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Asymmetric Synthesis of α-Methylphosphophenylalanine Derivatives Using Sulfinimine-Derived Enantiopure Aziridine-2-phosphonates

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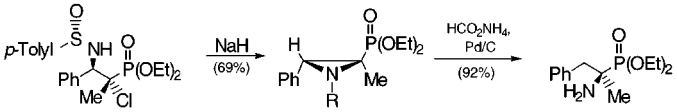
ABSTRACT



2-Methylaziridine-2-phosphonates were prepared from enantiopure sulfinimines and were demonstrated to be versatile synthetic intermediates for the synthesis of novel α-disubstituted and α,β-trisubstituted α-aminophosphonate derivatives. The first asymmetric synthesis of both enantiomers of α-methylphosphophenylalanine is described.

The asymmetric synthesis of α-aminophosphonates has become important due to their interesting biological properties. They have found widespread use as surrogates for α-amino acids,[1,2] enzyme inhibitors,[3−5] haptens for catalytic antibodies,[6] antibacterial agents,[7,8] and biotryticides.[9] Generally, biological activity is strongly dependent upon the chirality α to the phosphorus atom, and a number of asymmetric syntheses of α-aminophosphonates have been reported.[10] Particularly, enantiopure sulfinimines (*N*-sulfinyl imines) have been utilized in a direct α-aminophosphonate synthesis[11,12] and also via aziridinyl-2-phosphonates.[13] However, to the best of our knowledge, there are no reports of the asymmetric synthesis of α-disubstituted derivatives. The analogous α-methyl α-amino acids are of considerable interest because incorporation into peptides results in increased rigidity, resistance to protease enzymes, and often enhance bioactivity.[14] The aziridine-2-phosphonate route is especially attractive in that, like aziridine-2-carboxylates,[15,16] it should allow incorporation of substituents at both the α- and β-positions relative to phosphorus with control of chirality.

Herein, we disclose the first asymmetric synthesis of α-methylphosphophenylalanine derivatives from enantiopure

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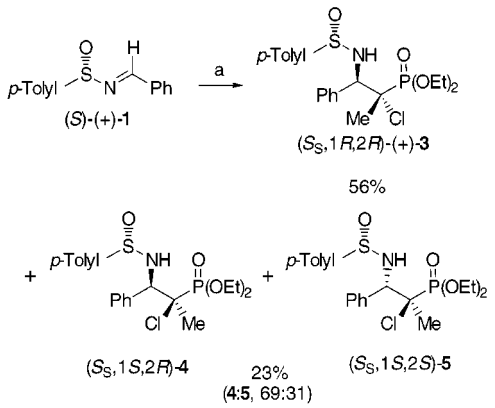
aziridine-2-phosphonates which are accessed via an aza-Darzens reaction of sulfinimine (*S*)-(+)-**1**[17] and diethyl 1-chloroethylphosphonate (**2**).[18] The reaction of (+)-**1** with 2.2 equiv of the lithium anion generated from **2** at −78 °C for 20 min afforded α-chloro *β*-amino adduct (+)-**3** in 56% isolated yield after chromatography and also an inseparable mixture of **4** and **5** in 23% isolated yield (**4**:**5**, 68:32) (Scheme 1).[19]

Scheme 1



a) ClCH(Me)P(O)(OEt)$_2$ (**2**), LiHMDS, THF, -78 °C, 20 min

The stereochemistry of (+)-**3** was established as (*S*$_S$,1*R*,2*R*) by single-crystal X-ray analysis since NOE experiments on the derived aziridines proved inclusive. Figure 1 shows the

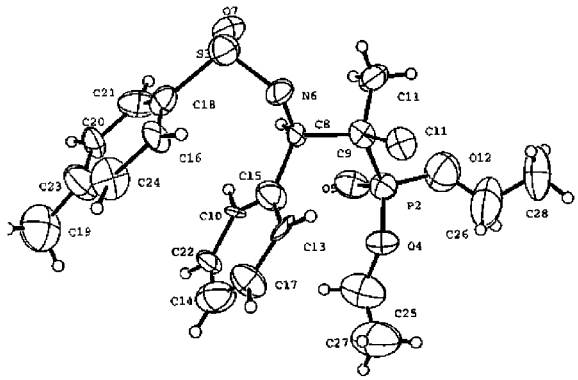
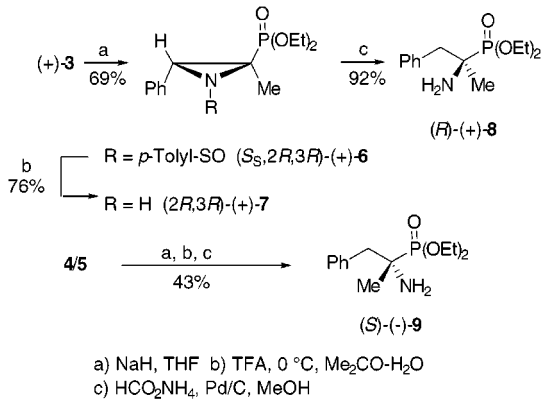


Figure 1. ORTEP view of α-chloro *β*-amino adduct (+)-**3**.

corresponding ORTEP drawing with the appropriate atom numbering. The stereochemistry of subsequent products derived from (+)-**3** using reactions of known stereochemical outcome can thus be assumed. Cyclization using sodium hydride to give aziridine (*S*$_S$,2*R*,3*R*)-(+)-**6** proceeded in 69% yield (S$_N$2 inversion α to phosphorus) and the sulfinyl auxiliary was removed in 76% yield using TFA in acetone−water to give (2*R*,3*R*)-(+)-**7** (Scheme 2).[19]

Scheme 2



a) NaH, THF b) TFA, 0 °C, Me_2CO-H_2O
c) HCO_2NH_4, Pd/C, MeOH

Transfer hydrogenation (Pd/C, HCO_2NH_4, MeOH) proceeded with conservation of the stereochemistry α to phosphorus to afford diethyl (*R*)-(+)-α-methylphosphophenylalanine (**8**) in 92% yield. Similarly, the minor product mixture of **4**/**5** was converted to (*S*)-(−)-α-methylphosphophenylalanine (**9**) in 43% yield over three steps. After removal of the sulfinyl group, the *N*-H aziridines were separable by chromatography and the aziridine derived from **5** was characterized as the enantiomer of (+)-**7**. The C(2) methyl displays a characteristic doublet ^{1}H NMR signal depending on whether it is cis (*δ* 1.0) or trans (*δ* 1.6) to the C(3) phenyl substituent.

The formation of (+)-**3** was rationalized through attack by the phosphonate anion at the imine face opposite to that sterically shielded by the sulfinyl oxygen in a six-membered transition state (Figure 2). The anion was expected to adopt

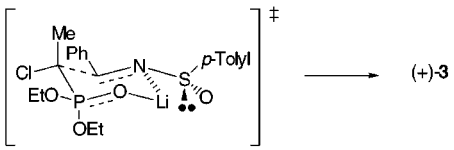


Figure 2. Proposed predominant transition state for phosphonate anion addition to sulfinimine (+)-**1**.

a conformation similar to the analogous *E* enolate,[20] but the barrier to rotation around the P−C bond in such compounds was expected to be low.[21] Consequently, minor adduct **4** may

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(19) Selected properties. (*S*$_S$,1*R*,2*R*)-(+)-**3**: mp 102 °C, [α]$^{20}_D$ 24.3 (*c* 1.01, $CHCl_3$), *δ*$_P$ 19.42. (*S*$_S$,2*R*,3*R*)-(+)-**6**: oil, [α]$^{20}_D$ 5.2 (*c* 1.4, $CHCl_3$), *δ*$_P$ 24.32. (2*R*,3*R*)-(+)-**7**: oil, [α]$^{20}_D$ 26 (*c* 0.56, $CHCl_3$), *δ*$_P$ 28.50. *ent*-**7**: oil, [α]$^{20}_D$ −26 (*c* 0.56, $CHCl_3$). (*R*)-(+)-**8**: oil, [α]$^{20}_D$ 1.5 (*c* 0.75, $CHCl_3$), *δ*$_P$ 30.94. (*S*)-(−)-**9**: oil, [α]$^{20}_D$ −1.4 (*c* 0.77, $CHCl_3$). (1*R*,2*S*)-(+)-**10**: oil, [α]$^{20}_D$ 63 (*c* 0.76, $CHCl_3$), *δ*$_P$ 29.66.

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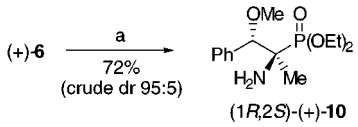
Scheme 3



a) MeOH, BF_3•OEt_2, $CHCl_3$, 55 °C, 2 d

results from interconversion of the methyl and chlorine positions, while the very minor adduct **5** results from the less favored attack at the imine face shielded by the sulfinyl oxygen.

Treatment of aziridine (+)-**6** with methanol in the presence of BF_3·OEt_2 afforded the β-methoxy-α-methylphosphophenylalanine derivative **10** in 90% de with complete control of the regiochemistry (Scheme 3).[19] After chromatography (1*R*,2*S*)-(+)-**10** was obtained in 72% yield. The reaction proceeded in two steps. In a fast step, the sulfinyl auxiliary was removed at room temperature and thus provided an alternative desulfinylation procedure for such compounds. Second, in a significantly slower step the aziridine ring was opened, presumably through BF_3 activation on nitrogen which required heating at 55 °C for 2 days.

In summary, 2-methylaziridine-2-phosphonates were prepared from enantiopure sulfinimines and were demonstrated to be versatile synthetic intermediates for the synthesis of novel α-disubstituted and α,β-trisubstitute α-aminophosphonate derivatives with control of the chirality at these centers.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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