Tetrahedron: Asymmetry Vol. 3, No. 3, pp. 377-378, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

Enantioselective Synthesis of α-Amino Phosphonic Acids by an Application of Stereoselective Opening of Homochiral Dioxane Acetals with Triethyl Phosphite

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(*Received* 7 *February* 1992)

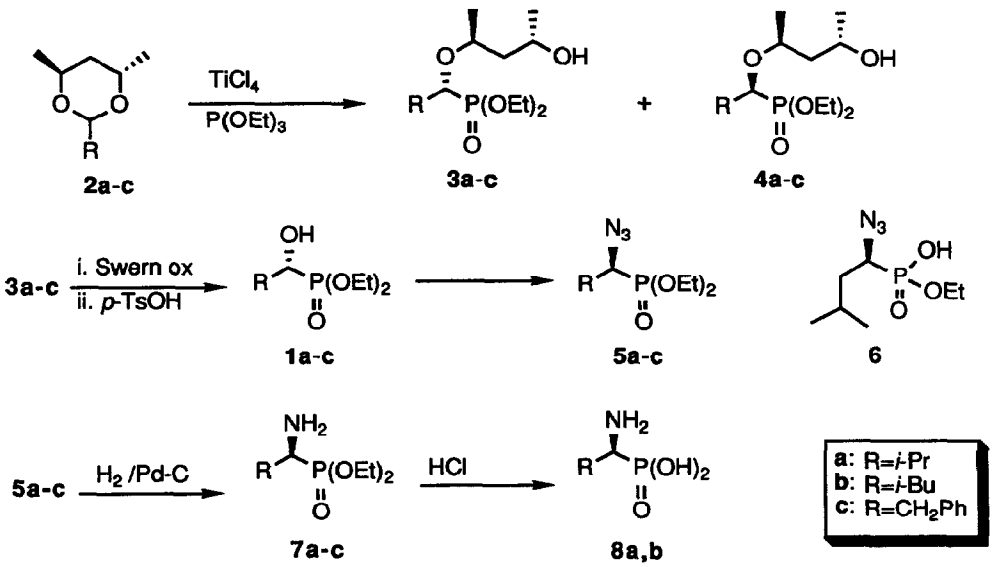
Summary: Stereoselective opening of homochiral acetals (**2a-c**) with triethyl phosphite was applied to the enantioselective synthesis of phosphono alcohols (**1a-c**), which were succssefully converted to the α-amino phosphonic acid diethyl esters (**6a-c**).

α-Amino phosponic acids, the phosphonic acid analogs of α-amino carboxylic acids, have received considerable attention over the past decade in medicinal and synthetic organic chemistry owing to their potential biological activity and their unique structural features.[1] They have recently proved to be effective components for the synthesis of transition state analog inhibitors for protease.[2] Although several methods for asymmetric synthesis of these important analogs was recently available,[3] there still exists a requirement for new methods which have simplicity and generality. In this communication, we disclose a new asymmetric synthesis of α-amino phoshonic acids which involves stereoselective opening of homochiral dioxane acetals[4] with heteroatomic nucleophile such as triethyl phosphite, in the presence of a Lewis acid as a key reaction.

Lewis acid promoted stereoselective cleavage of homochiral acetals with various nucleophiles has proved to be a valuable method for the synthesis of chiral secondary alcohols high of optical purity,[4] however, to the best of our knowlege, the level of asymmetric induction and usefulness of such reactions with heteroatomic nucleophiles are virtually unknown. Thus, we examined Lewis acid mediated cleavage of homochiral acetals by using triethyl phosphite as nucleophile to obtain chiral phosphono alcohols (**1**), useful intermediates for the synthesis of α-amino phosphonic acids.

Treatment of acetal (**2a**), derived from (+)-(2*S*,4*S*)-pentanediol, with triethyl phosphite (1.3 equiv.) in the presence of $TiCl_4$ (2 equiv.) in CH_2Cl_2 at –78 °C for 2 h gave a mixture of **3a** and **4a** in 86% yield.[5] ^{1}H- NMR (300 MHz) analysis of the product revealed diastereomeric ratio of 93 : 7. Similarly high diasteroselectivities were observed in the reaction of **2b,c** [**3b**:**4b** = 94:6, 87%; **3c**:**4c** = 91:9, 88%]. Other Lewis acids such as BF_3•Et_2O, $TiCl_4$-$Ti(OiPr)_4$, or TMSOTf were found to be ineffective under the same conditions as above and the starting acetals remained unchanged. Major diasteromers (**3a-c**) were readily separated by column chromatography on silica gel. Swern oxidation of **3a-c**, followed by treatment with *p*-TsOH in aqueous dioxane under reflux for 12 h yielded the desired phosphono alcohols (**1a-c**), [**1a**, 80%, $[\alpha]_D^{20}$ –4.0 (c 1.0, $CHCl_3$); **1b**, 87%, $[\alpha]_D^{20}$ –16.5 (c 0.5, $CHCl_3$); **1c**, 83%, $[\alpha]_D^{20}$ –21.3 (c 0.9, $CHCl_3$)]. The optical purities of **1a-c** were estimated as >95% ee by ^{1}H-NMR (300 MHz) analysis of their Mosher esters derived from both (+)- and (–)-α-methoxy-α-trifluoromethylphenylacetic acid. The absolute stereostructures of **1** were initially assigned as R on mechanistic grounds[4] and eventually confirmed by chemical correlation with known α-amino phosphonic acids.

Conversion of **1a-c** to the corresponding azides (**5a-c**) in an S_N2 manner was readily achieved by the Mitsunobu reaction. Reaction of **1a-c** with triphenylphosphine (1 equiv.), diethyl azodicarboxylate (1.2 equiv.), and diphenylphosphoryl azide (1.2 equv.) in THF at 0→25 °C for 12 h furnished the azides (**5a-c**) [**5a**, 72%, $[\alpha]_D^{20}$+45.1 (c 1.0, $CHCl_3$); **5b**, 65%, $[\alpha]_D^{20}$+36.3 (c 1.0, $CHCl_3$); **5c**, 46%, $[\alpha]_D^{20}$+57.8 (c 0.7, $CHCl_3$)]. Formation of mesylate of **1b** with mesylchloride in CH_2Cl_2 in the presence of triethylamine and subsequent displacement of the mesylate with sodium azide in DMF (18-crown-6) at 100 °C gave azide monoester (**6**) in 65% yield. Catalytic hydrogenation of **5a** with 10% Pd-C in EtOH under atomospheric pressure affored (+)-phosphovaline diethyl ester (**7a**), $[\alpha]_D^{20}$ +0.75 (c 2, $CHCl_3$), lit.,[3b] $[\alpha]_D^{25}$ +0.4 (c 1.7, $CHCl_3$), in 75% yield establishing its (S)-configuration. Likewise, **5b, c** were transformed to corresponding α-amino phosphonic acid diethyl esters (**7b, c**) in 78 and 60% yield, respectively, [**7b**, $[\alpha]_D^{20}$+18.4 (c 0.9, $CHCl_3$); **7c**, $[\alpha]_D^{20}$+11.0 (c 0.8, $CHCl_3$)]. Acidic hydrolysis (conc. HCl, 100 °C, 12 h) of **7a,b** gave **8a**, mp 272-273 °C, $[\alpha]_{577}^{20}$–0.6 (c 2.0, 1 N NaOH), and **8b**, mp 277-278 °C, $[\alpha]_{577}^{20}$+24.5 (c 1.0, 1 N NaOH). The physical data of **8a,b** were identical with those of (*S*)-phosphovaline and (*S*)-phospholeuicine in the literature[1] in all respects.



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5. All new compounds were obtained as oils unless stated otherewise, and provided satisfactory analytical and spectroscopic data.