Pergamon

Tetrahedron Letters, Vol. 38, No. 33, pp. 5811-5814, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01292-6

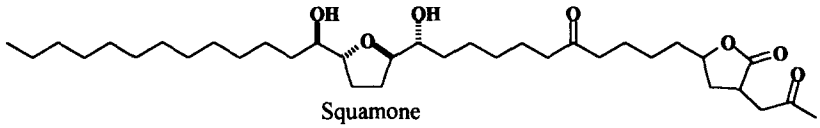
Synthesis of the THF Moiety of Annonacin Based on Aldolisation and Baeyer-Villiger Oxidation

Jean-Pierre Gesson*, Brigitte Renoux and Els Schulten[§]

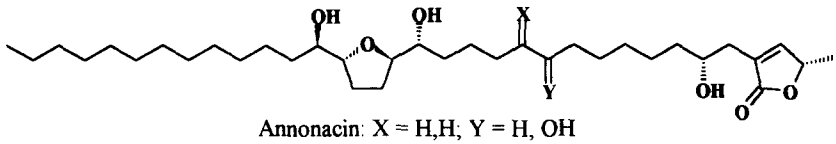
Laboratoire de Chimie 12, Université de Poitiers et CNRS, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex

Abstract : *Anti* aldolisation of cyclohexanone with an *E* or *Z* γ,δ-unsaturated aldehyde followed by epoxidation-cyclisation and stereoselective Baeyer-Villiger oxidation affords key THF synthons of annonaceous acetogenins related to the annonacin type. *Erythro* (or *threo*)-*trans* (or *cis*)-*threo* diastereoisomers are thus obtained in only 6 steps. © 1997 Published by Elsevier Science Ltd.

Acetogenins have been isolated in increasing number (over 220) from several genera of Annonaceae since 1982.[1] These compounds are potent inhibitors of mitochondrial NADH : ubiquinone oxidoreductase, a key enzyme in complex I of the electron transport system.[2] This may explain their various bioactivities (cytotoxic, immunosuppressive, pesticidal, ...). All these compounds are characterized by a fatty acid derived structure bearing one to three tetrahydrofuran (THF) rings and a terminal lactone moiety. Several total syntheses have already been published, most of them being based on the convergent preparation of THF and lactone synthons followed by Pd^0 coupling.[3] Enantiopure THF synthons have been prepared using the Sharpless asymmetric epoxidation[4] or dihydroxylation[5] or from natural pool (D or L-glutamic acid,[6] D-glucose[7]). Intramolecular nucleophilic substitution of an epoxide or sulfonate has been largely used to generate the THF ring. However most of these routes require a large number of steps to reach the target synthon.



Squamone

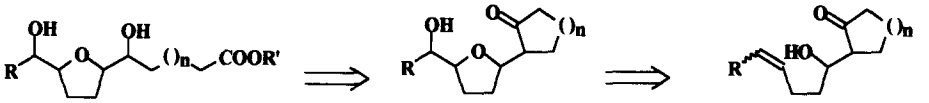


Annonacin: X = H,H; Y = H, OH
Annonacinone: X = H,H; Y = O
Reticulacinone X = O, Y = H,H

A new approach based on aldolisation and Baeyer-Villiger reaction is now proposed. This methodology should afford, in few steps, useful synthons for the preparation of mono-THF acetogenins such as squamone

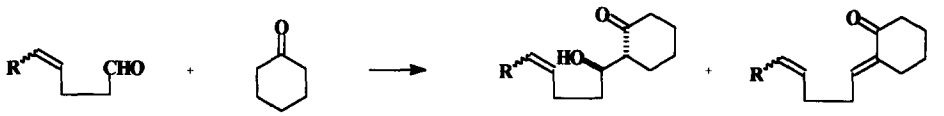
§: Present address: Dept of Chemistry, University of Leiden, The Netherlands.
Fax: 05 49 45 35 01. E-mail: jean.pierre.gesson@cri.univ-poitiers.fr

(n = 1, unknown absolute configurations), annonacin and annonacinone (n = 2) and reticulacinone (n = 3).[1] Preliminary studies carried out with cyclohexanone (n = 2) and commercially available *E* and *Z* decen-4-al are described below.



n= 1,2 or 3 aldol

Deprotonation of cyclohexanone (LDA, THF, -78°C) followed by addition of *E* (or *Z*) decen-4-al afforded a single aldol **1a** (or **1b**) in 60-70% isolated yield together with 10% of **2a** (or **2b**).



R= C_5H_{12} **1a** (*E*) **2a** (*E*)

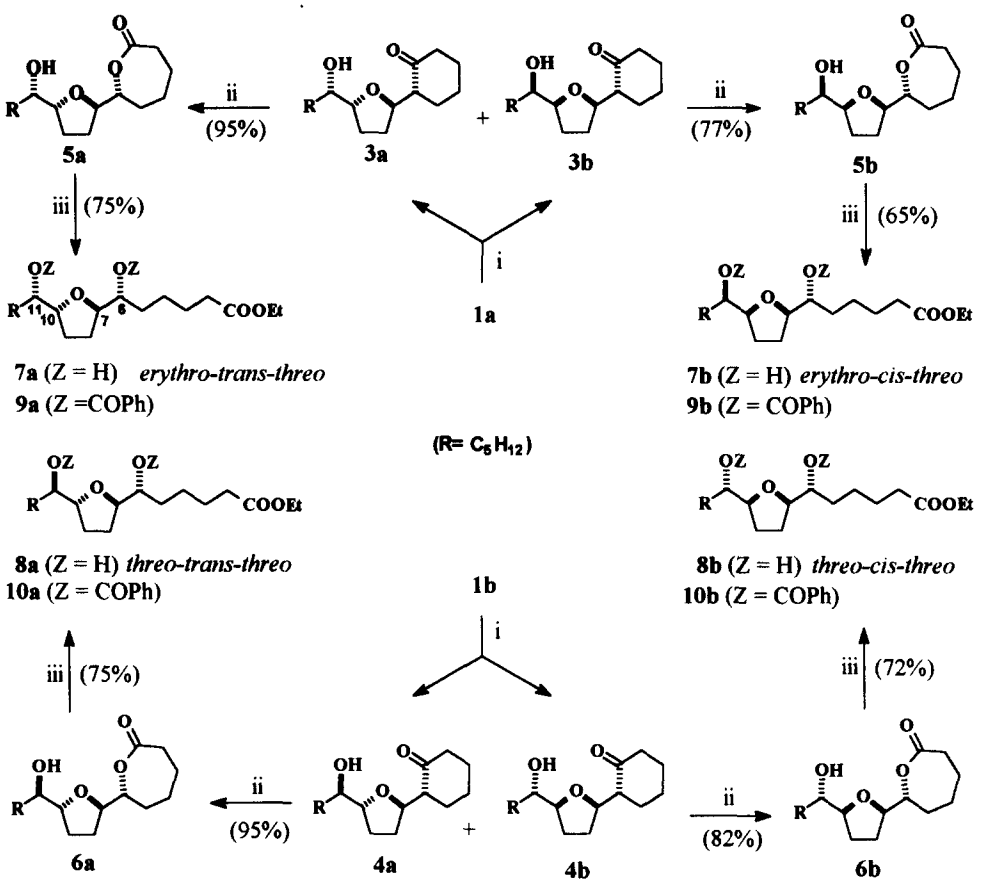
1b (*Z*) **2b** (*Z*)

At this stage, it was assumed that an *anti* aldol was obtained.[8] Aldol **1a** was then treated with *meta*chloroperbenzoïc acid (*m*CPBA) in CH_2Cl_2 at rt. After starting material comsumption (4 h as judged by ^1H NMR), 10 eq of AcOH were added to complete the intramolecular cyclisation of the intermediate epoxide. Flash chromatography afforded pure *trans* (**3a**) and *cis* (**3b**) ketones (1/1 ratio) in 50% overall isolated yield together with an unseparable mixture of lactones **5a** and **5b** (11%). Similar results were obtained from aldol **1b** leading to pure ketones **4a** and **4b** (60%) and a mixture of lactones **6a** and **6b** (11%).

Each ketone was then separately treated with *m*CPBA in presence of $NaHCO_3$ in CH_2Cl_2 (rt, 4 h). Lactones **5a,b** and **6a,b** obtained from the corresponding ketone, were then treated with cat. NaOEt in EtOH to give esters **7a,b** and **8a,b**. At this stage, unambiguous determination of the *erythro* or *threo* relative configurations was easily made by NMR: ^1H (H-6, H-11) and ^{13}C (C-6,C-11) chemical shifts are in agreement with *erythro/threo* configurations for **7a,b** and with *threo/threo* ones for **8a,b**.[9,10] Due to the known configuration of epoxidation-cyclisation, these data confirm that **1a,b** are *anti* aldols. However, at this stage, the *cis* or *trans* relationship between the ring substituents could not be unambiguously determined (the observed chemical shifts (^1H and ^{13}C) are similar for each pair of isomers as shown by Fujimoto[9]). This was done after dibenzoylation and comparison of the H-7 and H-10 chemical shifts for each pair of *cis/trans* isomers (**9a, b** and **10a, b**). H-7 and H-10 are more shielded in the case of *cis* isomers **9b** and **10b** (δ 4.10 ppm) compared to the *trans* ones **9a** (δ 4.16 ppm) and **10a** (δ 4.19 ppm) in agreement with the Cassady model.[11]

In conclusion a short strategy toward mono THF synthons is thus implemented in few steps from readily available compounds using diastereoselective aldolisation and Baeyer-Villiger oxidation. However, the epoxidation step is not selective and a chromatographic separation is required, precluding a one pot conversion

of **1a,b** to lactones **5a,b** and **6a,b** (separation is not possible at this stage). Extension of this strategy is anticipated to the preparation of enantiopure synthons either through enantioselective aldolisation[12] or resolution of aldols **1a,b**[13] together with the use of the Kennedy oxidative cyclisation[14] (instead of the epoxidation-cyclisation).



i: 1.2 eq *m*CPBA,CH_2Cl_2 then 10 eq AcOH, rt; *ii*: 3 eq *m*CPBA, 2 eq $NaHCO_3$, CH_2Cl_2, rt; *iii*: 0.2 eq NaOEt, EtOH, rt.

Acknowledgements

We thank ADIR and the Ligue Nationale contre le Cancer, Comité de Charente-Maritime for financial support.

References and Notes

1. Cavé, A; Figadère, B.; Laurens, A.; Cortes, D. Acetogenins from Annonaceae. In *Progress in the Chemistry of Organic Natural Products*, Vol 70, Herz, W.; Kirby, G.W.; Moore, R.E.; Steglich, W.; Tamm, Ch. Eds.; Springer: Wien, New-York, 1997, pp 81-288. Gu, Z.M., Zhao, G.X.; Oberlies, N.H.;

Zeng, L.; McLaughlin, J.L. *Recent Advances in Phytochemistry*, Arnason, J.T.; Mata, R.; Romeo, J.T. Eds.; Plenum Press: New-York, 1995, pp 249-310.

2. Londerhausen, M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. *Pesticide Sci.* **1991**, *33*, 427-438. Zafra-Polo, M.C.; Gonzalez, M.C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry*, **1996**, *42*, 253-271. Ye, Q.; He, K.; Oberlies, N.H.; Zeng, L.; Shi, G.; Evert, D.; McLaughlin, J.L. *J. Med. Chem.* **1996**, *39*, 1790-1796.
3. Figadère, B. *Acc. Chem. Res.* **1995**, *28*, 359-365. Hoppe, R.; Scharf, H.D. *Synthesis*, **1995**, 1447-1464.
4. Hoye, T.R.; Hanson, P.R.; Kovelesky, A.C.; Ocain, T.D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369-9371. Hoye, T.R.; Hanson, P.R. *Tetrahedron Lett.* **1993**, *34*, 5043-5046. Trost, B.M.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 7459-7460. Makake, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc. Perkin Trans I*, **1994**, 1975-1981. Hoye, T.R., Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981-1984. Sinha, S.C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257-9260. Naitao, H., Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419-4427. Hoye, T.R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801-1802.
5. Sinha, S.C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891-4892.
6. Figadère, B.; Harmange, J.-C.; Laurens, A., Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5189-5192. Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517-2520. Yao, Z.J.; Wu, Y.L. *J. Org. Chem.* **1995**, *60*, 1170-1176.
7. Bertrand, P.; Gesson, J.-P. *Tetrahedron Lett.* **1992**, *33*, 5177-5180.
8. Heathcock, C.H. *Asymmetric Synthesis*, Vol 3B, Morrison, J.D. Ed. Academic Press: Orlando, 1984, pp 111-212. Nógrádi, M. *Stereoselective Synthesis*, VCH: Weinheim, 1995, pp 177-210.
9. Fujimoto, Y.; Murasaki, C.; Shimada, Y.; Nishioka, S.; Kakinuma, K.; Singh, S.; Gupta, Y.K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175-1184. Harmange, J.-C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5749-5752. Born, L.; Lieb, F.; Lorentzen, J.P.; Moeschler, H.; Nonfon, M.; Sölner, R.; Wendisch, D. *Planta Med.* **1990**, *56*, 312-316.
10. ^{1}H and ^{13}C NMR data (BRUKER WP200SY, δ ppm, $CDCl_3$): *H-6, H-11:* 3.41, 3.84 (**7a**), 3.44, 3.84 (**7b**), 3.42 (**8a**), 3.42 (**8b**); *H-7, H-10:* 3.83 (**7a**), 3.84 (**7b**), 3.82 (**8a**), 3.79 (**8b**); *C-6,C-11:* 73.92, 71.68 (**7a**), 74.04, 72.40 (**7b**), 74.24, 73.95 (**8a**), 74.03, 73.77 (**8b**), *C-7, C-10:* 83.25, 82.31 (**7a**), 82.83, 82.26 (**7b**), 82.73, 82.64 (**8a**), 82.79, 82.68 (**8b**).
11. Gale, J.B.; Yu, J.-G.; Khare, A.; Hu, X.E.; Hu, D.K.; Cassady, J.M. *Tetrahedron Lett.* **1993**, *34*, 5851-5854.
12. Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041-1042. Ramachandran, P.V.; Xu, W.-C.; Brown, H.C. *Tetrahedron Lett.* **1996**, *37*, 1911-4914 and references cited therein.
13. Wong, C.-H.; Whitesides, G.M. *Enzymes in Organic Synthesis*, Baldwin, J.E.; Magnus, P.D. Eds.; Pergamon: Oxford, 1994.
14. Tang, S.; Kennedy, R.M. *Tetrahedron Lett.* **1992**, *33*, 3729-3732.

(*Received in France* 24 *April* 1997; *accepted* 26 *June* 1997)