Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 7, pp. 1907-1910, 1996
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0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00227-3

Synthesis of (5*R*, 7*S*, 13*S*)-13-Methoxy-1,6,8-Trioxadispiro[4.1.5.3]pentadecane

Rosa L. Dorta, Angeles Martín, Ernesto Suárez*

Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206-La Laguna, Tenerife, Spain

Thierry Prangé

L.U.R.E., Université Paris-Sud, Paris, 91405 ORSAY, Cedex, France

Abstract: The synthesis of (5*R*, 7*S*, 13*S*)- and (5*S*, 7*S*, 13*S*)-13-methoxy-1,6,8-trioxadispiro[4.1.5.3] pentadecane from tri-*O*-acetyl-D-glucal, by a convenient homologation of C-1 and C-6 atoms which led to an appropriate dihydroxyl intermediate **7**, is reported. The key steps for the construction of the two spiroacetal systems involved a double, step by step, radical abstraction promoted by (diacetoxyiodo)benzene and iodine.
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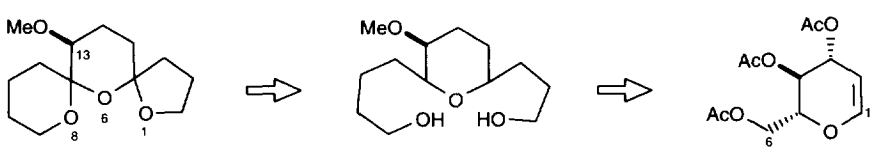
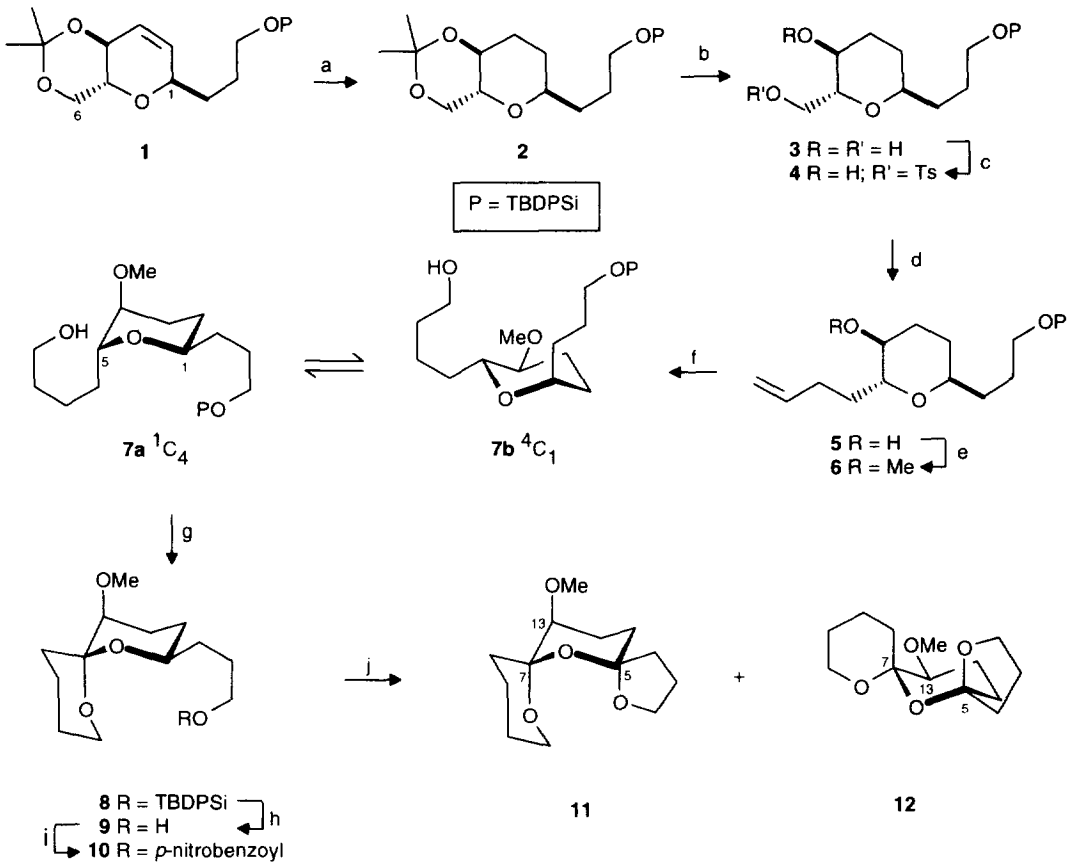
The remarkable interest in the area of the pharmacological and chemical behaviour of spiroacetals[1] prompted us to develop a convenient methodology for these compounds from available carbohydrates.[2] For the synthesis of analogous trioxadispiroacetals very few methods have been reported; thus, in the construction of polyether antibiotics containing a 1,6,8-trioxadispiro[4.1.5.3]pentadecane ring system in their skeletons such as salinomycin,[3] only two total syntheses have been achieved[4] and a few approaches published.[5] The potential versatility of our method for the formation of oxaspiro rings by H-abstraction promoted by hypervalent iodine reagents motivated us to apply it in the elaboration of tricyclic structures. As depicted in Scheme 1, starting from readily available tri-*O*-acetyl-D-glucal (C), a convenient homologation of the C-1 and C-6 atoms could lead to an intermediate (B), which could undergo simultaneously (or step by step) two cyclizations to give the trioxaspiroacetal derivative (A).



A B C

Scheme 1

Our synthetic approach to the trioxadispiro compound is outlined in Scheme 2. The intermediate **1** was obtained starting from tri-*O*-acetyl-D-glucal introducing allyltrimethylsilane at C-1 under Danishefsky condi-



Scheme 2 (a) $Pd(OH)_2/H_2$, EtOAc, 25 °C, (80%); (b) Amberlyst-15 (H^+) ion exchange resin, MeOH, 25 °C, 1 h, (88%); (c) TsCl, Py, 0 °C, 4 h, (88%); (d) $CH_2{=}CHCH_2MgBr$, Et_2O, 0 °C, 3 h, then rt, 1 h, (80%); (e) KOH, $(CH_3)_2SO_4$, acetone, 30 °C, then 50 °C, 4 h, (73%); (f) BH_3-THF, then NaOH, H_2O_2, (73%); (g) DIB, I_2, CCl_4, rt, 1.5 h, (43%); (h) Bu_4NF, THF, rt, 2 h, (86%); (i) *p*-nitrobenzoyl chloride, Py, rt, 4 h, (98%); (j) DIB, I_2, cyclohexane, rt, 2.3 h, (78%).

tions[6] and then following a similar methodology to that reported by Nicolaou.[7] After treatment of the olefin with hydrogen in the presence of $Pd(OH)_2$ as catalyst, which produced the reduced product **2**, our next target was the enlargement of the side chain at C-6. For this purpose the following group manipulations were realized: i) removal of the acetonide group by treatment with amberlyst-15 (H^+) ion exchange resin in MeOH; ii) tosylation of the resulting diol **3** which produced mainly the monotosyl derivative **4**; iii) treatment of **4** with allylmagnesium bromide in Et_2O affording **5**; iv) protection of the secondary alcohol on C-4 as its methyl ether **6** and v) hydroboration-oxidation of the olefin to produce the key intermediate **7**. This key molecule presents the number of carbons and the convenient functionality for subsequent elaboration to the trioxadispiro compound. Attempts to build the trioxadispiro compound directly from the diol of **7** (when P = H), by simultaneous double cyclization, failed affording the dioxaspiro[4.5] ring system and hindering further cyclization.[8] The 1,3-diaxial interactions with the group at C-1 seemed to hinder the radical abstraction of

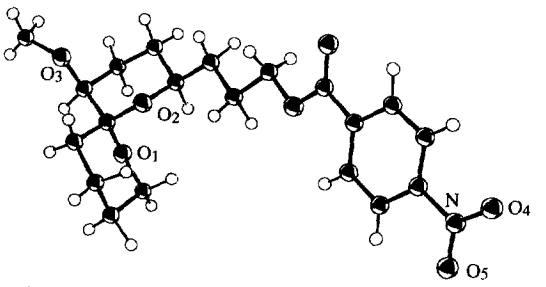


Figure 1. X-ray of compound **10**.

the C-5 proton through a seven-membered transition state.[2] A more efficient strategy involved first forming the dioxaspiro[5.5]undecane compound, accomplished by treatment of the alcohol **7** dissolved in CCl_4 with the DIB/I_2 system which gave compound **8**[9] as the sole product in 43% yield. The presence of a triplet at δ 2.92 (J = 2.5 Hz) indicates an equatorial disposition of the proton at C-13. A study by molecular mechanics using the MMX program[10] indicated that the energy for both chair conformers of **7** ($^4C_1$ and $^1C_4$) is similar (Δ = 0.09 Kcal/mol) allowing an equilibrium between them, the cyclization occurring from the conformation $^1C_4$ that avoids the 1,3-diaxial interactions between the hydrogen at C-5 and the side chain at C-1. The structure and stereochemistry of compound **8** were deduced from its spectroscopic data: COSY, TOCSY, HMBC and HMQC experiments; and confirmed by X-ray crystallography[11] (Fig. 1) of a crystalline *p*-nitrobenzoate ester derivative **10** (m.p. 82 °C), both ring systems adopting a chair conformation with a maximum number of anomeric effects and leaving the methoxy group in the axial disposition.

The treatment of compound **8** with tetrabutylammoniun fluoride afforded the alcohol **9**, which underwent intramolecular hydrogen abstraction when submitted to reaction with the DIB/I_2 system in cyclohexane at rt for 2.3 h to give the desired trioxadispiroacetals **11**[12] (58%) and **12**[13] (20%). The high instability of these compounds when traces of acid are present is noteworthy, and for this reason it was necessary to isolate them carefully. The NMR data of **11** showed a proton at δ 3.22 as a triplet J = 2.9 Hz, indicating the axial disposition for the methoxyl group at C-13, and a dramatic deshielding for the axial proton at C-14 (δ 2.67) owing to the 1,3-diaxial interactions with the oxygen atoms of the two adjacent rings. The molecular mechanics study gave this structure with the maximum number of anomeric effects as the thermodynamically more stable.

For compound **12**, we observed that the proton at C-13 appears as a double doublet (δ = 3.12, J = 3.9, 9.5 Hz) indicating an equatorial disposition for the methoxyl group. The correlation by ROESY between H-13 and H-4 revealed the preference for this minor compound to exist in the conformation $^4C_1$ for the central ring with two anomeric effects and the methoxyl group in equatorial position. The other conformation $^1C_4$, with the same number of anomeric effects but with an axial methoxyl group, is less favoured by 1.64 kcal/mol as determined by molecular mechanics. The structures of both compounds were confirmed by their spectroscopic data: COSY, ROESY, HMBC and HMQC.

Acknowledgement: This work was supported by the Investigation Programme no. B93-0171 of the Dirección General de Investigación Científica y Técnica and Programmes nos. 93/030 and 93/014 of the Dirección General de Universidades e Investigación del Gobierno de Canarias. We are grateful to Dr. J. A. Gavín for assistance with NMR experiments. A. M. thanks the Ministerio de Educación y Ciencia, Spain, for a fellowship.

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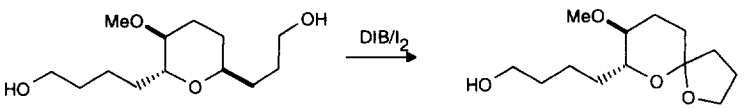
8. Compound i prepared by treatment of **7** with Bu_4NF was submitted to the DIB/I_2 system to give ii in 60% yield.



i ii

9. Compound **8**: $[\alpha]_D$ +47.1 ($CHCl_3$, *c* = 0.78); IR 3072, 2932, 2859, 1956-1823, 1112 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) 1.08-1.12 (1H, m), 1.17 (9H, s), 1.20-1.95 (12H, m), 2.25 (1H, br d, *J* = 12.0 Hz), 2.92 (1H, t, *J* = 2.5 Hz), 3.07 (3H, s), 3.50 (1H, m), 3.58-3.62 (2H, m), 3.71-3.77 (2H, m), 7.21-7.23 (6H, m), 7.78-7.81 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) 18.62 (t), 19.21 (s), 21.82 (t), 25.54 (t), 25.67 (t), 26.87 (3 x q), 29.23 (t), 32.19 (t), 32.64 (t), 56.56 (q), 60.04 (t), 64.35 (t), 68.80 (d), 78.61 (d), 96.36 (s), 127.74 (4 x d), 129.58 (2 x d), 134.25 (s), 134.28 (s), 135.74 (4 x d); MS (EI) *m/z* (rel intensity) 483 ($[M+H]^+$, 1), 451 (M^+-MeO, 1), 393 (31), 367 (13), 325 (8), 267 (22), 177 (56), 111 (19), 58 (100); Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.16; H, 8.78. Found: C, 72.31; H, 8.40.
10. MMX force field as implemented in PCMODEL (v. 4.0), Serena Software, Bloomington, IN 47402-3076.
11. The data were measured on a Philips PW-1100 four-circle diffractometer operating with Cu-K_α radiation (λ = 1.5418 Å) monochromated graphite. Crystal data for **10**: $C_{20}H_{27}O_7N$, tetragonal, space group $P4_32_12$, Z = 8, a = 11.258, b = 11.258, c = 33.46 Å. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
12. Compound **11**: $[\alpha]_D$ +38.6 ($CHCl_3$, *c* = 0.18); ^1H NMR (400 MHz, C_6D_6) 1.41-1.55 (1H, m), 1.59-1.66 (6H, m), 1.76 (1H, dddd, *J* = 13.60, 3.72, 3.72, 3.72 Hz), 2.00-2.09 (2H, m), 2.14 (1H, dd, *J* = 8.0, 8.3 Hz), 2.26 (1H, ddd, *J* = 13.3, 13.3, 4.0 Hz), 2.36 (1H, br d, *J* = 13.3 Hz), 2.67 (1H, m), 3.18 (3H, s), 3.22 (1H, t, *J* = 2.9 Hz), 3.79-3.89 (2H, m), 4.07-4.15 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) 19.1 (2 x t), 24.7 (t), 26.3 (t), 28.4 (t), 33.4 (t), 40.1 (t), 56.6 (q), 61.1 (t), 69.0 (t), 79.1 (d), 97.3 (s), 106.3 (s); MS (EI) m/z (rel intensity) 243 ($[M+H]^+$, 12), 242 (M^+, 16), 241 ($[M-H]^+$, 20), 225 (35), 211 (8), 209 (16), 193 (16), 142 (31), 84 (100); Anal Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.68; H, 8.78.
13. Compound **12**: $[\alpha]_D$ +22.2 ($CHCl_3$, *c* = 0.18); ^1H NMR (400 MHz, C_6D_6) 1.28-1.68 (6H, m), 1.84-2.03 (6H, m), 2.17 (1H, ddd, *J* = 2.7, 7.6, 7.6 Hz), 2.48 (1H, br d, *J* = 7.7 Hz), 3.12 (1H, dd, *J* = 3.9, 9.5 Hz), 3.38 (3H, s), 3.58-3.63 (1H, m), 3.70 (1H, ddd, *J* = 7.9, 7.9, 7.9 Hz), 3.99 (1H, ddd, *J* = 4.4, 8.2, 8.2 Hz), 4.06 (1H, ddd, *J* = 3.0, 11.0, 11.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) 1.91 (t), 23.2 (t), 24.7 (t), 26.1 (t), 29.1 (t), 32.5 (t), 38.4 (t), 58.0 (q), 61.5 (t), 68.0 (t), 81.9 (d), 98.0 (s), 106.8 (s).

(Received in UK 7 May 1996)