experiments

To a solution of 1-hydroxyphosphonate **5b**, **5c** or **5d** (0.026 mmol) in $CDCl_3$ (0.7 mL) mesyl anhydride (0.077 mmol) was added followed by injection of NEt_3 (0.13 mmol). The progress of mesylation was monitored by ^1H and ^{31}P NMR spectroscopy.

*4.4.3. 1-O-Mesylates (1R,2S)-**6b–d***

*4.4.3.1. Dimethyl (1R,2S)-2-(N,N-dibenzylamino)-1-mesyloxy-3-phenylpropylphosphonate (1R,2S)-**6b**.* ^1H NMR ($CDCl_3$) δ=7.35–7.12 (m, 15H), 5.53 (dd, J_{H1-P}=11.5 Hz, J_{H1-H2}=1.0 Hz, 1H, *H*CP), 3.98 (d, *J*=14.1 Hz, 2H, Ph*H*CHN), 3.73 and 3.71 (2×d, *J*=10.7 Hz, 6H, CH_3OPOCH_3), 3.58 (d, *J*=14.1 Hz, 2H, PhHC*H*N), 3.55 (ddd, J_{H2-H3b}=J_{H2-H3a}=7.2 Hz, J_{H2-H1}=1.0 Hz, 1H, *H*CCP), 3.27 (s, 3H, CH_3SO_2), 3.15–3.03 (m, 2H, PhH_aCH_bCCP). ^{13}C NMR ($CDCl_3$) δ=139.23, 138.84, 129.68, 128.74, 128.19, 128.10, 126.92, 126.30, 74.43 (d, *J*=160.3 Hz, C1), 59.11 (d, *J*=4.5 Hz, C2), 53.65 (s, PhCH_2N), 53.98 and 53.36 (2×d, *J*=7.5 Hz, CH_3OPOCH_3), 40.07, 33.22 (s, C3). ^{31}P NMR ($CDCl_3$) δ=21.74.

*4.4.3.2. Dimethyl (1R,2S)-2-(N,N-dibenzylamino)-1-mesyloxy-3-methylbutylphosphonate (1R,2S)-**6c**.* ^1H NMR ($CDCl_3$) δ=7.30–7.10 (m, 10H), 5.50 (dd, J_{H1-P}=13.5 Hz, J_{H1-H2}=1.5 Hz, 1H, *H*CP), 3.92 (d, *J*=13.8 Hz, 2H, Ph*H*CHN), 3.79 and 3.69 (2×d, *J*=10.7 Hz, 6H, CH_3OPOCH_3), 3.46 (d, *J*=13.8 Hz, 2H, PhHC*H*N), 3.19 (s, 3H, CH_3SO_2), 2.96 (ddd, J_{H2-P}=10.8 Hz, J_{H2-H3}=8.1 Hz, J_{H2-H1}=1.2 Hz, 1H, *H*CCP), 2.20 (dsp, J_{H3-H2}=8.1 Hz, J_{H3-Me}=6.5 Hz, 1H, C*H*CCP), 1.09 and 0.89 (2×d, *J*=6.5 Hz, 6H, CH_3CCH_3). ^{31}P NMR ($CDCl_3$) δ=23.04.

*4.4.3.3. Dimethyl (1R,2S)-2-(N,N-dibenzylamino)-1-mesyloxy-3,3-dimethylbutylphosphonate (1R,2S)-**6d**.* ^{31}P NMR ($CDCl_3$) δ=23.46.

*4.4.4. Aziridinium mesylates (2S,3S)-**7b–d***

*4.4.4.1. (2S,3S)-1,1,2-Tribenzyl-3-(dimethoxyphosphoryl)aziridinium mesylate (2S,3S)-**7b**.* ^1H NMR ($CDCl_3$) δ=7.6–7.1 (m, 15H), 5.89 (dd, J_{H2-P}=7.8 Hz, J_{H2-H3}=3.0 Hz, 1H, *H*CP), 5.35 (br d, *J*=14.1 Hz, 1H, PhH_ACHN), 4.65 (br d, *J*=14.1 Hz, 1H, PhH_ACHN), 4.25 (d, *J*=14.1 Hz, 1H, PhHCH_BN), 4.21 (dd, *J*=14.1, 4.5 Hz, 1H, PhHCH_bN), 4.06 (localised by COSY) (m, *H*CCP), 3.91 and 3.85 (2×d, *J*=11.1 Hz, 6H, CH_3OPOCH_3), 3.58 (d, *J*=14.1 Hz, 2H, PhHC*H*N), overlapped by signals of major components (m, 2H, PhH_aCH_bCCP), 2.75 (s, 3H, CH_3SO_2). ^{13}C NMR ($CDCl_3$) δ=resonances of aromatic carbons are overlapped by signals of major components, 58.60 (d, *J*=2.2 Hz, C3), 57.70 (s, PhCH_2N), 57.41 (d, *J*=1.5 Hz, PhCH_2N), 55.54 and 54.82 (2×d, *J*=6.9 Hz, CH_3OPOCH_3), 47.22 (d, *J*=173.2 Hz, C2), 39.77, 31.80 (s, *C*CCP). ^{31}P NMR ($CDCl_3$) δ=13.97.

*4.4.4.2. (2S,3S)-1,1-Dibenzyl-3-(dimethoxyphosphoryl)-2-isopropyl aziridinium mesylate (2S,3S)-**7c**.* ^1H NMR ($CDCl_3$) δ=7.75–7.65 (m, 2H), 7.60–7.45 (m, 6H), 7.43–7.32 (m, 2H), 5.66 (dd, J_{H2-H3}=8.3 Hz, J_{H2-P}=5.4 Hz, 1H, *H*CP), 5.12 (br d, *J*=13.5 Hz, 1H, PhH_ACHN), 4.61 (br d, *J*=13.8 Hz, 1H, PhH_ACHN), 4.37 (d, *J*=13.8 Hz, 1H, PhHCH_BN), 4.23 (dd, *J*=13.5, 4.2 Hz, 1H, PhHCH_bN), 4.09 and 3.89 (2×d, *J*=11.1 Hz, 6H, CH_3OPOCH_3), 3.44 (ddd, J_{H3-P}=15.1 Hz, $J_{H3-H3'}$=10.7 Hz, J_{H3-H2}=8.3 Hz, 1H, *H*CCP), 2.83 (dsp, $J_{H3-H3'}$=10.7 Hz, $J_{H3'-Me}$=6.7 Hz, 1H, *H*CCCP), 2.78 (s, 3H, CH_3SO_2), 1.31 and 0.81 (2×d, *J*=6.7 Hz, 6H, CH_3CCH_3). ^{13}C NMR ($CDCl_3$) δ=131.10, 130.89, 130.80, 130.45, 129.69, 129.55, 129.13, 128.94, 60.60 (d, *J*=2.9 Hz, C3), 57.78 (s, PhCH_2N), 57.15 (s, PhCH_2N), 55.73 and 54.63 (2×d, *J*=6.9 Hz, CH_3OPOCH_3), 48.49 (d, *J*=176.0 Hz, C2), 39.56, 25.82 (d, *J*=3.1 Hz, *C*CCP), 20.53, 19.88. ^{31}P NMR ($CDCl_3$) δ=14.56.

*4.4.4.3. (2S,3S)-1,1-Dibenzyl-2-(tert-butyl)-3-(dimethoxyphosphoryl)-aziridinium mesylate (2S,3S)-**7d**.* ^1H NMR ($CDCl_3$) δ=7.66 (d, *J*=7.6 Hz, 2H), 7.51 (t, *J*=7.4 Hz, 2H), 7.48 (m, 2H), 7.46 (t, *J*=7.1 Hz, 2H), 7.35 (d, *J*=7.4 Hz, 2H), 5.26 (dd, J_{H2-H3}=9.4 Hz, J_{H2-P}=2.3 Hz, 1H, *H*CP), 4.74 (d, *J*=13.6 Hz, 1H, PhH_aCHN), 4.46 (d, *J*=13.6 Hz, 1H, PhH_ACHN), 4.40 (dd, *J*=13.6, 4.5 Hz, 1H, PhHCH_bN), 4.39 (d, *J*=13.6 Hz, 1H, PhHCH_BN), 4.00 and 3.93 (2×d, *J*=11.1 Hz, 6H, CH_3OPOCH_3), 3.57 (dd, J_{H3-P}=16.7 Hz, J_{H3-H2}=9.4 Hz, 1H, *H*CCP), 2.68 (s, 3H, CH_3SO_2), 1.12 [s, 9H, (CH_3)$_3$C]. ^{13}C NMR ($CDCl_3$) δ=131.14, 131.04, 130.58, 130.52, 129.70, 129.56, 129.14, 129.00, 63.02 (s, C3), 59.04 (s, PhCH_2N), 58.84 (s, PhCH_2N), 55.36 and 54.90 (2×d, *J*=6.7 Hz, CH_3OPOCH_3), 48.53 (d, *J*=178.5 Hz, C2), 39.42, 32.59 (s, *C*CCP), 28.35 [s, (CH_3)$_3$C]. ^{31}P NMR ($CDCl_3$) δ=13.93.

*4.4.5. 2-O-Mesylates (1S,2R)-**8b–d***

*4.4.5.1. Dimethyl (1S,2R)-1-(N,N-dibenzylamino)-2-mesyloxy-3-phenylpropylphosphonate (1S,2R)-**8b**.* ^1H NMR ($CDCl_3$) δ=7.35–7.10 (m, 15H), 5.27 (dddd, J_{H2-P}=14.7 Hz, J_{H2-H3a}=7.2 Hz, J_{H2-H3b}=6.9 Hz, J_{H1-H2}=3.3 Hz, 1H, *H*CCP), 4.08 (dd, *J*=13.5, 3.0 Hz, 2H, Ph*H*CHN), 3.76 and 3.60 (2×d, *J*=10.8 Hz, 6H, CH_3OPOCH_3), 3.68 (d, *J*=13.5 Hz, 2H, PhHC*H*N), 3.50 (dd, $J_{H3a-H3b}$=13.8 Hz, J_{H2-H3a}=7.2 Hz, 1H, PhH_aCH_bCCP), 3.45 (dd, J_{H1-P}=21.0 Hz, J_{H1-H2}=3.3 Hz, 1H, *H*CP), 3.16 (dd, $J_{H3a-H3b}$=13.8 Hz, J_{H2-H3b}=6.9 Hz, 1H, PhH_aCH_bCCP), 2.68 (s, 3H, CH_3SO_2). ^{13}C NMR ($CDCl_3$) δ=138.73, 136.28, 130.01, 129.30, 128.99, 128.39, 127.34, 127.34, 81.92 (d, *J*=7.7 Hz, C2), 57.26 (d, *J*=147.4 Hz, C1), 56.04 (d, *J*=4.9 Hz, PhCH_2N), 52.83 and 52.43 (2×d, *J*=6.9 Hz, CH_3OPOCH_3), 39.46 (s, C3), 39.27. ^{31}P NMR ($CDCl_3$) δ=26.18.

*4.4.5.2. Dimethyl (1S,2R)-1-(N,N-dibenzylamino)-2-mesyloxy-3-methylbutylphosphonate (1S,2R)-**8c***. ^{1}H NMR ($CDCl_3$) δ=7.35–7.20 (m, 10H), 4.85 (ddd, J_{H1-H2}=9.1 Hz, J_{H2-P}=5.4 Hz, J_{H2-H3}=1.6 Hz, 1H, *H*CCP), 3.95 (d, J=12.9 Hz, 2H, Ph*H*CHN), 3.88 (dd, J=12.9, 4.8 Hz, 2H, PhHC*H*N), 3.86 and 3.82 (2×d, J=10.9 Hz, 6H, CH_3OPOCH_3), 3.33 (dd, J_{H1-P}=15.3 Hz, J_{H1-H2}=9.1 Hz, 1H, *H*CP), 3.12 (s, 3H, CH_3SO_2), 2.28 (dsp, J_{H3-Me}=6.9 Hz, J_{H3-H2}=1.6 Hz, 1H, *H*CCCP), 1.04 and 0.31 (2×d, J=6.9 Hz, 6H, CH_3CCH_3). ^{13}C NMR ($CDCl_3$) δ=138.44, 138.43, 129.52, 129.48, 128.55, 128.51, 127.60, 127.55, 85.16 (d, J=2.6 Hz, C2), 56.22 (d, J=134.3 Hz, C1), 55.63 (d, J=1.7 Hz, Ph*C*H$_2$N), 52.28 and 52.00 (2×d, J=7.2 Hz, *C*H$_3$OPOCH_3), 39.50, 29.26 (d, J=7.2 Hz, C3), 20.41 (d, J=1.4 Hz, *C*H$_3$CCH$_3$), 14.39 (s, CH$_3$*C*CH$_3$). ^{31}P NMR ($CDCl_3$) δ=29.59.

*4.4.5.3. Dimethyl (1S,2R)-1-(N,N-dibenzylamino)-2-mesyloxy-3,3-dimethylbutylphosphonate (1S,2R)-**8d***. ^{1}H NMR ($CDCl_3$) δ=7.30–7.16 (m, 10H), 4.78 (dd, J_{H1-H2}=3.0 Hz, J_{H2-P}=6.1 Hz, 1H, *H*CCP), 3.85 (d, J=13.0 Hz, 2H, Ph*H*CHN), 3.82 (d, J=13.0 Hz, 2H, PhHC*H*N), 3.81 and 3.76 (2×d, J=10.9 Hz, 6H, CH_3OPOCH_3), 3.45 (dd, J_{H1-P}=22.2 Hz, J_{H1-H2}=3.0 Hz, 1H, *H*CP), 3.24 (s, 3H, CH_3SO_2), 0.69 [s, 9H, (CH_3)$_3$C]. ^{13}C NMR ($CDCl_3$) δ=138.54, 129.47, 128.18, 127.32, 69.92 (s, C2), 57.70 (d, J=142.2 Hz, C1), 55.76 (s, Ph*C*H$_2$N), 52.71 and 50.96 (2×d, J=6.6 Hz, *C*H$_3$OPOCH_3), 39.44, 36.39 (s, C3), 26.10 [s, (*C*H$_3$)$_3$C]. ^{31}P NMR ($CDCl_3$) δ=26.19.

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