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Approach to the Synthesis of Annonaceous Acetogenins from D-Glucose

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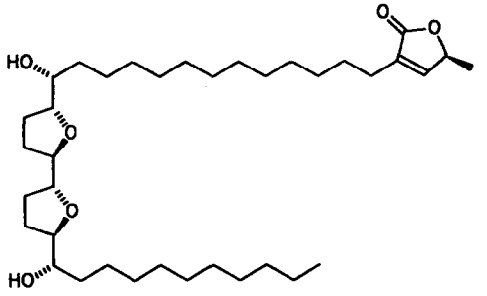
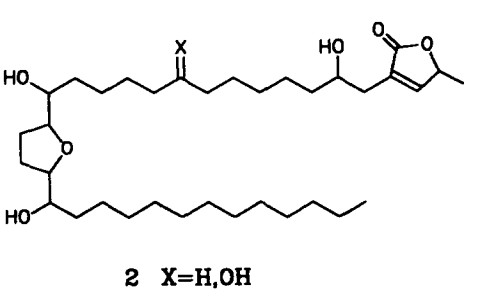
Abstract: *The preparation from D-glucose of threo-trans-threo and threo-cis-threo synthons **12** and **13** for the monochiral synthesis of mono (or eventually bis) tetrahydrofuran acetogenins is described. Their structure have been proven by degradation and comparison with a racemic sample of a threo-cis-threo aldehyde prepared by permanganate oxidation of the corresponding diene.*

More than thirty tetrahydrofuran acetogenins have been isolated from Annonaceae since the discovery of uvaricin **1** in 1982[1] and shown to have various potent biological activities such as cytotoxic, antitumoral, antimalarial, immunosuppressive, pesticidal or antifeedant.[2] This new class of compounds, with a C_{35}-C_{37} skeleton, is characterized by the presence of one or two (generally adjacent) tetrahydrofuran ring(s) and a lactone moiety, together with hydroxyl (or scarcely carbonyl) functions. Examples of such monotetrahydrofuran acetogenins are annonacin **2**[3] and annonacinone **3**.[4]



1



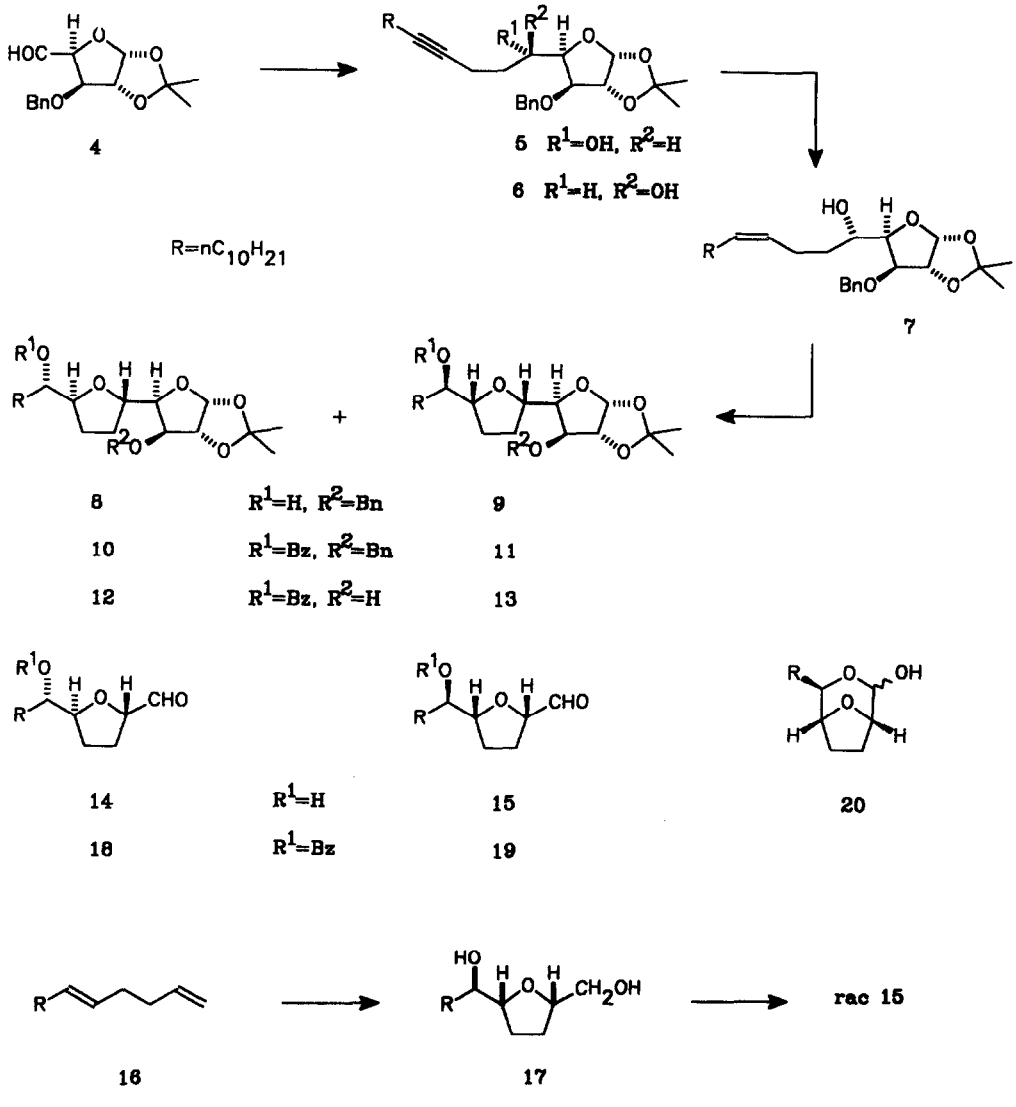
2 X=H,OH

3 X=O

The determination of the relative stereochemistry of these acetogenins is difficult due to their waxy properties and to the large number of CH-O bonds. However synthetic studies of model bistetrahydrofurans by Hoye et al.,[5] X-Ray analysis of derivatives of rolliniastatin by Pettit[6] and annonin I (or squamocin) by Born[7], together with extensive ^{1}H and ^{13}C NMR analysis have demonstrated that the most common arrangement involving the tetrahydrofuran ring(s) is *threo-trans-threo* (as for **2** and **3**) although *erythro-*

trans-threo, *erythro-cis-threo* and *threo-cis-threo* relative configurations are also known such as respectively in uvaricin, rolliniastatin[8] and annonin VI.[7] The absolute configurations of all the acetogenins are uncertain apart for the asymmetric centers of the lactone moiety determined for some acetogenins using CD spectra and degradation to (S)-lactic acid.[2] Recently Hoye has shown that the chirality of uvaricin is probably as depicted in 1 after having synthesized a (15,16,19,20,23,24)-hexepimer, but, as quoted by Hoye, any prediction of absolute configurations for other acetogenins is hazardous taking into account a probable polyepoxide biosynthetic pathway.[9]

In order to gain more information on their structures and later on their structure-activity relationships, the synthesis of monochiral acetogenins has thus been undertaken from carbohydrates such as D-glucose and preliminary results are reported here.



The known aldehyde **4**[10] is first reacted with the Grignard reagent of 1-bromo-3-tetradecyne[11] to give an easily separable 4 to 1 mixture of **5**,[12] mp 79-80°C, $[\alpha]_D$ -33 (c 1, CCl_4) and **6**[12] as an oil, in agreement with similar results reported by Hanessian[13] and Inch,[14] best explained by the Cram chelation controlled model. After Lindlar reduction of **5** to the Z-alkene **7**,[12] mp 60-61°C, $[\alpha]_D$ -27 (c 1, CCl_4), epoxidation (metachloroperbenzoïc acid, CH_2Cl_2) affords as expected a 1/1 unseparable mixture of the two possible epoxides leading (AcOH, CH_2Cl_2, 20°C, 12h) to the *trans* and *cis* tetrahydrofurans **8** and **9**. Although these compounds can only be separated by HPLC, it was expected that further protecting groups modification will permit easier separation on a preparative scale. Thus it was found that benzoylation to **10** and **11** followed by hydrogenolysis (H_2, Pd/C) affords as oils **12**,[12] $[\alpha]_D$ -22.2 (c 1.1, CCl_4) and **13**[12] $[\alpha]_D$ 2.6 (c 0.9, CCl_4) which are then isolated (30% each overall from **7**) by flash chromatography (silica, AcOEt/hexane 30/70 V/V, **12**: R_F 0.6, **13**: R_F 0.4). Unfortunately at this stage ^1H and ^{13}C NMR analysis does not allow an unambiguous determination of the *cis* or *trans* relationship in the newly created tetrahydrofuran ring. Therefore **12** and **13** were respectively degradated to aldehydes **14**[12] and **15**[12] in two steps (AcOH-H_2O 4-1, 50°C, overnight then 3 eq. $NaIO_4$, H_2O, 20°C). A racemic sample of the *cis* aldehyde **15** was prepared from diene **16** through $KMnO_4$ oxidation[15] to the *cis* tetrahydrofuran **17** (15%), protection of the primary alcohol group ($tBuMe_2SiCl$), benzoylation (PhCOCl, pyridine), deprotection ($nBu_4N^+F^-$) and oxidation (PCC, CH_2Cl_2). The ^1H and ^{13}C NMR spectra of this latter compound are identical to those of aldehyde **15** obtained from the more polar alcohol **13** and clearly different from those of **14**. A further confirmation arised from the base catalyzed hydrolysis of **14** and **15** which gave respectively a single hydroxyaldehyde **18** and a mixture of the free aldehyde **19** and hemiacetal **20**.[16]

In conclusion, the preparation of *threo-trans-threo* and *threo-cis-threo* tetrahydrofuran derivatives **12** and **13** is easily carried out from diacetone D-glucose in 8 steps and these intermediates will be used in the synthesis of mono and bistetrahydrofuran acetogenins.[17] The use of other conditions to carry out the alkene epoxidation is also considered and if oxone® gives also after acid treatment a 1/1 ratio of **8** and **9**, the use of tBuOOH-$VO(Acac)_2$ favors, as expected,[18,19] the *cis* isomer **9** (2/1 ratio). Finally the R alcohol **6** has been submitted to the same sequence of reactions and the two corresponding *trans* and *cis* tetrahydrofurans have also been shown to be easily separable at the same stage.

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REFERENCES AND NOTES

1. Jolad, S.D.; Hoffmann, J.J.; Schram, K.H.; Cole, J.R. *J.Org.Chem.* **1982**, *47*, 3151.
2. Rupprecht, J.K.; Hui, Y.-H.; McLaughlin, J.L. *J.Nat.Prod.* **1990**, *53*, 237.
3. McCloud, T.G.; Smith, D.L.; Chang, C.-J.; Cassady, J.M. *Experientia*, **1987**, *43*, 947.
4. Xu, L.Z.; Chang, C.-J.; Yu, J.G.; Cassady, J.M. *J.Org.Chem.* **1989**, *54*, 5418.
5. Hoye, T.R.; Suhaldonik, J.C. *J.Am.Chem.Soc.* **1985**, *107*, 5312.
   Hoye, T.R.; Suhaldonik, J.C. *Tetrahedron*, **1986**, *42*, 2855.
6. Pettit, G.R.; Cragg, G.M.; Polonsky, J.; Herald, D.L.; Goswami, A.; Smith, C.R.; Moretti, C.; Schmidt, J.M.; Weisleder, D. *Can.J.Chem.* **1987**, *65*, 1433.
7. Born, L.; Lieb, F.; Lorentzen, J.P.; Moeschler, H.; Nonfon, M.; Sollner, R.; Wendisch, D. *Planta Med.* **1990**, *56*, 312.

8. Pettit, G.R.; Riesen, R.; Leet, J.E.; Polonsky, J.; Smith, C.R.; Schmidt, J.M.; Dufresne, C.; Schaufelberger, D.; Moretti, C. *Heterocycles*, **1989**, *28*, 213.
9. Hoye, T.R.; Hanson, P.R.; Kovelevsky, A.C.; Ocain, T.D.; Zhuang, Z. *J.Am.Chem.Soc.* **1991**, *113*, 9369.
10. Freudenberg, K.; Durr, W.; Von Hochstetter, H. *Chem.Ber.* **1928**, *61*, 1735.
11. This compound was prepared (74% overall) from 1-dodecyne in 3 steps: 1-BuLi, ethylene oxide; 2-TsCl, pyridine; 3-$MgBr_2$, ether.
12. All new compounds have been characterized by ^1H (200 MHz) and ^{13}C NMR (50.3 MHz), IR, MS and HRMS or elemental analysis. Selected NMR data ($CDCl_3$ as solvent, TMS as internal standard, J in Hz) are given below.

5: δ 0.88 (t, 3H, J= 7), 1.48 (s, 3H), 1.60 (s, 3H), 2.11 (m, 2H), 2.33 (m, 2H), 2.83 (s, OH), 3.97 (d, 1H, J= 3.3), 4.49 (d, 1H, J= 11.8), 4.65 (d, 1H, J= 3.8), 4.72 (d, 1H, J= 11.8), 5.99 (d, 1H, J= 3.8), 7.35 (s, 5H) ppm.

6: δ 0.88 (t, 3H, J=7), 1.32 (s, 3H), 1.48 (s, 3H), 2.12 (m, 2H), 2.33 (m, 2H), 4.06 (m, 3H), 4.53 (d, 1H, J= 11.8), 4.63 (d, 1H, J= 3.8), 4.73 (d, 1H, J= 11.8), 5.96 (d, 1H, J= 3.8), 7.33 (s, 5H) ppm.

7: δ 0.88 (t, 3H, J= 7), 1.34 (s, 3H), 1.49 (s, 3H), 2.02 (m, 2H), 2.20 (m, 2H), 2.78 (s, OH), 4.46 (d, 1H, J= 11.8), 4.65 (d, 1H, J= 3.9), 4.72 (d, 1H, J= 11.8), 5.3 (m, 2H), 5.99 (d, 1H, J= 3.8), 7.33 (s, 5H) ppm.

12: δ 0.88 (t, 3H, J= 7), 1.31 (s, 3H), 1.47 (s, 3H), 2.14 (m, 4H), 4.07 (s, 1H), 4.24 (s, 1H), 4.32 (q, 1H, J= 6), 4.70 (d, 1H, J= 1.6), 5.14 (q, 1H, J= 5), 5.94 (d, 1H, J= 3.6), 7.44 (t, 2H, J= 7.4), 7.56 (t, 1H, J= 7), 8.05 (d, 2H, J= 7.4) ppm; δ 14.04, 22.67, 25.41, 26.23, 26.89, 27.48, 29.28, 29.31, 29.44, 29.55, 31.26, 31.91, 75.72, 78.48, 80.12, 81.78, 85.60, 93.17, 104.81, 111.53, 128.43, 129.69, 130.51, 132.93, 166.40 ppm (77.7 masked).

13: δ 0.88 (t, 3H, J= 7), 1.31 (s, 3H), 1.47 (s, 3H), 1.88 (d, 1H, J= 7), 1.91 (d, 1H, J= 7), 2.10 (m, 2H), 4.05 (s, 1H), 5.25 (q, 1H, J= 6.2), 5.92 (d, 1H, J= 3.6), 7.43 (t, 2H, J= 7), 7.55 (t, 1H, J= 7.4), 8.08 (d, 2H, J= 7.4) ppm; δ 14.05, 22.67, 25.34, 26.28, 26.95, 27.47, 29.31, 29.46, 29.55, 29.58, 29.71, 31.18, 31.92, 75.80, 77.10, 78.53, 80.30, 82.19, 85.81, 104.95, 111.64, 128.33, 129.84, 130.62, 132.82, 166.48 ppm.

14: δ 0.87 (t, 3H, J=6), 1.75 (m, 2H), 2.0 (m, 2H), 4.31 (td, 1H, J= 5 and 2.5), 4.41 (t, 1H, J= 8), 5.18 (td, 1H, J= 8 and 5), 7.45 (d, 2H, J= 7.4), 7.55 (t, 1H, J= 7), 8.05 (d, 2H, J= 7.4), 9.66 (d, 1H, J= 1.2) ppm; δ 14.05, 22.67, 25.50, 26.80, 27.34, 27.63, 29.32, 29.47, 29.56, 29.59, 31.31, 31.92, 75.65, 81.45, 83.25, 128.46, 129.76, 130.53, 132.98, 166.38, 202.20 ppm.

15: δ 0.86 (t, 3H, J= 7), 2.10 (m, 4H), 4.29 (m, 2H), 5.21 (td, 1H, J= 6.7 and 5), 7.47 (t, 2H, J= 7.4), 7.56 (t, 1H, J= 7), 8.04 (d, 2H, J= 7.4), 9.78 (d, 1H, J= 1.5) ppm; δ 14.06, 22.69, 25.50, 27.78, 28.01, 29.33, 29.48, 29.57, 29.59, 31.50, 31.94, 75.67, 81.75, 83.42, 128.50, 129.74, 130.45, 133.02, 166.38, 203.11 ppm.

13. Wolfrom, M.L.; Hanessian, S. *J.Org.Chem.* **1962**, *27*, 1800.
14. Inch, T.D. *Carbohydr.Res.* **1967**, *5*, 45.
15. Klein, E.; Rojan, W. *Tetrahedron*, **1965**, *21*, 2353. Walba, D.M.; Wand, M.D.; Wilkes, M.C. *J.Am.Chem.Soc.* **1979**, *101*, 4396.
16. Noda, I.; Horita, K.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 1917.
17. The side chain introduced using dodecyne corresponds to the bis-tetrahydrofuran acetogenins such as uvaricin. The same synthesis using tetradecyne has been carried out to prepare mono-tetrahydrofuran acetogenins such as annonacin (unpublished results).
18. Hanessian, S.; Cooke, N.G.; DeHoff, B.; Sakito, Y. *J.Am.Chem.Soc.* **1990**, *112*, 5276.
19. Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J.Org.Chem*, **1991**, *56*, 2299.

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