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An Approach towards 2,5-Disubstituted Tetrahydrofurans of Annonaceous acetogenins

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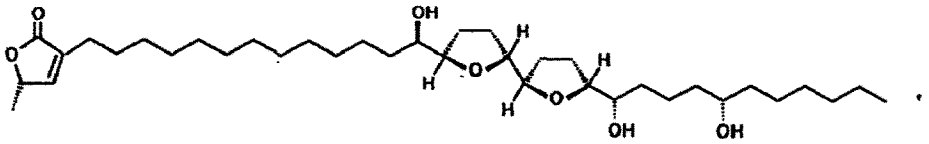
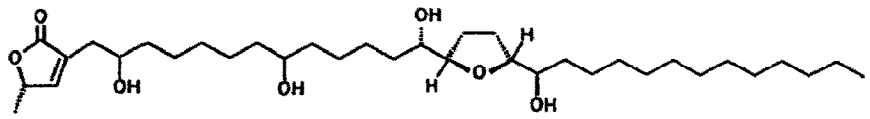
Abstract: A large scale approach with Sharpless asymmetric epoxidation (AE) as key steps to 2,5-linked tetrahydrofurans is described. With this strategy it is possible to synthesize various Annonaceous acetogenins.

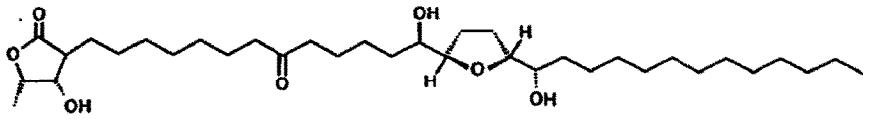
The isolation of uvaricin by Cole and coworkers[1] reveals a class of Annonacaeous acetogenins, whose exceptional biological activities such as fungicidal, insecticidal or cancerostatic effects[2] have aroused much scientific interest. Since neither the structure-activity relationship nor the mode of action is known,[3] it is important to obtain these substances and their analogues for biological testing. To facilitate the necessary biological assays, our aim is to develop a synthetic strategy in which each stereogenic centre can be varied.



Annonin I



Annonacin A



Jetein

Figure 1.

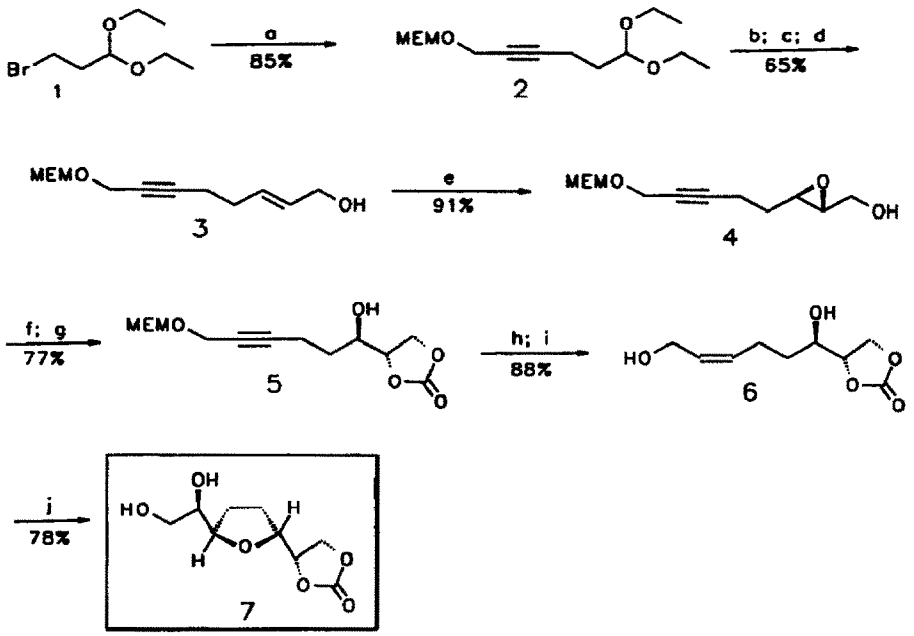
For our studies we chose acetogenins with an erythro/ trans/ threo or a threo/ trans/ threo/ trans/ erythro configuration at the tetrahydrofuran cores, as they appear in jetein[4], annonacin A[5] or annonin I (also called squamocin)[6] (figure 1).

In contrast to known literature syntheses,[7] scheme 1 illustrates a synthesis in which each stereogenic centre may be controlled independently. The same facile methodology allows the construction of all the possible configurations without any problems arising from unnatural chiral-pool reagents.[8] Additional benefits include the ease of purification (no chromatography required) and recovery of the diisopropyltartrate (DIPT) by distillation.

Starting with the readily available[9] 1-bromopropionaldehyde-diethylacetal **1** (scheme 1), the synthesis of the monoprotected enynol **3** is straightforward (scheme 1). The acetal **1** is coupled to lithiated and protected[10] propargylic alcohol in a one mole scale to give compound **2**. The β-methoxyethoxymethyl (MEM) protecting group is chosen because of its stability to the acidic cleavage conditions of the diethylacetal **2** and its ease of removal by treatment with Lewatit S 100^{R}.[11] After cleavage of the acetal **2** under pH-controlled conditions the aldehyde so obtained is converted with triethyl phosphonoacetate to the unsaturated ester (Horner reaction[12]) and finally reduced to the corresponding allylic alcohol **3**. Isolation and purification of the intermediates is not necessary. After acidic workup of this allylic alcohol no cis-isomer can be detected.

The first two stereogenic centres are now introduced by the Sharpless AE. The ability to use either tartrate enantiomer at each successive epoxidation increases the number of stereochemical possibilities as demonstrated by Paterson's macrolide synthesis.[13] As expected, this reaction yields the desired enantiomer **4** in over 96% ee.[14] The unnatural diisopropyltartrate can be recycled quantitativly. Generation of the carbonate **5**, following the protocol of Roush,[15] predetermines the direction of the ring-closure reaction and prevents racemisation in this step.[16] Formation of the cis-allylic alcohol **6** allows the introduction of the next two stereogenic centres, again by the method of Sharpless. As the known difficulties using Sharpless AE in connection with cis-allylic alcohols, best results were obtained by the following procedure: acidic workup, azeotropic drying with CH_2Cl_2, filtration of the precipitate, separation of the tartrate and compound **7**[17] by filtration over silica gel. The selectivity in this case is 85:15 in favour of the desired diastereomer.[18]

With this synthesis it is possible to arrive the 2,5-disubstituted tetrahydrofuran core in at least 19% overall yield (32g scale) based on **1** (scheme 1). Structure **7** allows the synthesis of acetogenins like annonacin A or jetein as well as the construction of a bis-tetrahydrofuran segment, which occurs naturally in annonin I. A full paper with all experimental details and spectroscopic data will follow.



a) Li-C≡C-CH_2-OMEM, THF, DMPU, 60°C; b) H^+, H_2O; c) $(EtO)_2P(O)CH_2C(O)OEt$, LiBr, NEt_3, THF; d) DIBAH, CH_2Cl_2, -10°C; e) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -15°C; f) Ph-NCO, NEt_3, CH_2Cl_2; g) $SnCl_4$, CH_2Cl_2, -20°C; h) H^+, MeOH, 40°C; i) Pd-$CaCO_3$-PbO, MeOH; j) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -5°C;

Scheme1.

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References and Notes

1. Cole, J.R.; Schramm, K.H.; Hoffmann, J.J.; Jolad, S.D. *J. Org. Chem.*, **1982**, *47*, 3151-3153.
2. a) McLaughlin, J.L., Hui, Y.H.; Rupprecht, J.K. *J. of Nat. Prod.*, **1990**, *53*, 237-278. b) McLaughlin, J.L.; Zhao, G.; Gu, Z.; Rieser, M.J.; Fang X. *Phytochem. Anal.*, **1993**, *4*, 27-67.

3. a) Londershausen, M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. Pestic. Sci., **1991**, *33*, 427-438. b) Friedrich, T.; Van Heek, P.; Leif, H.; Ohnishi, T.; Forche, E., Kunze, B.; Jansen, R.; Trowitzsch-Kienast, W.; Höfle, G.; Reichenbach, H; Weiss, H. *Eur. J. Biochem.*, **1994**, in press.
4. Cortes, D.; Myint, S.H.; Leboeuf, M.; Cavé, A. *Tetrahedron Lett.*, **1991**, *32*, 6133-6134.
5. Lieb, F.; Nonfon, M.; Wachendorff-Neumann, U.; Wendisch, D. *Planta Med.*, **1990**, *56*, 317-319.
6. a) Moeschler, H.F.; Pflüger, W.; Wendisch, D. D. (1984/86) Ger.Offen. DE 3438763,23, **23.10.1984-24.4.1986** (*Chem. Abstr.*, 1986, *105*, 3751t). b) Born, L.; Lieb, F.; Lorentzen, J.P.; Moeschler, H.; Nonfon, M.; Sölner, R.; Wendisch, D. *Planta Med.*, **1990**, *56*, 312-316. c) Fujimoto, Y.; Eguchi, T; Kakinuma, K.; Ikekawa, N.; Sahai, M.; Gupta, Y.K. *Chem. Pharm. Bull.*, **1988**, *36*, 4802-4806.
7. a) Hoye, T.R.; Hanson, P.R.; Kovelesky, A.C.; Ocain, T.D.; Zhuang, Z. *J. Am. Chem. Soc.*, **1991**, *113*, 9369-9371. b) Hoye, T.R.; Hanson, P.R. *Tetrahedron Lett.*, **1993**, *34*, 5043-5046. c) Sinha, S.C.; Keinan, E. *J. Am. Chem. Soc.*, **1993**, *115*, 4891-4892.
8. a) Harmange, J.-C.; Cavé, A.; Figadère, B. *Tetrahedron Lett.*, **1992**, *33*, 5749-5752. b) Bertrand, P.; Gesson J.-P. *Tetrahedron Lett.*, **1992**, *33*, 5177-5180.
9. Büchi, G.; Wüest, H. *J. Org. Chem.*, **1969**, *34*, 1122-1124. The reported yield can be increased by working at lower temperatures.
10. Corey, E.J.; Giras, J.-L.; Ulrich, P. *Tetrahedron Lett.*, **1976**, *11*, 809-812.
11. Strong acidic ion-exchange polymer.
12. Rathke, M.W.; Nowak, M. *J. Org. Chem.*, **1985**, *50*, 2624-2626.
13. Paterson, E.; Boddy, I.; Mason I. *Tetrahedron Lett.*, **1987**, *28*, 5205-5208 and literature cited therein.
14. The ee was determined as de of the Mosher-ester; >96% none of the undesired diastereomer can be detected by NMR spectroscopy.
15. Roush, W.R.; Brown, R.J.; DiMare M. *J. Org. Chem.*, **1983**, *48*, 5083-5088.
16. Hoye, T.R.; Suhadolnik, J.C. *J. Am. Chem. Soc.*, **1985**, *107*, 5312.
17. All isolated new intermediates were characterized by NMR, IR, MS and CH analysis. The data are in agreement with the proposed structures. Selected data for compound **7** are given: ^{1}H NMR (300 MHz,DMSO d_6, ref. to TMS) δ ppm: 1.78 (m,4H); 3.34 (m,3H); 4.01 (m,1H); 4.18 (m,1H); 4.28 (dd,J=6Hz,8Hz,1H); 4.51 (m,3H); 4.79 (m,1H). ^{13}C NMR (75 MHz, DMSO d_6) δ ppm: 26.811; 26.989; 62.948; 65.637; 73.372; 77.475; 77.751; 80.180; 154.779. IR cm^{-1}: 3600 - 3200; 1480; 1385; 1110.
18. The configuration of compound **7** is given by the chirality of the DIPT, used in the Sharpless epoxidation. The NMR data are in good agreement with literature data of corresponding acetogenins (see reference 2).

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