Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2005, 15(3), 98–99

Mendeleev Communications

Methyl *ent*-16α-dichlorophosphitobeyeran-19-oate as the first example of phosphorylated diterpenoid derivatives of the beyerane series

Vera L. Mamedova, Kristina A. Nikitina, Vakhid A. Mamedov, Vladimir E. Kataev and Vladimir A. Alfonsov*

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 73 2253; e-mail: alfonsov@iopc.knc.ru

DOI: 10.1070/MC2005v015n03ABEH001990

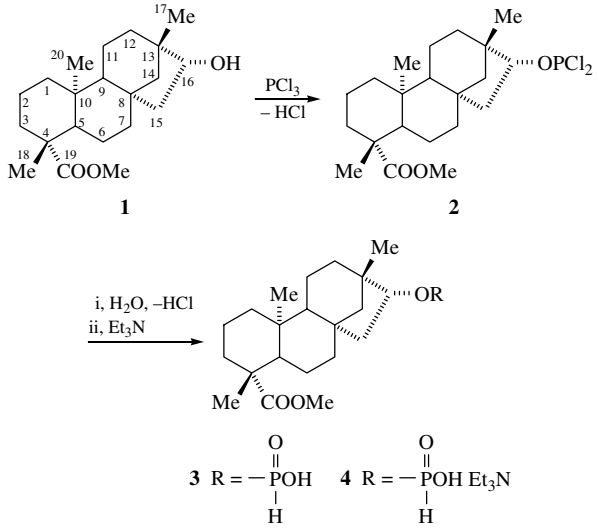
The interaction of *ent*-16α-hydroxybeyeran-19-oate with PCl_3 yielded methyl *ent*-16α-dichlorophosphitobeyeran-19-oate, whose hydrolysis resulted in methyl *ent*-16α-phosphitobeyeran-19-oate, a promising reagent for stereoselective synthesis and analysis.

A brisk demand for enantiopure compounds in pharmaceutical industry and fine organic synthesis to obtain chiral organometallic catalysts makes the search of new inexpensive natural and synthetic sources of chirality vitally important.[1,2] The progress achieved in supramolecular chemistry allowed one to use enantiopure compounds for the synthesis of chiral molecular receptors.[3]

We have studied[4] the synthetic potential of the natural diterpenoid isosteviol and its derivatives, easily available from the plant Stevia.[5] The advantages of this compound are as follows: (i) 100% enantiomeric purity in contrast to other terpenoids, which exist in a scalemic form; (ii) its reasonably high content (up to 10%) and easy isolation from natural raw materials;[5] (iii) the presence of highly reactive centres capable

of functionalization; and (iv) stability of its stereochemical configuration and high stereoselectivity upon its modification.[4,6] Until recently, isosteviol was not used in organoelement synthesis, including organophosphorus synthesis. At the same time, organophosphorus compounds, in particular, trivalent phosphorus derivatives such as hydrophosphoryl compounds,[7] are rarely used in asymmetric synthesis and chiral modification.[8]

Here we report the phosphorylation of methyl *ent*-16α-hydroxybeyeran-19-oate **1**. The compound was obtained in an enantiopure form by the reduction of isosteviol methyl ester.[6] It has seven chiral carbon atoms in the beyerane skeletone, namely, (*R*)-C^4, (*S*)-C^5, (*R*)-C^8, (*S*)-C^9, (*S*)-C^{10}, (*S*)-C^{13} and (*R*)-C^{16}.



The interaction of **1** with an excess of phosphorus trichloride results in the formation of a corresponding Menshutkin chloroanhydride, methyl *ent*-16α-dichlorophosphitobeyeran-19-oate **2**. Its structure was proved by NMR spectra.† (^{31}P NMR, δ: 176.10. ^{1}H NMR, δ: 4.60 (HCOP, $^3J_{HP}$ 14.9 Hz, $^3J_{HH_a}$ 10.5 Hz, $^3J_{HH_b}$ 3.5 Hz). Hygroscopic dichlorophosphite **2** is easily hydrolysed in air to form methyl *ent*-16α-phosphitobeyeran-19-oate **3**,‡ the first hydrophosphoryl compound with a chiral beyerane substituent at phosphorus. Compound **3** crystallised from the reaction mixture in 84% yield, and it had a characteristic ^{31}P NMR spectrum with a doublet of doublets [δ_P 8.01 (J_{PH} 705.3 Hz, $^3J_{PH}$ 13.6 Hz) in $CDCl_3$].

The ^{1}H NMR spectra of compound **3** and its precursor **1** are very similar. The ^{1}H NMR spectrum of **1** has a doublet of doublets of the methyne proton HCOH with δ 3.87 ($^3J_{HH_a}$ 10.8 Hz, $^3J_{HH_b}$ 4.5 Hz). The ^{1}H NMR spectrum of compound **3** has a multiplet of the methyne proton HCOP with δ 4.47 ($^3J_{PH}$ 13.6 Hz, $^3J_{HH_a}$ 10.6 Hz, $^3J_{HH_b}$ 3.9 Hz). The proton bonded to phosphorus has δ 6.80 (J_{HP} 705.3 Hz). Similar coupling constants for compounds **1**, **2** and **3**, the absence of any additional signals in the spectrum give evidence that phosphite **3** is diastereomerically pure. Thus, no racemization of the C^{16} atom is observed upon phosphorylation of alcohol **1** and hydrolysis of dichlorophosphite **2**.

Compound **3**, being an acid, is able to form salts with organic bases. For example, its interaction with triethylamine gives salt **4**.§

This property of enantiopure phosphite **3** may be used for analytical purposes, for example, to determine the enantiomeric purity of chiral amines.[9]

References

1 M. Rouhi, *Chem. Eng. News*, 2002, **80** (23), 43.
2 *Chirality in Industry II: Developments in the Commercial Manufacture and Applications of Optically Active Compounds*, eds. A. N. Collins, G. Sheldrake and J. Crosby, John Wiley & Sons, New York, 1997.
3 J.-M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, VCH, Weinheim, New York, Basel, Cambridge, Tokyo, 1995.
4 V. A. Alfonsov, O. V. Andreeva, G. A. Bakaleynik, D. V. Beskrovny, V. E. Kataev, G. I. Kovyljaeva, I. A. Litvinov, O. I. Militsina and I. Yu. Strobykina, *Mendeleev Commun.*, 2003, 234.
5 K. C. Phillips, *Dev. Sweeteners*, 1987, 1.
6 V. A. Alfonsov, G. A. Bakaleynik, A. T. Gubaidullin, V. E. Kataev, G. I. Kovyljaeva, A. I. Konovalov, I. A. Litvinov, I. Yu. Strobykina, O. V. Andreeva and M. G. Korochkina, *Zh. Obshch. Khim.*, 2001, **71**, 1213 (*Russ. J. Gen. Chem.*, 2001, **71**, 1144).
7 E. E. Nifantyev, *Khimiya gidrofosforil'nykh soedinenii* (*Chemistry of Hydrophosphoryl Compounds*), Nauka, Moscow, 1983 (in Russian).
8 O. I. Kolodiazhnyi, *Tetrahedron Asymmetry*, 1998, 1279.
9 D. Parker, *Chem. Rev.*, 1991, 1441.

Received: 1st July 2004; Com. 04/2315

† The ^{31}P NMR spectra were recorded on a Bruker CXP-100 (36.48 MHz) spectrometer with an external standard of 85% H_3PO_4. The ^{1}H NMR spectra were recorded on an AVANCE-600 spectrometer (600 MHz). In all the cases, $CDCl_3$ was used as a solvent except for compound **2**, recorded in a soltuion of PCl_3. IR spectra were recorded using a Vector 22 Bruker Fourier spectrometer.

Methyl ent-*16α-dichlorophosphitobeyeran-19-oate* **2**. 0.298 mmol of methyl *ent*-16α-oxybeyeran-19-oate **1** and 3 ml of PCl_3 were mixed at room temperature. After 1 h from the beginning of the reaction, the ^{31}P and ^{1}H NMR spectra of the reaction mixture were measured. The rotation angle was measured in the reaction mixture. $[\alpha]_D^{20}$ = –96.4 (*c* 1.17, PCl_3 + benzene). Concentration *c* was calculated taking into account the quantitative yield of **2**.

‡ *Methyl* ent-*16α-phosphitobeyeran-19-oate* **3**. The reaction mixture from the previous experiment was left to stand in air for 24 h to give crystalline **3**. The crystals were washed with petroleum ether, filtered off and dried in a vacuum. Mp 148.5 °C. $[\alpha]_D^{20}$ = –39.8° (*c* 0.65, benzene). Compound **3** can be obtained faster if the reaction mixture is treated with water. IR (Nujol, ν/cm^{-1}): 1035 (P–O–C), 1252 (P=O), 1735 (C=O), 2444 (P–H), 3100–3600 (OH). Found (%): C, 63.28; H, 8.89; P, 7.80. Calc. for $C_{21}H_{35}O_5P$ (%): C, 63.30; H, 8.85; P, 7.77.

§ *Methyl* ent-*16α-phosphitobeyeran-19-oate triethylammonium salt* **4**. To 0.673 mmol of compound **3**, 3 ml of triethylamine was added, the reaction mixture was heated to boiling and left for 12 h. The crystals were filtered off, washed with petroleum ether and dried in a vacuum. Yield 93%. Mp 41 °C. $[\alpha]_D^{20}$ = –42.0° (*c* 0.70, benzene). ^{1}H NMR ($CDCl_3$) δ: 0.70 (s, 3H, 10-Me), 0.93 (s, 3H, 13-Me), 1.15 (s, 3H, 4-Me), 1.32 (t, 9H, MeCN, $^3J_{HH}$ 7.1 Hz), 3.06 (q, 6H, CH_2N), 3.61 (s, 3H, COOMe), 4.25 (ddd, 1H, 16-CH, $^3J_{PH}$ 14.6 Hz, $^3J_{HH_a}$ 10.4 Hz, $^3J_{HH_b}$ 3.9 Hz). IR (Nujol, ν/cm^{-1}): 1051 (P–O–C), 1202 (P=O), 1721 (C=O), 2367 (P–H), 2492, 2677, 2738 (N$^+$–H). Found (%): C, 65.01; H, 10.11; N, 2.77; P, 6.32. Calc. for $C_{27}H_{50}NO_5P$ (%): C, 64.90; H, 10.09; N, 2.80; P, 6.20.