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Silicon Directed Asymmetric Synthesis of (*1R, 2S*)-(-)-(1,2-Epoxypropyl)phosphonic Acid (Fosfomycin) from (*S*)-Lactaldehyde.

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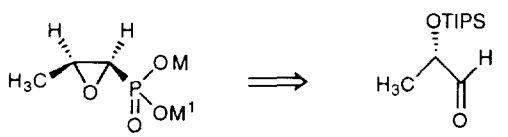
Abstract: The title compound is obtained in high diastereomeric purity based on the stereoselective addition of trimethylsilyldibenzylphosphite (TMSDBP) to *O*-triisopropylsilyloxy (*S*)-lactaldehyde.

Over the years, the synthesis of α-alkyl phosphonic acids and the related phosphonopeptides has been an important area of study, particularly in connection with the search for biologically active surrogates for the corresponding carboxylic acids.[1,2] (1*R*, 2*S*)-(-)-(1,2-Epoxypropyl)phosphonic acid **1a** (fosfomycin)[3] is a very interesting representative of this class of compounds. It is an antibiotic of unusual structure originally isolated from fermentation broth of *Streptomyces fradiae* [4] or *Pseudomonas syringae* [5]. Fosfomicyn is present on the pharmaceutical market as the disodium **1b**[6], calcium **1c** and tris(hydroxymethyl)ammonium **1d**[7] salts. Presently a number of methods are available for its synthesis[8].

Recently we have been involved in a study directed towards the stereospecific addition of diethylphosphite or its trimethylsilylderivative to enantiopure α-silyloxy aldehydes[9] or α-silyloxy-*N*-trimethylsilyl imines[10] in view to achieving a highly diastereoselective route to α-hydroxy phosphonic acids or α-amino phosphonic acids to be used for the preparation of biologically significant molecules.

We now extend our work in this area by describing the asymmetric synthesis of fosfomycin **1** based on the stereoselective addition of trimethylsilyldibenzylphosphite[11] **3** (TMSDBP) to the (*S*)-triisopropylsilyloxy-lactaldehyde[12] **2**. (Fig. 1 and Scheme 1)

Fig. 1

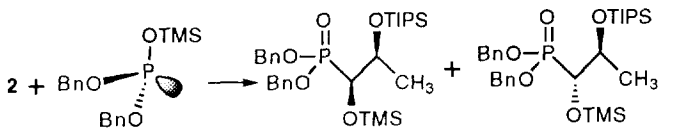


1a: M=M[1]=H
b: M=M[1]=Na
c: M=M[1]=Ca
d: M=H, M[1]=$NH_3[C(CH_2OH)_3]$

2

The silylation of the phosphorylating reagent is crucial for the formation of the hydroxyphosphonic esters since, under our reaction conditions, dibenzylphosphite (DBP) does not give the desired ester. This behaviour is not surprising: it was shown[13], in fact, that the spontaneous tautomerism of dialkylphosphites favours the tetra-coordinate electrophilic species, $(RO)_2P(O)H$ rather than the tri-coordinate nucleophilic species $(RO)_2P(OH)$. In order to increase the nucleophilicity of the phosphorylating agent the latter must be frozen by means of silylation. Accordingly to a stirred solution of **3** (2 mmol), [prepared from DBP (2 mmol), TEA (2.4 mmol), TMSCl (2.4 mmol), 45 m, 0°C in CH_2Cl_2 (30 ml)] was added at -78°C a solution of (*S*)-triisopropylsilyloxy lactaldehyde **2** (2 mmol, 0.46 g) in CH_2Cl_2 (2 ml). The reaction mixture was stirred for 3 hr at -78°C. A saturated solution of NH_4Cl in water was added and the reaction extracted with additional 50 ml of CH_2Cl_2. Usual work up furnished the crude adducts[14] **4a** and **4b**.

Scheme 1

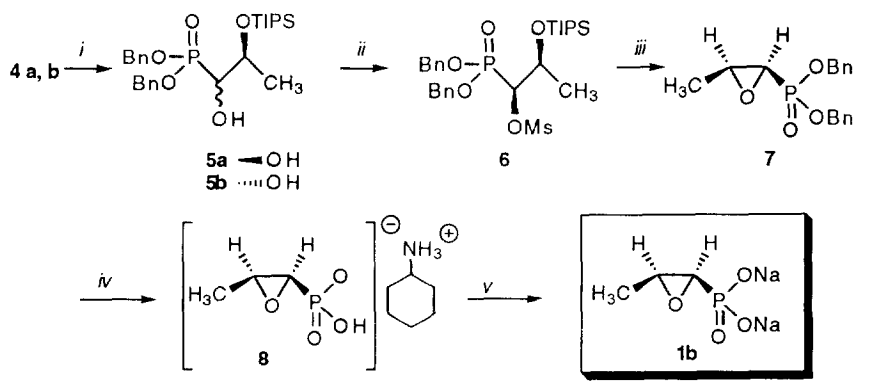


3 **4a** **4b**

90 10

Exposure (6 hr, r.t., monitoring t.l.c. until disappearance of the starting material) of the crude reaction mixture to citric acid (4.8 mmol, 0.92g) in methanol (30 ml), removal of methanol followed by flash chromatography (hexane/ethyl acetate 60/40), afforded the corresponding α-hydroxy derivatives **5a** and **5b** (0.78g, 80% yield, 90/10 ratio)[15]. Treatment of the α-hydroxy phosphonates **5** (1 mmol, 0.5g) with methanesulfonyl chloride (2 mmol, 0.23g) and TEA (2 mmol, 0.2g), in CH_2Cl_2 (20 ml) afforded, after work-up and flash column chromatography, the corresponding methansulfonate **6** (0.38 gr, 65 % yield).

Scheme 2

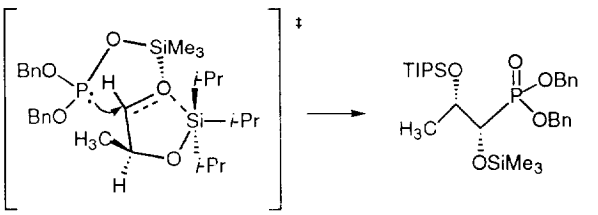


Reagents and conditions: *i*: Citric acid/MeOH; *ii*: MsCl/TEA/CH_2Cl_2/Flash chromatography; *iii*: TBAF/SiO_2/THF/r.t./8 h; *iv*: H_2, Pd/C 10%/ Cyclohexylamine/ methanol; *v*: Dowex 50WX8 (Na^+).

Compound **6** (0.17 mmol, 0.1g) was treated overnight at r.t. with TBAF on silica gel (Fluka) (0.15g) in THF (5 ml) with the aim to simultaneously deprotect the hydroxy functionality and to achieve the required ring closure (Scheme 2). Compound **7** was obtained in 77% yield (0.043 g) as a single diastereoisomer[16]. Hydrogenolysis of this product in the presence of cyclohexylamine (2eq) in MeOH, followed by purification on Dowex 50WX8 (Na^+ form) furnished the sodium salt of fosfomycin **1b** in 76% .

The effect of the triisopropylsilyl protecting group including its bulkiness[17] on the stereochemical outcome of the reaction is very surprising and confirms the trend shown by other α-silyloxy aldehydes when reacted with TMSDEP[9]. If the *syn* diastereoselectivity is explained by a cyclic Cram model, a bicyclic transition state **A** involving two penta-coordinate silicon atoms[18] (Fig. 2) must be invoked. Hypervalent silicon intermediates have been proposed in the allylation of carbonyl compounds, in the reaction of *O*-silyl *N,O*-ketene acetals with aldehydes and in uncatalyzed aldol addition.[19] Neverthless we are fully aware that the mechanism proposed is only *a working hypothesis* and invites criticism, so currently much more work in terms of theoretical and experimental studies is being undertaken.

Figure 2



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14 The diastereomeric disilyloxy derivatives **4a** and **4b**, as well as the intermediates **5,6,7,8** were fully characterized by ^1H, ^{13}C, and ^{31}P NMR, IR, MS and elemental analyses; the absolute configuration at C_1 and C_2 was assigned on the basis of the absolute configuration of **1b**, taking into account that the configuration at C_1 is inverted in the epoxidation step. For an elegant structural study of fosfomycin see: von Carstenn-Lichterfeld, C.; Fernandez-Ibanez, M. *J. Chem. Soc., Perkin Trans. II* **1983**, 943. Selected spectral data are as follows:

Compound **5a:** $[\alpha]_D^{20}$=+4.06 (*c* 1.62, $CDCl_3$); $[\alpha]_{365}^{20}$ =+11.4 (*c* 1.62, $CDCl_3$). ^1H NMR ($CDCl_3$) p.p.m.: 7.33 (s, 10H); 5.06 (m, 4H); 4.32 (1H, ddq J=5.84, 7.84, 6.16); 3.69 (1H, ddd, J=5.84, 5.84, 3.7); 3.07 (1 H, dd, J=3.7 , 14.4); 1.33 (3H, d, J=6.16); 1.04 (21H, bs). ^{13}C NMR ($CDCl_3$) p.p.m.: 12.7, 17.9, 18.0, 21.41 (d, J=6.2), 67.75 (d, J=6.74), 68.13 (d, J=7.0), 68.35 (d, J=5.3), 73.33 (d, J=160.8), 128.03, 128.31, 128.36, 128.49, 128.52, 136.30 (d, J=5.85), 136.42 (d, J=6.5). ^{31}P NMR ($CDCl_3$) p.p.m.: 21.09.

Compound **6:** $[\alpha]_D^{20}$= +3.6 (*c* 1.50, $CHCl_3$); $[\alpha]_{365}^{20}$ = +11.0 (*c* 1.50, $CHCl_3$). ^1H NMR ($CDCl_3$) p.p.m.: 7.33 (s, 10H); 5.06 (m, 4H); 4.78 (1H, dd, J=5.8, 9.5); 4.38 (1H, ddq, J=5.8, 6.28, 16.6); 2.97 (3H, s); 1.41 (3H, d, J=6.28); 1.04 (21H, bs). ^{13}C NMR ($CDCl_3$) p.p.m.: 12.66, 17.95, 18.02, 20.10 (d, J=6.0), 38.92, 67.75 (d, J=6.7), 68.28 (d, J=7.0), 68.40 (d, J=5.3), 79.59 (d, J=163.0), 128.19, 128.28, 128.61, 135.8 (d, J=5.0). ^{31}P ($CDCl_3$) p.p.m.: 16.08.

Compound **7:** $[\alpha]_D^{20}$ = +4.4 (*c* 2.15, $CDCl_3$); $[\alpha]_{365}^{20}$= +11.6 (*c* 2.15 $CDCl_3$). ^1H NMR ($CDCl_3$) p.p.m.: 7.35 (bs, 10H); 5.10 (m, 4H); 3.23 (1H, ddq, J=4.5, 5.5, 6.14); 2.95 (1H, dd, J=4.52, 28.0); 1.55 (3H, d, J=5.5). ^{13}C NMR ($CDCl_3$) p.p.m.: 14.10, 50.1 (d, J=203), 53.64, 67.76 (d, J=6.1), 68.12 (d, J=6.1), 128.01, 128.08, 128.54, 128.59, 135.89 (d, J=6). ^{31}P ($CDCl_3$) p.p.m.: 18.24.

Compound **1b:** $[\alpha]_{365}^{20}$= -18.0 (*c* 1.25, H_2O) [Lit.8c $[\alpha]_{365}^{20}$= -19.0 (*c* 10, H_2O)]. ^1H NMR (D_2O) p.p.m.: 3.09 (1H, ddq, J=5.3, 5.5, 5.6); 2.64 (1H, dd, J=5.3, 18.6); 1.30 (3H, d, J=5.6). ^{13}C NMR (D_2O) p.p.m.: 16.06, 57.01 (d, J=1.75), 57.5 (d, J=174.8). ^{31}P NMR (D_2O) p.p.m.: 10.68.

15 The diastereomeric ratio was determined by a combinated ^1H and ^{31}P NMR analysis of the crude reaction mixture both of TMS derivatives and hydroxy phoshonic ester derivatives. The diastereomeric alcohols may be separated using as eluent methylene chloride/pentane/acetone 45/45/10. Nevertheless the separation of the diastereomers as mesylate derivatives is more efficient.

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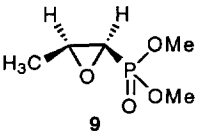

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