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ASYMMETRIC SYNTHESIS OF AZIRIDINE 2-PHOSPHONATES AND AZIRINYL PHOSPHONATES FROM ENANTIOPURE SULFINIMINES

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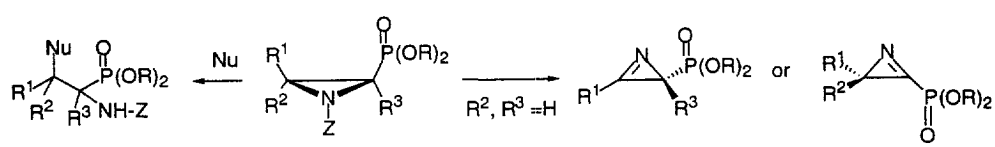
Summary: *Enantiopure sulfinimine (S)-4 was employed in a Darzens-type synthesis of aziridine 2-phosphonates (-)-7/(+)-8 which were transformed into α-amino phosphonates (S)-11/(R)-12 and the first enantiopure examples of azirinyl phosphonates 13-15.*

Enantiomerically pure aziridine 2-carboxylate esters are important building blocks for the asymmetric construction of β-substituted α-amino acids because they undergo highly regiocontrolled and stereoselective ring-opening reactions with nucleophiles.[1,2] Furthermore, these aziridines are precursors of enantiopure 2*H*-azirine carboxylate esters, the smallest of the nitrogen unsaturated heterocycles, which are themselves valuable building blocks for the synthesis of chiral amines.[3-5] For these reasons nonracemic aziridine 2-phosphonates **1** are expected to play a similar role in the enantioselective synthesis of α-amino phosphonates **2** and azirinyl phosphonates **3** (Scheme 1). α-Amino phosphonates **2**[6] are of considerable utility as surrogates for α-amino acids[7] and have been utilized as enzyme inhibitors,[8-11] haptens for catalytic antibodies,[12] and antibacterial agents.[13] Although methods for the synthesis of aziridine 2-carboxylate esters are well estabilished,[1,2] there are only a few reports of the synthesis of aziridinyl 2-phosphonates **1** and a single example of a racemic azirinyl phosphonate **3**.[14] Racemic **1** have been prepared by the copper catalyzed aziridination of vinylphosphosphonates with [*N*-(*p*-toluenesulfonyl)imino]-phenyliodonane[15] and the Darzens-type addition of lithiated chloromethylphosphonate anions to imines.[16] Hanessian and co-workers employed the latter method in the highly diastereoselective asymmetric synthesis of **1** (OR = NR_2) from nonracemic bicyclic chloromethyl phosphonamide and imines.[17]

Scheme 1



2 **1** **3**

Earlier studies from these laboratories described the preparation of *cis*-*N*-sulfinylaziridine-2-carboxylic acids *via* a Darzens-type reaction involving the addition of the lithium enolate of methyl bromoacetate to

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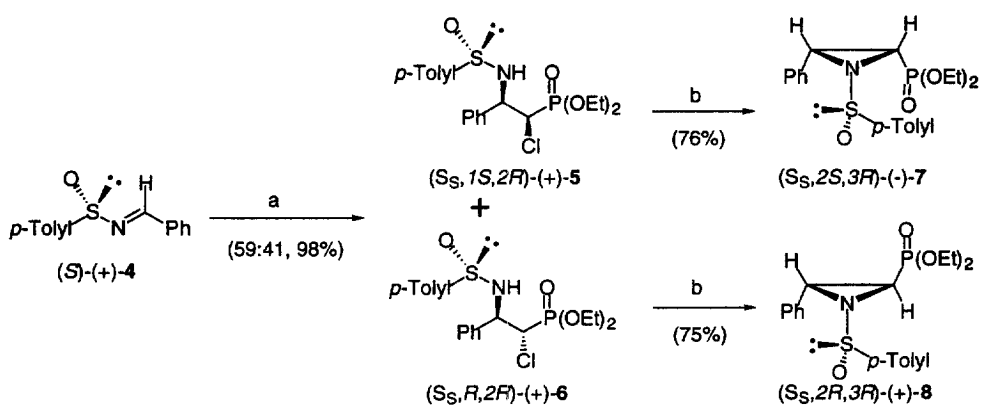
enantiopure sulfinimines.[18] When this protocol was applied to the lithium anion of diethyl chloromethylphosphonate, no aziridine was found, but the α-chloro-β-amino adducts (+)-**5** and (+)-**6** were produced in high yield. Thus, diethyl chloromethylphosphonate (17.0 mmol) and (*S*)-(+)-**4** (7.52 mmol) were treated with (17.0 mmol) of lithium bis(trimethylsilylamide) in THF at -78 °C. After 30 min the reaction was quenched at this temperature by addition of NH_4Cl (aq). The ratio of (+)-**5**/(+)-**6** in the crude reaction mixture was 59:41 which after isolation by flash chromatography afforded (S_S,*1S*,*2R*)-(+)-**5** and (S_S,*1R*,*2R*)-(+)-**6** in 58% and 40% yield respectively. Treatment of (+)-**5** and (+)-**6** with 2 equivalents of sodium hydride readily afforded aziridines (S_S,*2S*,*3R*)-(-)-**7** (76%) and (S_S,*2R*,*3R*)-(+)-**8** (75%), respectively (Scheme 2). The absolute stereochemistry of (-)-**7** and (+)-**8** was established by conversion to known compounds (*vide infra*) and the *cis* or *trans* relationships of the C-2 and C-3 substituents assigned by proton-proton coupling constants of 8 Hz and 4.5 Hz, respectively.[19] Interestingly, the exclusive (*R*)-absolute induction at C-2 in the formation of (+)-**5**/(+)-**6** is opposite to that found in the analogous carboxylic ester case,[18] and the same as that observed for the addition of phosphites[20] and α-phosphonate carbanions[21] to (*S*)-**4** leading to α- and β-amino phosphonic acids, respectively. The selectivity for metal enolate additions to sulfinimines has been rationalized in terms of chair-like transition states where the metal is coordinated to both the sulfinyl oxygen and imine nitrogen.[18,22] On the other hand, transition state rationales for phosphite and α-phosphonate carbanion additions to (*S*)-**4** have these species reacting from the least hindered direction, i.e. opposite to the *p*-tolylsulfinyl group.[20,21] This difference may reflect the greater steric bulk of metal phosphonate anions compared to enolates as well as their tetrahedral structure.

Scheme 2



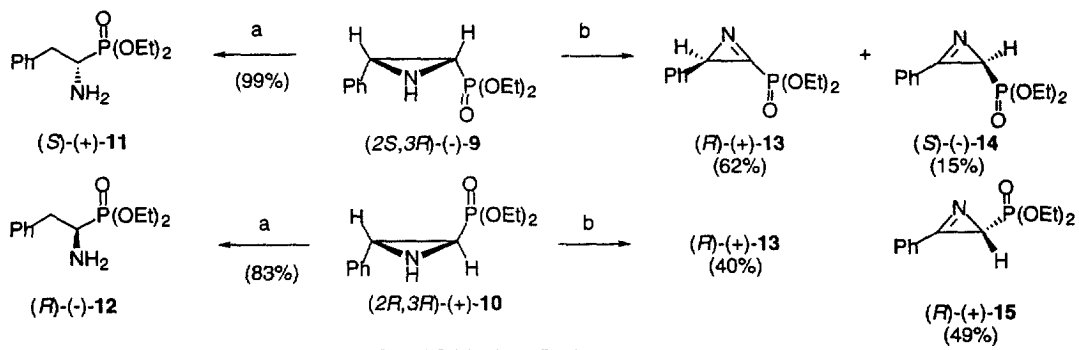
a) $ClCH_2P(O)(OEt)_2$, LiHMDS, -78 °C, 30 min. b) NaH

It has been proposed that aziridinyl phosphonate formation results from a reversible equilibration of the α-chloro-β-amino adducts on warming to give cyclized aziridinyl phosponate.[16] We found no evidence for such behavior in our system. On warming the mixture of (+)-**5**/(+)-**6** over 3 h to -5 °C, a retained ratio of (-)-**7**/(+)-**8** was obtained in 71% yield which proved tedious to separate by flash chromatography. If the warming process was conducted over a longer period (>12 h), an improved ratio of (-)-**7**/(+)-**8** did occur (78:22) in 17% yield and was shown to result from the faster decomposition of (+)-**8** than (-)-**7** in the presence of excess base, rather than any interconversion of the adducts. Accordingly, the low rotational barrier of the carbanion

adjacent to phosphorus is likely to be responsible for the interchange of the α-chlorine and α-hydrogen positions.[23] If diethyl iodomethyl phosphonate is reacted with (*S*)-**4** in this Darzens-type synthesis and the reaction mixture allowed to warm to -40 °C then (-)-**7**/(+)-**8** are formed directly in 71% yield with a considerably improved diastereomeric ratio of 81:19.

The removal of the sulfinyl auxiliary was performed under acidic conditions. Treatment of *N*-sulfinyl aziridine (-)-**7** with 50 equivalents of trifluoroacetic acid at rt for 1 h afforded aziridine (*2S,3R*)-(-)-**9** in 84% yield (Scheme 3). Similar treatment of (+)-**8** gave aziridine (+)-**10** in only 22% yield with extensive ring opening and decomposition products, indicating again the lesser stability of *trans*-3-phenylaziridine 2-phosphonate compounds than their *cis* counterparts. By performing the reaction at 0 °C for only 15 min, 5 equivalents of trifluoroacetic acid was found to afford aziridine (*2R,3R*-)-(+)-**10** in 91% isolated yield. The aziridines (-)-**9**/(+)-**10** were ring opened using phase transfer hydrogenolysis conditions to give (*S*)-(+)-**11**[24] and (*R*)-(-)-**12**[25] in 99% and 83% isolated yield, respectively, despite the lack of an activating group on nitrogen. Preparation of the Mosher amide derivatives of (+)-**11**/(-)-**12** using (+)-Mosher's acid chloride showed each α–amino phosphonate to be enantiopure.[24]

Scheme 3



a) Pd/C, HCO_2NH_4, MeOH b) DMSO/$(COCl)_2$ then Et_3N

Initial attempts to eliminate the sulfinyl group in (-)-**7**/(+)-**8** with LDA or LDA/MeI led to no azirinyl phosphonate formation as was observed for the analogous *N*-sulfinyl aziridine carboxylate esters.[3,4] However, when aziridines (-)-**9**/(+)-**10** were subjected to Swern oxidation conditions, as first reported by Zwanenburg for the preparation of 2*H*-azirine-2-carboxylic esters as the exclusive regioisomer,[5] regioisomeric mixtures of azirinyl phosphonates **13-15** were produced (Scheme 3). To the best of our knowledge, this is the first asymmetric synthesis of azirinyl phosphonates.[14] In the case of (-)-**9**, the phosphonate ester presumably has a more pronounced acidifying effect on the C-2 proton leading to the major azirine product (*R*)-(+)-**13** in 62% yield. Removal of the C-3 proton gave the minor azirine product (*S*)-(-)-**14** in 15% yield. In the case of (+)-**10**, a rapidly inverting *N*-sulfonium intermediate is expected, leading to equal removal of C-2 and C-3 protons despite their acidity difference. A 1:1 mixture of azirinyl phosphonates (*R*)-(+)-**13** and (*R*)-(+)-**15** was observed by crude ^{1}H NMR (500 MHz) and isolated by flash chromatography in 40% and 49% yield, respectively. Our interpretation also explains the results of Zwanenburg and co-workers,[5] in that the acidifying effect of a C-2 carboxylic ester is much less than the phosphonate ester since the former cannot readily stabilize a pyramidal α-anion on an aziridine ring.[26]

In summary, new methodology was presented employing enantiopure sulfinimines, chiral imine equivalents, for the asymmetric synthesis of *cis*- and *trans*-aziridine 2-phosphonates. These valuable chiral building blocks were readily transformed into α-amino phosphonate esters and the first chiral examples of azirinyl phosphonates.

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27. Selected physical properties: (S_S,*1S*,*2R*)-(+)-**5**: mp 96-97 °C, $[\alpha]_D^{20}$ +30.8 (c 3.20, $CHCl_3$); (S_S,*1R*,*2R*)-(+)-**6**: mp 71-71.5 °C, $[\alpha]_D^{20}$ +28.1 (c 2.15, $CHCl_3$); (S_S,*2S*,*3R*)-(-)-**7**: oil, $[\alpha]_D^{20}$ -33.7 (c 1.08, $CHCl_3$); (S_S,*2R*,*3R*)-(+)-**8**: oil, $[\alpha]_D^{20}$ +147 (c 0.455, $CHCl_3$); (*2S*,*3R*)-(-)-**9**: oil, $[\alpha]_D^{20}$ -36.5 (c 0.85, $CHCl_3$); (*2R*,*3R*)-(+)-**10**: oil, $[\alpha]_D^{20}$ +38.5 (c 0.89, $CHCl_3$); (*S*)-(+)-**11**: oil, $[\alpha]_D^{20}$ +16.9 (c 0.86, $CHCl_3$), Mosher amide $\delta^{19}F$ -69.44; (*R*)-(-)-**12**: oil, $[\alpha]_D^{20}$ -16.5 (c 0.89, $CHCl_3$), Mosher amide $\delta^{19}F$ -69.55; (*R*)-(+)-**13**: oil, $[\alpha]_D^{20}$ +342 (c 1.34, $CHCl_3$); (*S*)-(-)-**14**: oil, $[\alpha]_D^{20}$ -202 (c 0.36, $CHCl_3$); (*R*)-(+)-**15**: oil, $[\alpha]_D^{20}$ +195 (c 0.36, $CHCl_3$).