Pergamon

Tetrahedron Letters, Vol. 38, No. 50, pp. 8623-8626, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10370-7

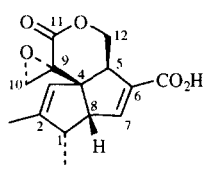
Enantiospecific approach to a quinane skeleton related to pentalenolactones

Silvina C. Pellegrinet and Rolando A. Spanevello*

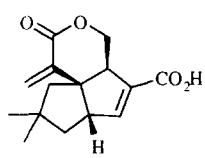
Instituto de Química Orgánica de Síntesis. CONICET - Universidad Nacional de Rosario.
Facultad de Ciencias Bioquímicas y Farmacéuticas. Casilla de Correo 991. 2000 Rosario, Argentina.

Abstract: A novel and general approach has been delineated for the enantiomerically pure synthesis of the angularly fused tricyclic system of the pentalenolactone family of compounds. D-Glucose is used as starting material and a diasteroselective Diels-Alder reaction sets the elements for the ring junctions.
© 1997 Elsevier Science Ltd.

The pentalenolactone type sesquiterpenoids are a growing family of structurally unprecedented natural products produced by prokaryotic organisms and share a unique tricyclic ring skeleton. Pentalenolactone (**1**)[1] was the first metabolite in this class to be isolated, its structure and absolute configuration were established in 1970 and more recently several new co-metabolites were isolated.[2] This substance has revealed a broad spectrum of activity as antibiotic, tumor inhibitor agent and also as a potent and specific antiviral agent.[3] Lately, special efforts have been devoted to study the inhibitory effect of this compound over the glyceraldehyde-3-phosphate dehydrogenase in *Trypanosoma brucei*.[4] The selective inhibition of the enzyme in this haemoflagellate protozoan has shown to block its glycolytic pathway, thus provoking a rapid disappearance of the parasite from the host's bloodstream. This fact renders this enzyme an excellent target for new drug design[4d,e] and the *in vitro* tests have demonstrated that pentalenolactone is a promising model since it is not only the most potent but also specific inhibitor of the glycolytic enzyme in *Trypanosoma brucei*. Surprisingly, despite of two decades of sustained interest in the chemistry of these natural products,[5] only Mori's work[6] addressed the issue of optical purity in the synthesis of (-)-pentalenolactone E (**2**) methyl ester by an enzymatic resolution of an advanced synthetic intermediate. However, to the best of our knowledge, no general enantiospecific approach towards the synthesis of these highly compacted and functionalized structures has yet been recorded.[7]

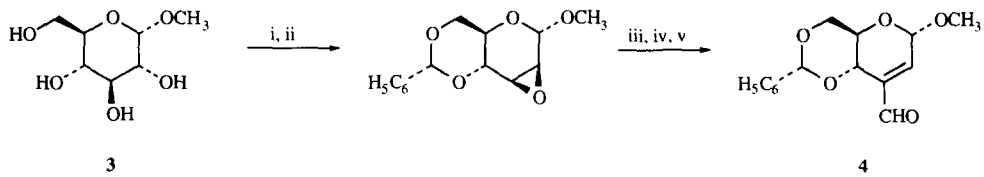


1: Pentalenolactone



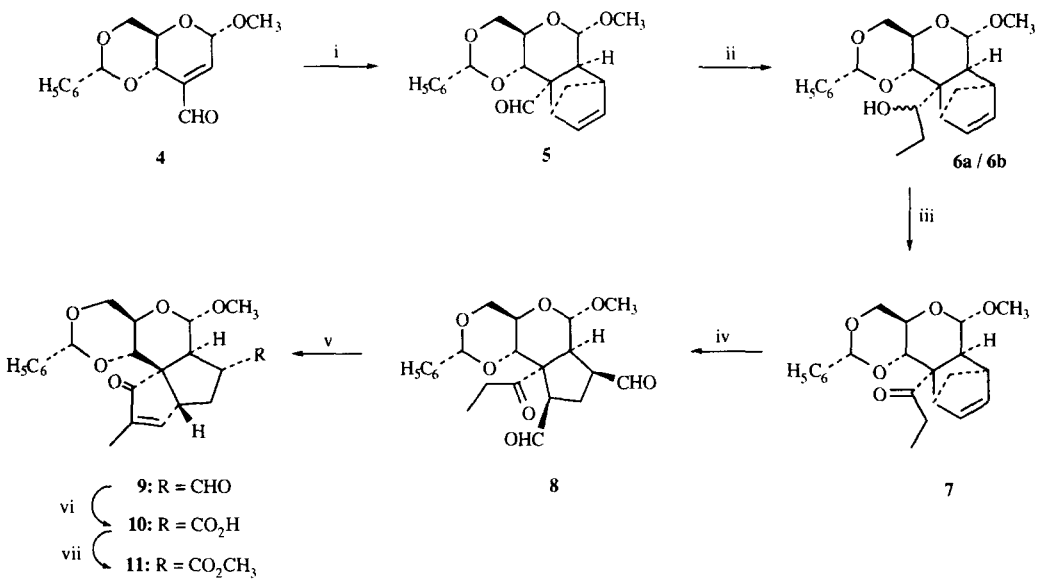
2: Pentalenolactone E

In light of these considerations and the striking biological activities of these compounds we were prompted to devise a simple means for building the pentalenolactone quinane skeleton in an optically pure form. Our asymmetric strategy relies on the use of D-glucose as source of chirality. This raw material offers several advantages in terms of cost, purity and availability. In a simple and straightforward synthetic sequence we have converted the methyl-α-D-glucopyranoside **3** into a cyclic α,β-unsaturated aldehyde **4** (Scheme 1).[8]



Scheme 1 *Reagents and conditions:* i, $C_6H_5CH(OCH_3)_2$ (1.4 equiv.), CSA (0.14 equiv.), $CHCl_3$, reflux until complete dissolution of the solid; ii, NaH (3.3 equiv.), DMF, room temp., 45 min., then N-tosylimidazole (1 equiv.) in DMF slow addition during 45 min., room temp., 1 h; iii, Et_2AlCN (2 equiv.), bencene, room temp., 20 hs.; iv, DiPEA (5 equiv.), $LiClO_4$ (10 equiv.), DMAP (0.2 equiv.), TsCl (2 equiv.), CH_3CN, 0 °C then room temp., 16 hs.; v, DIBAL-H (1.3 equiv.) slow addition, CH_2Cl_2, -98 °C, 15 min.

Treatment of aldehyde **4** with freshly cracked cyclopentadiene afforded the *exo*-β adduct **5**,[9] $[\alpha]_D^{25}$ +55.7 (*c* 1.01, $CHCl_3$), as the only detectable product in 85%. Although the Diels–Alder reaction could generate four isomers, the outcome of this cycloaddition is highly diastereoselective and proceeds through the β face of the dienophile with the diene in an *exo* manner (Scheme 2). Even though the *exo*-β isomer has the olefin bridge with the opposite configuration (it is *trans* to the aldehyde group), we found it is equally suitable to fulfill our objective. Furthermore, we rely upon this reaction to establish the configuration of the quaternary carbon, pivot of the angular tricyclic junction.



Scheme 2 *Reagents and conditions:* i, $LiClO_4$ anhydrous (5 equiv.), CH_3CN, room temp., 30 min., then cyclopentadiene (10 equiv.), room temp., 18 hs.; ii, Li wire (17 equiv.), EtBr (15 equiv.) and aldehyde **5** added together in 10 min., THF, sonication, room temp., 30 min.; iii, $(COCl)_2$ (6 equiv.), DMSO (9.6 equiv.), CH_2Cl_2, -78 °C, 1 h., then -30 °C, 1 h., then TEA (15 equiv.), -78 °C to room temp., 1 h.; iv, O_3, CH_2Cl_2, -78 °C, then DMS (8 equiv.), -78 °C to room temp., 20 min.; v, KOH (6 equiv.), CH_3OH, reflux, 5 hs.; vi, Jones reagent, acetone, 0 °C, 5 min.; vii, CH_2N_2 (excess), Et_2O–$CHCl_3$ (1:1), 0°C, 5 min.

The construction of the core bicycle [3.3.0] octane framework would ultimately require the epimerization of the carbon bridge head next to the quaternary center. It was reasoned that an intramolecular aldolic cyclization

under basic conditions would be the method of choice to achieve our goal.

The addition of the alkyl side chain to the carbonyl group was initially troublesome due to its hindered nature. Interestingly, the use of ethyl bromide and lithium wire in a Barbier type reaction under sonication[10] made available the addition product as a 4:5 mixture of the epimeric alcohols **6a**, $[\alpha]_D^{20}$ +36.4 (*c* 1.00, $CHCl_3$), and **6b**, $[\alpha]_D^{18}$ +52.9 (*c* 1.00, $CHCl_3$), in 70 %. The two isomers were easily separated by flash chromatography in order to characterise them.

Subsequently, Swern oxidation of the epimeric mixture afforded the corresponding ketone **7**, $[\alpha]_D^{24}$ +34.8 (*c* 1.07, $CHCl_3$), in quantitative yield. The oxidative cleavage of the double bond with ozone followed by a work up with dimethyl sulfide released the polysubstituted cyclopentane moiety bearing two aldehyde groups, and it was immediately used in the next step without further purification.

The crucial assembly of the second *cis* fused five membered ring was carried out by the proposed aldolic reaction involving the carbon adjacent to the ketone function and the appropriate aldehyde group through a 5–*exo*–trigonal process.[11] Gratifyingly, the basic conditions produced the anticipated *in situ* epimerization of the carbon attached to the aldehyde group, paving the way for an efficient cyclization. Although the stereogenic center α to the unreacted aldehyde function has no relevance in our synthetic strategy (since it will lose the tetrahedral character in further transformations), it is noteworthy to mention that we also observed its complete isomerization.

As it was verified by the ^1H NMR spectrum of the crude reaction mixture, the cyclic product **9**, $[\alpha]_D^{15}$ –20.1 (*c* 0.535, $CHCl_3$), was the only reaction product formed. We obtained higher overall yields if the crude reaction mixture was carried out to the next step without any chromatographic purification, but for identification purposes, product **9** was purified by flash chromatography and recrystallized from petroleum ether–ethyl acetate as white needles, mp = 138–140 °C. The structure determination was based on spectroscopic evidences. All its ^1H and ^{13}C NMR signals were unequivocally assigned by using homo and heteronuclear 2D NMR techniques. The coupling constant found between C_5–H and C_6–H (pentalenolactone numbering)[12] was 12.0 Hz, which indicated a *trans* relationship between these protons. In addition, the NOE observed between C_5–H and the formyl proton suggested the proximity of these nuclei verifying C_6 epimerization during the aldolic ring closure. Finally, Jones oxidation and esterification with diazomethane afforded the methyl ester **11** $[\alpha]_D^{16}$ –33.4 (*c* 0.935, $CHCl_3$), in 60% overall yield from **7**.[13]

Compound **11**,[14] embodies the carbon skeleton associated with the sesquiterpene family of pentalenolactone and possesses such a functionality that it would make possible its further transformation into any of the natural products of this class.

In conclusion, the strategic use of a synthon derived from glucose and simple chemical reactions provided the entrance to a complex quinane structure in an efficient way and optically pure form.

Acknowledgments

We thank the International Foundation for Science, Fundación Antorchas, Universidad Nacional de Rosario and CONICET for financial support and Prof. M. González Sierra for his NMR assistance. SCP thanks CONICET for the award of a fellowship.

References

1. Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1970,** 4901.
2. For pentalenolactone A to P see: Cane, D. E.; Sohng, J. K.; Williard, P. G. *J. Org. Chem.* **1992**, *57*, 844 and references therein cited.
3. Nakagawa, A.; Tomoda, H.; Hao, M. V.; Okano, K.; Iwai, Y.; Omura, S. *J. Antibiot.* **1985**, *38*, 111.
4. For enzyme inhibitions studies see: a.– Duszenko, M.; Mecke, D. *Mol. Biochem. Parasitol.* **1986**, *19*, 223; b.– Cane, D. E.; Sohng, J. K. *Arch. Biochem. Byophys.* **1989**, *270*, 50; c.– Fröhlich, K. U.; Wiedmann, M.; Lottspeich, F.; Mecke, D. *J. Antibiot.* **1989**, *171*, 6696; d.– Lambeir, A. M.; Loiseau, A. M.; Kuntz, D. A.; Vellieux, F. M.; Michels, P. A. M.; Opperdoes, F. R. *Eur. J. Biochem.* **1991**, *198*, 429; e.– Willson, M.; Lauth, N.; Perie, J.; Callens, M.; Opperdoes, F. R. *Biochem.* ***1994,33***, 214; f.– Cane, D. E.; Sohng, J. K. *Biochem.* **1994**, *33*, 6524.
5. First total synthesis of (±) pentalenolactone: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536.
6. Mori, K.; Tsuji, M. *Tetrahedron Lett.* **1988**, *44*, 2835.
7. For a recent review on the syntheses of polyquinanes including the pentalenolactones see: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671 and references therein cited.
8. Spanevello, R. A.; Pellegrinet, S. C. *Synth. Comm.* **1995**, *25*, 3663.
9. Pellegrinet, S. C.; Spanevello, R. A. *Tetrahedron: Asymmetry* **1997**, *8*, 1983.
10. Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7927.
11. Baldwin, J. *Chem. Commun.* **1976,** 734.
12. The numbering used for pentalenolactone corresponds to the one given in references 1 and 2.
13. All new compounds exhibited satisfactory IR, MS, ^{1}H and ^{13}C NMR spectra. HRMS confirmed the structure of compounds **5**, **6b**, **7**, **9** and satisfactory elemental analysis were obtained for compounds **5**, **6a**, **9** and **11**.
14. Compound **11**: IR (film): ν_{max} (cm^{-1})= 2938, 2875, 1740 (CO ester), 1715 (CO ketone), 1650, 1470, 1390, 1110. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.45-7.28 (m, 5H, arom.), 7.00 (s broad, 1H, C_1–H), 5.45 (s, 1H, benzylic), 4.88 (td, J_1= 10.4 Hz, J_2= 9.9 Hz, J_3= 5.3 Hz, 1H, C_{11}–H), 4.65 (s, 1H, anomeric), 4.32 (dd, J_1= 10.4 Hz, J_2= 5.3 Hz, 1H, CH_2O, H_{ec}), 3.72 (d, J= 9.9 Hz, 1H, C_9–H), 3.70 (s, 3H, CO_2CH_3), 3.56 (dd, J_1= J_2= 10.4 Hz, 1H, CH_2O, H_{ax}), 3.40 (s, 3H, OCH_3), 3.25 (m, 2H, C_8–H, C_6–H), 2.44 (m, 1H, C_7–H), 2.41 (d, J= 12.6 Hz, 1H, C_5–H), 1.71 (s broad, 3H, methyl), 1.65 (m, 1H, C_7–H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 204.9 (s, ketone), 173.3 (s, ester), 156.4 (d, C_1), 139.2 (s, C_2), 137.4 (s, $C_{arom.}$), 128.9 (d, $C_{arom.}$), 128.0 (d, $2C_{arom.}$), 126.3 (d, $2C_{arom.}$), 102.3 (d, $C_{benzylic}$), 98.7 (d, $C_{anomeric}$), 79.2 (d, C_9), 69.5 (t, CH_2O), 57.9 (d, C_{11}), 55.6 (s, C_4), 55.1 (q, OCH_3), 51.9 (q, $CO_2\underline{C}H_3$), 49.1 (d, C_8), 48.8 (d, C_6), 48.4 (d, C_5), 32.4 (t, C_7), 10.2 (q, methyl). Anal. Calcd for $C_{23}H_{26}O_7$: C= 66.65, H= 6.32, O= 27.02. Found: C= 66.50, H= 6.40

(*Received in USA* 1 *September* 1997; *accepted* 7 *October* 1997)