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Triphenylphosphonium salts bearing an L-alanyl substituent: short synthesis and enantiomeric analysis by NMR

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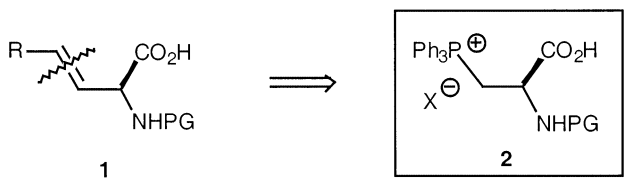
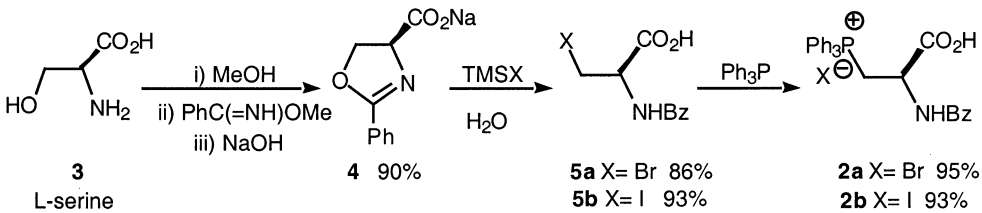
Abstract—A short, practical stereospecific synthesis of triphenylphosphonium salts bearing an L-(*N*-benzoyl)-alanyl substituent from L-serine is described. The key step is the ring opening of an oxazoline salt derived from serine with trimethylsilyl halide, giving β-bromo or β-iodo alanine, which were used for the quaternization of triphenylphosphine. The phosphonium salts were obtained in 80% overall yield from serine, and their enantiomeric purity was easily determined by ^{31}P NMR in the presence of a cinchona alcaloid. © 2001 Elsevier Science Ltd. All rights reserved.

Hemisynthetic methods are widely used for the preparation of enantiomerically pure unnatural or non-classical α-aminoacids.[1] The main synthetic route requires the construction of C–C or C–X (X = heteroatoms) single bonds by nucleophilic, electrophilic or radical reactions at the β position of an alanine equivalent, e.g. β-iodoalanine,[2] β-lactone,[3] α,β-aziridine,[4] α,β-sulfamidate[5] or β-sulfone,[6] derived from the readily available D- or L-serine. Although β,γ-unsaturated-α-aminoacids **1** have attracted attention as antibiotic[7] and potential suicide enzyme inhibitors,[8] or also as synthetic intermediates,[9,10] few hemisyntheses involving the direct formation of a C_β=C_γ double bond have been described.[10–12]

Despite the pioneering work of Itaya, the Wittig reagent **2** has not been extensively investigated, due in particular to the low yield of the resulting olefination (<43%).[10] In addition, the seven-step preparation of the synthon **2** from serine poses a serious obstacle for its application in hemisynthesis. The main synthetic difficulty arises from the presence of the free carboxylic acid group in compounds **2**, which is necessary in order to avoid elimination or racemization during the Wittig process. Thus, while the quaternization of PPh_3 requires a β-bromo or a β-iodo alanine derivative, the free carboxylic acid group could not be obtained from the benzyl ester by debenzylation, since hydrogenolysis is unsuccessful with these phosphonium salts.[10,13]

With this in mind, and continuing our work on the oxazolines derived from serine as alanine β-cation equivalents,[14] we examined their application for the





Scheme 1.

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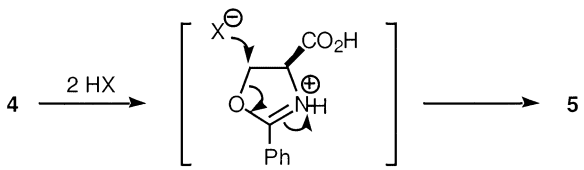
synthesis of phosphonium derivatives. We report here a short stereospecific synthesis of the *N*-protected amino acid phosphonium salts **2** (PG = Bz) from L-serine **3** and a practical ^{31}P NMR method for the determination of their enantiomeric purity.

The (*S*)-oxazoline sodium salt **4** was easily obtained in 90% overall yield from **3** by successive esterification with methanol, condensation with the phenyl iminoether derived from benzonitrile and saponification (Scheme 1).[15]

Stirring the oxazoline sodium salt **4** with three equivalents of a TMSBr/H_2O (1:1) mixture in chloroform at room temperature for 48 h, led to the corresponding *N*-benzoyl-β-bromo-alanine **5a** in 86% yield. No significant elimination or racemization was detected under these conditions, and compound **5a** was of sufficient chemical purity to allow its use in the following reaction without further purification. Under similar conditions, TMSI led to the corresponding β-iodo derivative **5b**, which was isolated in 93% yield. Therefore, we assume that the ring opening product **5** resulted mainly from the reaction of the oxazoline sodium salt **4** with the HBr (or HI), which is generated in situ by the TMSX hydrolysis. Thus, the oxazolinium salt formed by nitrogen protonation underwent attack by halide at the C(5) position, leading to the ring opening by C–O bond cleavage (Scheme 2).[16]

Quaternization of triphenylphosphine with the corresponding *N*-benzoyl-β-halogeno-α-amino acid **5a** or **5b** was achieved in refluxing chloroform to give the corresponding phosphonium salts **2a** and **2b** in 95% yield. The analytically pure phosphonium salts **2a** and **2b**[17] were easily recovered by simple filtration and obtained in 80% overall yield from L-serine **3**. Interestingly, the phosphonium salts could also be obtained by an alternative one-pot procedure, namely, reaction of the oxazoline sodium salt **4** with a TMSBr/H_2O (1:1) mixture at room temperature for 48 h, followed by quaternization with 2.5 equivalents of PPh_3 in refluxing chloroform.



Scheme 2.

The enantiomeric purity of compound **2a** was checked by ^{31}P NMR using a chiral phosphate anion,[18a] as previously described for phosphonium salts.[18b] However, the analysis could also be performed by a simple ^{31}P NMR experiment in the presence of cinchona alcaloid. Thus, the NMR spectra of a sample of racemic **2b** with cinchonidine revealed two signals at +23.2 and +23.3 ppm (Fig. 1b), while the compound prepared above showed only one signal (Fig. 1a). In the case of the bromide **2a**, cinchonine gave better results in the enantiomeric analysis.

In summary, we have reported a short, practical stereospecific synthesis of triphenylphosphonium salts bearing L-(*N*-benzoyl)-alanyl substituents in 80% overall yield from L-serine. The key step of the synthesis is the ring opening of the oxazoline salt derived from serine with a trimethylsilyl halide, giving β-bromo or β-iodo alanine in 93% yield. The advantage of this pathway is the generation of HX under mild conditions, allowing the reaction to occur without side-products or racemization. Moreover, triphenylphosphine is cleanly quaternized by the *N*-benzoyl-β-halogeno-α-amino acid, giving the desired phosphonium salt in 80% overall yield from serine. The enantiomeric purity was easily determined by ^{31}P NMR of their diastereoisomeric salts formed in situ with cinchonine or cinchonidine. Further developments and applications of the phosphonium salts and their ylides derivatives are currently under study in our laboratory.

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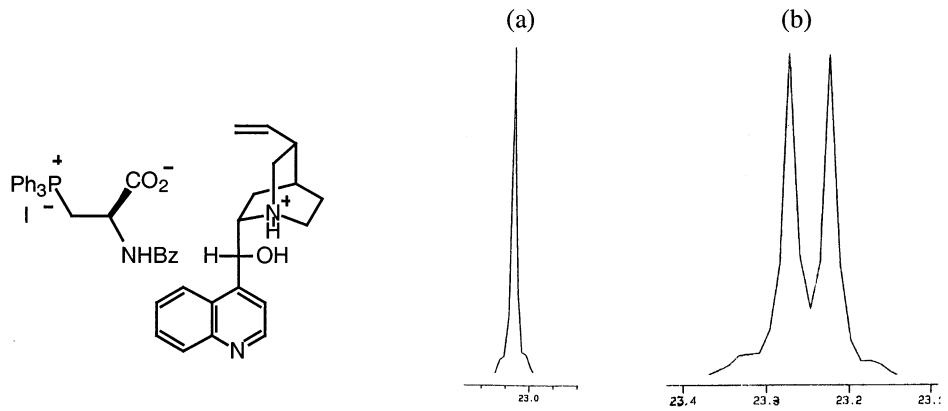

Figure 1. ^{31}P NMR enantiomeric analysis of the phosphonium salt **2b** in the presence of cinchonidine: (a) prepared using the chemistry described above; (b) racemic sample.

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16. Typical procedure for the synthesis of the *N*-benzoyl-β-halogeno-α-amino acid **5**: 20 mmol of halogeno trimethylsilane was added to a suspension of 2.13 g (10 mmol) oxazoline sodium salt **4** in 30 mL of $CHCl_3$. The mixture was stirred at room temperature for 48 h. The solvent was removed under vacuum and the compound **5** was extracted with acetone. The acetone was removed and the solid was washed with CH_2Cl_2 to give a white powder.
(*R*)-(−)-2-(*N*-Benzoyl-amino)-3-bromo propanoic acid **5a**: White solid; mp = 106°C; IR (KBr, $\bar{\nu}$ cm^{-1}): 3378, 3285, 1717, 1635, 719; ^1H NMR (250 MHz acetone-d_6) δ 7.97 (2H, dd, $J=1.5$, $J=7$, *H* arom.), 7.53 (3H, m, *H* arom.), 5.12 (1H, t, $J=4.8$, C*H*), 4.02 (2H, d, $J=4.2$, CH_2Br); ^{13}C NMR (62.9 MHz acetone-d_6) δ 171.1 (*C*OPh), 168.5 (CO_2H), 135, 133.3, 129.9, 129.1 (*C* arom.), 55.2 (*C*H), 33.9 (CH_2Br). HRMS (FAB+) calcd for $C_{10}H_{11}BrNO_3$ [M+1]: 271.9922; found: 271.9916.
(*R*)-(−)-2-(*N*-Benzoyl-amino)-3-iodo propanoic acid **5b**: White solid; mp = 127°C; IR (KBr, $\bar{\nu}$ cm^{-1}): 3366, 1714, 1631, 1198, 712; ^1H NMR (250 MHz acetone-d_6) δ 8.00 (3H, m, N*H*, *H* arom.), 7.64–7.49 (3H, m, *H* arom.), 4.95 (1H, td, $J=4.5$, $J=7.3$, C*H*), 3.89 (1H, dd, $J=4.5$, $J=10.4$, C*H*HI), 3.80 (1H, dd, $J=7.1$, $J=10.4$, CH*H*I); ^{13}C NMR (62.9 MHz acetone-d_6) δ 171.3 (*C*OPh), 168.2 (CO_2H), 135.5, 133.3, 130, 128.9 (*C* arom.), 55.6 (*C*H), 6.7 (CH_2I). HRMS (FAB+) anal. calcd for $C_{10}H_{11}INO_3$ [M+1]: 319.9784; found: 319.9771.
17. Typical procedure for β-halogeno phosphonium salts **2**: 1.05 g (4 mmol) of triphenylphosphine was added to 0.51 g (1.6 mmol) of iodo aminoacid **5b** in 10 mL of $CHCl_3$. The mixture was heated under reflux for 48 h. A part of the phosphonium salt **2b** was recovered by filtration, the residue was evaporated and was stirred in ether to extract the phosphine excess. The combined precipitates gave a white powder with 95% yield.
(*R*)-(−)-[2-(Carboxy)-2-(*N*-benzoyl-amino]-ethyl triphenylphosphonium bromide **2a**:
White solid; mp = 135°C; $[\alpha]_D^{20} = -37.4$ ($c=0.76$, MeOH) e.e. = 99%; IR (KBr, $\bar{\nu}$ cm^{-1}): 3413, 2904, 1741, 1623, 1439, 747; ^1H NMR (250 MHz CD_3OD) δ 7.93–7.42 (20H, m, *H* arom.), 5.06 (1H, ddd, $J=2.7$, $J=10.4$, $J=13.3$, C*H*), 4.26 (1H, ddd, $J=2.8$, $J=14.2$, $J=16.8$ C*H*HP), 4.03 (1H, ddd, $J=11.1$, $J=15.9$, $J=22.1$, CH*H*P); ^{13}C NMR (62.9 MHz CD_3OD) δ 172.9 (d, $J=15.8$, CO_2H), 170.4 (*C*OPh), 137.1, 135.8, 135.7, 135.3, 134.5, 134.1, 132.4, 132.2, 130.1, 129.3, 120.7, 119.3 (*C* arom.), 48.8 (*C*H), 26.3 (d, $J=55$, CH_2P); ^{31}P NMR (101 MHz CD_3OD) δ 22.32. HRMS (FAB+) anal. calcd for $C_{28}H_{25}PNO_3$ [M−Br]: 454.1572; found: 454.1560.
(*R*)-(−)-[2-(Carboxy)-2-(benzoyl-amino]-ethyl triphenylphosphonium iodide **2b**:
White solid; mp = 195°C; $[\alpha]_D^{20} = -42$ ($c=1.03$, MeOH) e.e. = 99%; IR (KBr, $\bar{\nu}$ cm^{-1}): 3413, 2925, 1741, 1624, 1439, 746; ^1H NMR (250 MHz CD_3OD) δ 7.92–7.38 (20H, m, *H* arom.), 5.10 (1H, ddd, $J=2.7$, $J=10.6$, $J=13.3$, C*H*), 4.29 (1H, ddd, $J=2.8$, $J=14.2$, $J=16.7$,

CHHP), 4.05 (1H, ddd, $J=11$, $J=16$, $J=22$, CHHP); ^{13}C NMR (62.9 MHz CD_3OD) δ 172.1 (d, $J=15.1$, CO_2H), 169.7 (COPh), 136.4, 136.3, 135, 134.9, 133.8, 133.3, 131.6, 131.4, 129.3, 128.4, 119.9, 118.5 (C arom.), 48.5 (CH), 25.6 (d, $J=54.7$, CH_2P); ^{31}P NMR (101 MHz CD_3OD) δ 22.20. Anal. calcd for $C_{28}H_{25}PINO_3$ (581): C, 57.83; H, 4.30; N, 2.41; found: C, 57.99; H, 4.36; N, 2.29. HRMS (FAB+) anal. calcd for $C_{28}H_{25}PNO_3$ [M–I]: 454.1572; found: 454.1582.

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