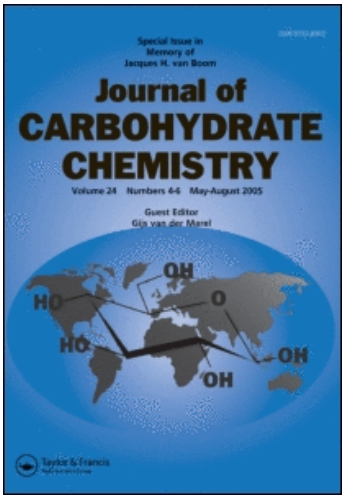

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COMMUNICATION

SYNTHETIC APPROACH TO OLGUINE: EPC[1] PREPARATION OF ETHYL 6,7-ANHYDRO-4-O-BENZYL-2,3-DIDEOXY-α-D-ALTRO-OCT-2-ENO-1,8-DIALDO-1,5-PYRANOSIDE

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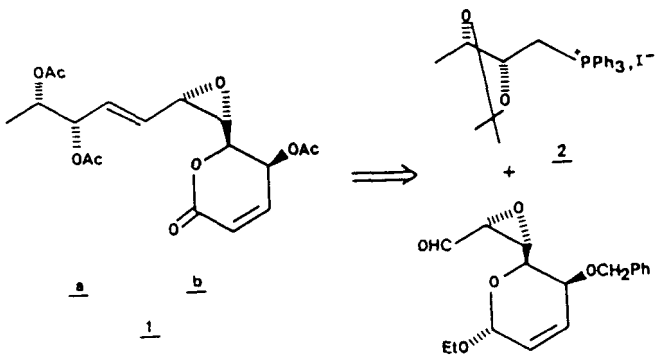
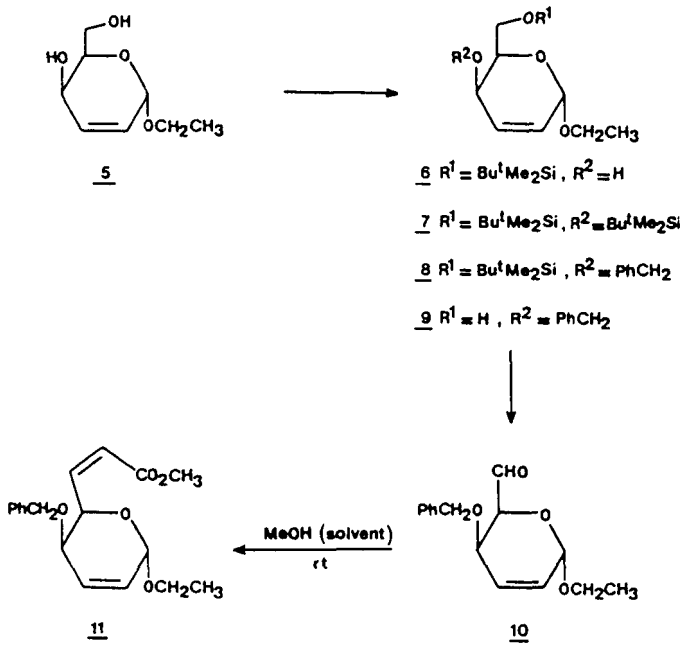
(+)-Olguine (**1**) is a natural product isolated in our laboratory[2] from a non-classified species of the genus Hyptis. It shows antileukemic activity *in vitro*[3]. We are interested in the synthesis of olguine and related compounds (such as diastereomers) in order to test their physiological activity.

Our synthetic plan relies on the coupling of the two compounds **2** and **3**, synthetic equivalents of the fragments a and b *(Scheme 1)*. Recently,[4] we have prepared the phosphonium salt **2**, in enantiomerically pure form, starting from (R,R)-tartaric acid.

In the present communication, we report the synthesis of ethyl 6,7-anhydro-4-O-benzyl-2,3-dideoxy-α -D-altro-oct-2-eno-dialdo-1,5-pyranoside (**4**), the enantiomer of compound **3**, starting from D-glucose *(Scheme 3)*.



Scheme 1

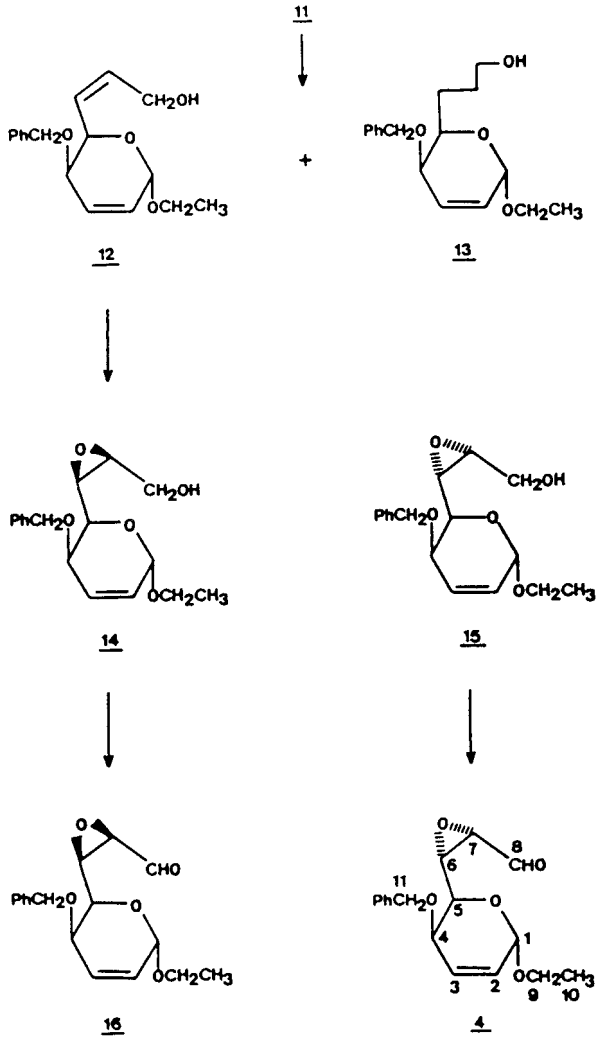


Scheme 2

Compound **5** was prepared from D-glucose by known methods,[5]. Selective monosilylation of **5** was achieved using the conditions reported by Chaundhary and Hernández[6] to afford **6**[7] (96% yield), $|\alpha|_D^{25} = -83°$, and **7**[7] (3% yield), $|\alpha|_D^{25} = -73°$. The benzylation of **6** was quantitative using 5.0 equivalents of sodium hydride and 2.0 equivalents of benzyl bromide in THF at room temperature,[8] affording **8**,[7] $|\alpha|_D^{25} = -133°$. The desilylation of **8** was very smooth using tetrabutylammonium fluoride trihydrate in THF at room temperature, affording **9**[7] (99% yield), $|\alpha|_D^{25} = -238°$. This alcohol was oxidized to the aldehyde **10**[7] (75% yield), $|\alpha|_D^{25} = -13°$, with PCC[9] in the presence of 4Å molecular sieves.[10]

The elongation of the chain was achieved through Wittig methodology. The reaction of **10**, with methoxycarbonylmethylenetriphenylphosphorane[11] in methanol at room temperature was stereospecific[12] yielding the ester **11**,[7] $|\alpha|_D^{25} = -255°$, as the only product (78% yield), *(see Scheme 2)*.

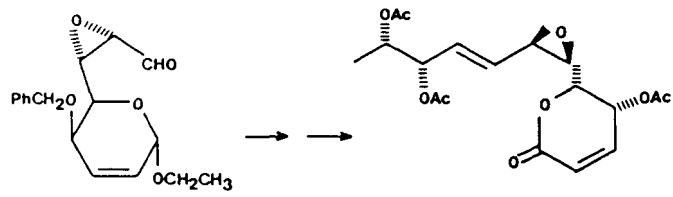
The reduction of **11** with $LiAlH_4$ in THF at -20 °C yielded a mixture of the allylic alcohol **12** (66% yield), and the corresponding saturated compound **13** (25% yield), difficult to separate either by column chromatography or fractional crystallization. DIBAH reduction of **11** in ether at 0 °C yielded a 10:1 mixture



Scheme 3

of **12** and **13** with 86% overall yield, from which **12**[7] could be purified, $|\alpha|_D^{25} = -156°$.

The epoxidation of **12** with tert-butylhydroperoxide, in the presence of vanadium acetoacetate[13] in CH_2Cl_2 at 0 °C was very slow. An inseparable mixture of the two possible epoxyalcohols **14** and **15** was obtained *(see Scheme 3)* in 3% overall yield; 45% of the starting material was also recovered. The analysis of the ^1H NMR spectrum of the mixture indicated an approximate ratio of 4:6, compound **15** being the major one.



4 17

Scheme 4

When the reaction was carried out with *m*-CPBA in $CHCl_3$ solution at room temperature, the epoxidation was practically quantitative (98%) yielding a mixture of **14** and **15** which, without separation, was oxidized with PCC/molecular sieves to the epoxialdehydes **16**[15] and **4**[15] respectively (1.8:1.0 ratio) in 72% overall yield. The stereoselectivity observed in the epoxidation of **12** with *m*-CPBA and TBHP/V^{5+} was in agreement with that reported for model compounds.[4]

The reaction of **12** with TBHP in the presence of titanium tetraisopropoxide and diethyl (S,S)-tartrate as an additive at -10 °C during one month, gave **15**[14] as the only product (70% yield). Pure epoxyalcohol **14**[14] was obtained by $NaBH_4$ reduction of **16** in ethanol at 0° C (77% yield). The stereochemistry of the oxirane ring has been assigned as indicated *(see Scheme 3)* considering the results obtained by the Sharpless procedure,[16] and also the different chemical shifts of the two oxirane carbon atoms; this is in agreement with previous results obtained with oxiranes of identical configuration.[17]

Further work is being carried out in our laboratory, in order to transform **4** into the compound **17** *(see Scheme 4)*.

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14. Spectroscopic data: **14:** $|\alpha|_D^{25} = -187°$ ($CHCl_3$, c = 0.2). ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, t, J = 6 Hz, H-10), 2.15 (1H, s, broad, exchangeable with D_2O, OH), 3.10-3.95 (8H, m), 4.50 (1H, d, J = 12 Hz, OCH_2Ph), 4.70 (1H, d, J = 12 Hz, OCH_2Ph), 5.10 (1H, d, J = 2 Hz, H-1), 6.05 (2H, m, H-2, H-3), 7.25 (5H, s, aromatics) ppm. ^{13}C NMR (20 MHz) ($CDCl_3$): δ 138.2, 130.1, 128.5, 128.1, 120.1 (aromatics and olefinics), 93.8 (C-1), 70.9 (C-11), 70.1 (C-4), 67.6 (C-5), 64.0 (C-9), 60.7 (C-8), 56.8 (C-7)*, 55.7 (C-6), 15.3 (C-10) ppm.

15: $|\alpha|_D^{25} = -143°$ ($CHCl_3$, c = 0.1). ^{1}H NMR ($CDCl_3$): δ 1.17 (3H, t, J = 6 Hz), 1.84 (1H, s broad, exchangeable with D_2O, OH), 3.43 (4H, m), 3.80 (4H, m), 4.63 (2H, s, OCH_2Ph), 4.97 (1H, d, J = 2 Hz, H-1), 5.98 (2H, m, H-2, H-3), 7.30 (5H, s, aromatics) ppm. ^{13}C NMR (20 MHz) ($CDCl_3$): δ 137.9, 129.3, 128.5, 128.4, 127.9, 127.7, 126.7 (aromatics and olefinics), 93.9 (C-1), 71.7 (C-11), 68.4 (C-4)*, 67.5 (C-5)*, 64.2 (C-9)*, 61.0 (C-8), 56.7 (C-7), 54.2 (C-6), 15.2 (C-11) ppm.

* Exchangeable signals.

15. Spectroscopic data. **4:** $|\alpha|_D^{25} = -173°$ ($CHCl_3$, c = 0.15). ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.10 (3H, t, J = 6 Hz, H-10), 3.35-3.70 (4H, m, H-6, H-7, H-9a, H-9b), 3.75 (1H, dd, J = 5 Hz, 3 Hz, H-5), 4.10 (1H, dd, J = 5 Hz, 3 Hz, H-4), 4.55 (2H, s, H-11), 4.90 (1H, d, J = 3 Hz, H-1), 5.70-6.20 (2H, m, H-2, H-3), 7.30 (5H, s, aromatics), 9.45 (1H, d, J = 5 Hz, H-8) ppm. ^{13}C NMR (20 MHz) ($CDCl_3$) δ 197.5 (C-8),138.1, 133.8, 129.8, 128.5, 127.8, 126.2 (aromatics and olefinics), 93.8 (C-1), 71.2 (C-11), 67.7 (C-4), 67.4* (C-5), 64.1 (C-9), 57.7* (C-6), 15.1 (C-10) ppm.

16: $|\alpha|_D^{25} = -117°$ ($CHCl_3$, c = 0.32). ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.15 (3H, t, J = 7 Hz, H-10), 3.25-3.85 (5H, m, H-5, H-6, H-7, H-9a, H-9b), 4.15 (1H, dd, J = 5 Hz, 3 Hz, H-4), 4.45 (1H, d, J = 18 Hz, H-11a), 4.55 (1H, d, J = 18 Hz, H-11b), 5.10 (1H, d, J = 2 Hz, H-1), 5.95-6.10 (2H, m, H-2, H-3), 7.30 (5H, s, aromatics), 9.40 (1H, d, J = 5 Hz, H-8) ppm.

^{13}C NMR (20 MHz) ($CDCl_3$) δ 198.0 (C-8), 138.0, 129.9, 128.5, 127.9, 125.9 (aromatics and olefinics), 94.0 (C-1), 70.9 (C-11), 68.3* (C-4), 68.0* (C-5), 64.2 (C-9), 58.9 (C-7), 56.6 (C-6), 15.2 (C-10) ppm.

*Exchangeable signals.

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