Tetrahedron Letters, Vol.22, No.45, pp 4557 - 4560, 1981
Printed in Great Britain

0040-4039/81/454557-04$02.00/0

AN EFFICIENT STEREOSPECIFIC TOTAL SYNTHESIS OF (±) TERREIN

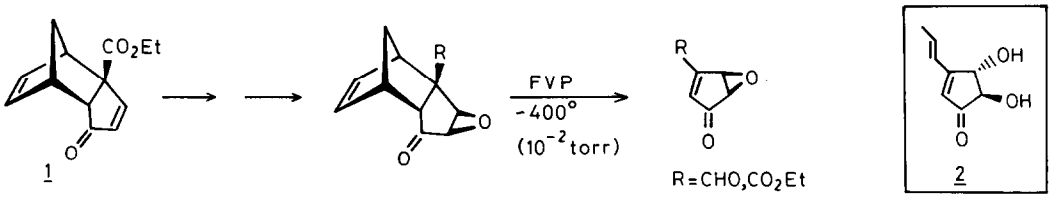
A.J.H. Klunder, W. Bos and B. Zwanenburg*

Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED NIJMEGEN, The Netherlands

Summary. Flash vacuum pyrolysis of functionalized tricyclo|5.2.1.$0^{2,6}$|decenone epoxide 5, and acetals 3 and 4 affords cyclopentadienone epoxide 6 and acetals 10 and 8, respectively. These epoxides are suitable precursors for the synthesis of (±) terrein.

Oxygenated monocyclic cyclopentenones and cyclopentanones are notable structures since many of them show a remarkable antibiotic and antitumor activity. Examples are prostaglandins[1], pentenomycins[2], methylenomycins[3] and sarkomycin[4]. In the preceding paper we described the synthesis of 3-substituted cyclopentadienone epoxides and their dimethyl acetals from readily available tricyclo-|5.2.1.$0^{2,6}$|decenones[5] (Scheme 1).

scheme 1

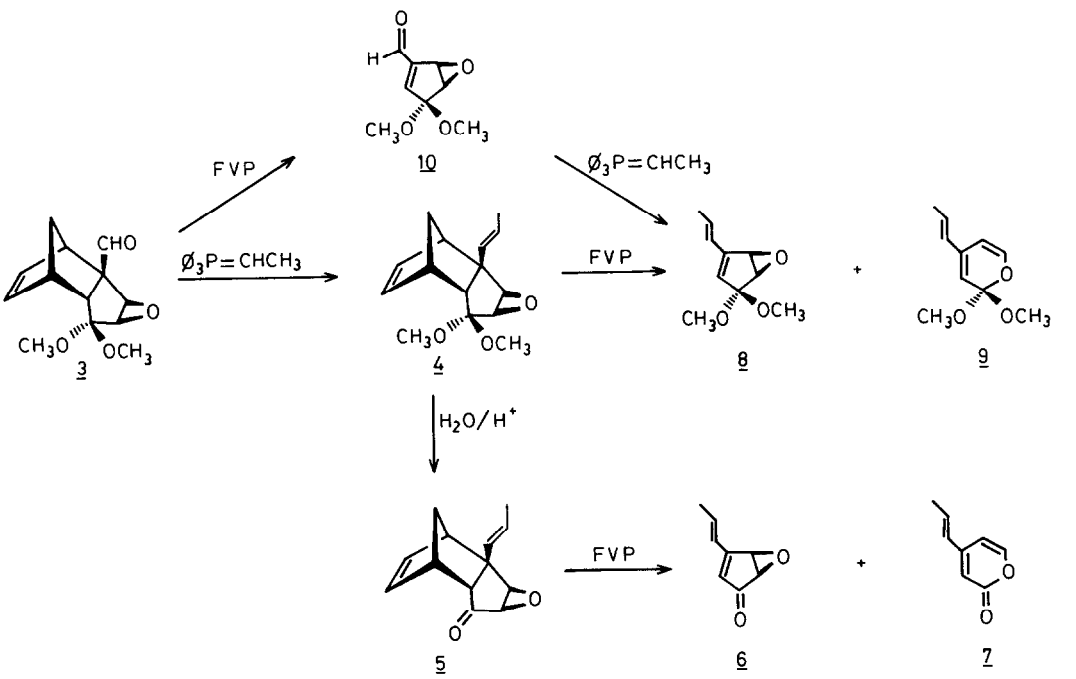


These epoxides are potentially useful for the synthesis of a variety of oxygenated cyclopentanoids. In this communication we wish to report on an efficient synthesis of terrein 2[6,7], a mould metabolite from *Aspergillus terreus*, employing appropriate cyclopentadienone epoxides as the key intermediates.

Although already isolated in 1935, terrein was synthesized only recently. Most likely, its sensitivity to acid and base precluded an earlier synthesis. Auerbach and Weinreb[8] obtained (±) terrein in a low overall yield in a laborious nine step synthesis from *cis*-1,4-bisbenzyloxy-2,3-epoxycyclopentane. Barton and Hulshof[9] prepared (±) terrein by photochemical ring contraction of an appropriate 3-hydroxy-4-pyrone which was obtained from kojic acid (overall yield 4.5%).

In our route to terrein we started off with the tetracyclic aldehyde 3 which could conveniently be prepared in three steps from tricyclodecenone ester 1 in an overall yield of 75% (Scheme 2).

scheme 2



The *trans*-propenyl side chain could be stereoselectively introduced via a Wittig olefination of 3 with ethylidenetriphenylphosphorane. *Trans*-alkene 4 was isolated in 95% yield together with a small amount (less than 5%) of the *cis*-isomer. Deprotection of the ketone function in 4 with diluted HCl aq. afforded 5 in almost quantitative yield. Tetracyclic compounds 4 and 5 were both subjected to flash vacuum pyrolysis (FVP)[5]. At an optimum temperature of 420° ($2x10^{-2}$ torr) ketone 5 gave the desired cyclopentadienone epoxide 6 in 48% yield together with some α-pyrone 7[10] (10%) and a small amount of starting material (6%). Both products 6 and 7 could easily be isolated from the mixture by prep. TLC or high performance liquid chromatography (HPLC)[11] on silicagel. Thermolysis of precursor 4, still containing the acetal as the ketone protecting group, gave at an optimum temperature of 450° ($2x10^{-2}$ torr) a mixture of dimethoxy epoxide 8 and its rearranged product 9.

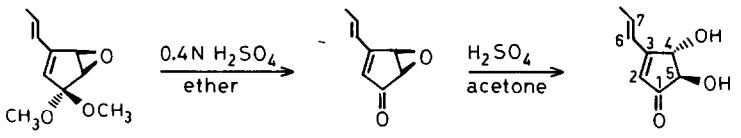
An alternative approach for the synthesis of 8 involves the introduction of the propenyl side chain *after* the thermal cycloreversion of the cyclopentenone precursor 3.

As described in the preceding paper[5], epoxy aldehyde 10 can be obtained in nearly quantitative yield by pyrolysis of 3. Subsequent Wittig-ethenylidation

afforded the *trans*-propenyl derivative 8 in 55% yield. Although both routes lead to 8, the latter sequence is considerably more convenient since no α-pyrone derivatives are formed during the thermolysis of 3 and consequently no chromatographic separation step is needed. The IR and NMR spectra of 6 and 8 were entirely in accordance with the proposed structures.

The epoxide ring in 6 as well as in 8 was found to be significantly less sensitive to acid as anticipated[12]. Thus, selective hydrolysis of the dimethyl ketal function could be accomplished by stirring 8 with 0.4 N H_2SO_4 aq. in ether at room temperature for 3 h (Scheme 3). Epoxyketone 6 was isolated in

scheme 3



8 6 2

65% yield after prep. HPLC on silicagel. The synthesis of terrein was completed by the acid catalyzed epoxy ring opening of 6. After careful experimentation the hydrolysis was found to be most effective in acetone containing 1% of a 5 N H_2SO_4 aq. solution. Treatment of 6 in this manner for 4 days at room temperature afforded (±) terrein 2 in a yield of 55%. Recrystallization from isopropanol/cyclohexanol gave 2 as a white crystalline material, m.p. 99-100°C[13]. The spectral data of 2 |m/e 154.063±0.003, $C_8H_{10}O_3$; UV(C_2H_5OH) λmax 273 nm (ε25.600); IR ν_{max}^{KBr} 3420,1683,1632,1560 cm^{-1}; 'H NMR ($CDCl_3$) δ1.89 (d, J_{CH_3,H_7}=6.6 Hz, CH_3), ~3 (broad s,OH), 4.31(d, J_{H_4,H_5}=2.6 Hz, H_4), 4.83(d, J_{H_5,H_4}=2.6 Hz, H_5), 5.97 (s,H_2), 6.35 (broad d, J_{H_6,H_7}=15.6 Hz, H_6), 6.80 ppm (d of q, J_{H_7,H_6}=15.6 Hz, J_{H_7,CH_3}=6.6 Hz, H_7); ^{13}C NMR($CDCl_3$) δ19.3, 76.8, 81.6, 124.8, 125.1, 141.4, 168.8, 203.2 ppm| are entirely consistent with the terrein structure[14]. In particular the 'H NMR spectrum clearly reveals the *trans*-relationship of the OH-groups and E-geometry of the propenyl chain.

The work presented here not only constitutes an efficient synthesis of terrein (overall yield from aldehyde 3 is 20%) but also demonstrates the versatility of functionalized cyclopentadienone epoxides as synthons for the synthesis of cyclopentanoid natural products. Further exploration of these epoxides is under active investigation in our laboratory.

REFERENCES and NOTES

1. J.S. Bindra and R. Bindra, 'Prostaglandin Synthesis', Acedamic Press, New York (1977); A. Mitra, 'The Synthesis of Prostaglandins', J. Wiley, New York (1977).

2. K. Umino, T. Furamai, N. Matsuzawa, Y. Awataguchi, Y. Ito and T. Okuda, J. Antibiot. 26, 506 (1973); K. Hatano, T. Hasegawa, M. Izawa, M. Asai and H. Iwasaki (Takeda Chem. Industries, Ltd), Japan Kokai 75,70,597 (June 1975); Chem. Abstr. 84, 3287u (1976). See for a recent synthesis: S.J. Branca and A.B. Smith, III, J. Amer. Chem. Soc. 100, 7767 (1978).
3. T. Haneishi, N. Kitahara, Y. Takiguchi and M. Ari, J. Antibiot. 27, 386 (1974); T. Haneishi, A. Terahara, M. Ari, T. Hata and C. Tamura, ibid., 27, 393 (1974); T. Haneishi, A. Terahara, K. Hamano and M. Arai, ibid., 27, 400 (1974). For recent syntheses see M. Koreeda and Y.P. Liang Chen, Tetrahedron Letters 1981, 15; D. Boschelli, R.M. Scarborough and A.B. Smith, III, ibid., 1981, 19; R.M. Scarborough, B.H. Toder and A.B. Smith, III, J. Amer. Chem. Soc. 102, 3904 (1980); J. Jernow, W. Tautz, P. Rosen and J.F. Blount, J. Org. Chem. 44, 4210 (1979).
4. H. Umezawa, T. Yamamoto, T. Takeuchi, T. Osato, Y. Okami, S. Yamaoka, T. Okuda, K. Nitta, K. Yagishata, R. Utahara and S. Umezawa, Antibiotics and Chemotherapy 4, 514 (1954). For recent syntheses see R.K. Boeckman, P.C. Naegely and S.D. Arthur, J. Org. Chem. 45, 752 (1980); J.N. Marx and G. Minaskamian, Tetrahedron Letters 1979, 4175.
5. A.J.H. Klunder, W. Bos, J.M.M. Verlaak and B. Zwanenburg, ibid., 1981, preceding paper.
6. H. Raistrick and G. Smith, Biochem. J. 29, 606 (1935), P.W. Clutterbuck, H. Raistrick and F. Reuter, ibid., 31, 987 (1937); J.F. Grove, J. Chem. Soc. 1954, 4693; D.H.R. Barton and E. Miller, ibid., 1955, 1028.
7. Although terrein itself is biologically inactive, several chlorinated derivatives have interesting antifungal and antibacterial activity; see e.g. W.J. McGahren, J.H. van den Hende and L.A. Mitscher, J. Amer. Chem. Soc. 91, 157 (1969); G.M. Strunz and A.S. Count, ibid., 95, 3000 (1973).
8. J. Auerbach and S.M. Weinreb, J.C.S. Chem. Commun. 1974, 298.
9. D.H.R. Barton and L.A. Hulshof, J.C.S. Perkin I, 1977, 1103.
10. Satisfactory elemental composition (combustion analyses or exact mass spectroscopy) and spectral data were obtained for all new compounds.
11. Some decomposition was observed during the separation which was carried out on a Jobin-Yvon miniprep LC.
12. The cyclopentadienone epoxides and its dimethyl acetals are actually thermally quite stable and can be stored at -30° without noticeable deterioration.
13. There is some discrepancy concerning the m.p. of (±) terrein reported by Weinreb (m.p. 88-89°)[8] and Barton (m.p. 99-100°)[9]. Our finding clearly established Barton's m.p. of terrein to be the correct one.
14. Our spectral data of (±) terrein correspond in all respects with those of natural (+) terrein: A.W. Dunn, I.D. Entwisk and R.A.W. Johnstone, Phytochem. 14, 2081 (1975).

(Received in UK 25 August 1981)