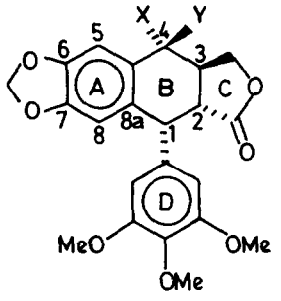
Tetrahedron Letters,Vol.26,No.32,pp 3871-3874,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (±)-PODOPHYLLOTOXIN AND (±)-EPIPODOPHYLLOTOXIN.

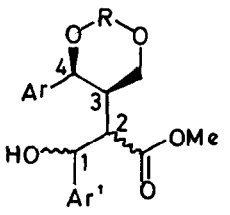
J. Van der Eycken[1], P. De Clercq[2] and M. Vandewalle*
State University of Ghent - Department of Organic Chemistry
Laboratory for Organic Synthesis, Krijgslaan 281/S4, B-9000 Gent (Belgium)

ABSTRACT
A novel approach to (±)-epipodophyllotoxin (2) and hence also (±)-podophyllotoxin (1) is described, involving as a key-step the stereoselective ring closure of the TMS-ester derived from 14a to the tetralin derivative 15 with mesyl chloride.

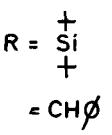
Podophyllotoxin (1) and epipodophyllotoxin (2) are two naturally occuring lignans[3] with potent antimitotic activity[4]. Apart from the first non-stereoselective synthesis reported by Gensler[5], to date only two total synthesis of 1 have been disclosed[6]. This is due to problems associated with the highly strained trans B/C ring junction and the axially locked C-1 aryl substituent. As 1 and 2 can be interconverted[7], stereocontrol at C-4 is of less importance.

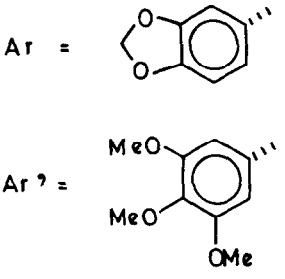


1 X = OH ; Y = H
2 X = H ; Y = OH



3





Our synthetic strategy centers around the construction of the tetraline involving as crucial step the 1-8a bond formation. Although efforts along this line have been reported[8], ring closure via an electrophilic substitution process has until now failed to produce the correct relative stereochemistry at C-1, 2 and 3. It should be noted that the configuration at these three contiguous chiral centers in 1 or 2 is thermodynamically unstable (epimerization at C-2)[3a]. It seemed to us that a study of the stereochemical outcome of this ring closure on a conformationally less flexible system (such as present in diastereoisomers 3) could be rewarding. Inspection of molecular models suggested that induction at the centers C-1 and C-2 would be optimal with both the aryl group at C-4 and the side chain at C-3 in a cis-relationship as in 3 [9]. Therefore, epipodophyllotoxin (2) became the primary target molecule. Although the expectation concerning the 2-position was not completely fulfilled, the present study led to the discovery of a viable route to 1 and 2.

Intermediate 7 was obtained via initial aldol condensation of the tin-(II)-enolate[10] of N-(4-pentenoyl)-thiazolidine-2-thione (4)[11] with piperonal, yielding exclusively the desired erythro-isomer (90%). Subsequent methanolysis then gave 5 (62%)[10]. Reduction of 5 yielded the diol which was protected (81%) as the di-t.butylsilylene derivative[12,13], using Corey's procedure[13]. Unmasking the latent carboxyl group was best effected via a 3-step procedure, leading to 6 in 82% overall yield[14,15].

In contrast with our expectations, aldol condensation of 7 with 3,4,5-trimethoxybenzaldehyde showed low stereocontrol. By properly choosing the reaction conditions, either 8d (enolate formation in THF; addition of the aldehyde at -78° C, followed by warming up to -10° C over 90 min, and quenching with NH_4Cl; 44%), or a 1:1 mixture of 8a and 8b with only minor amounts of 8c and 8d could be obtained (enolate formation in ether; addition of the aldehyde at -100°C, followed by immediate quench with acetic acid at -100°C; 68%).[16]

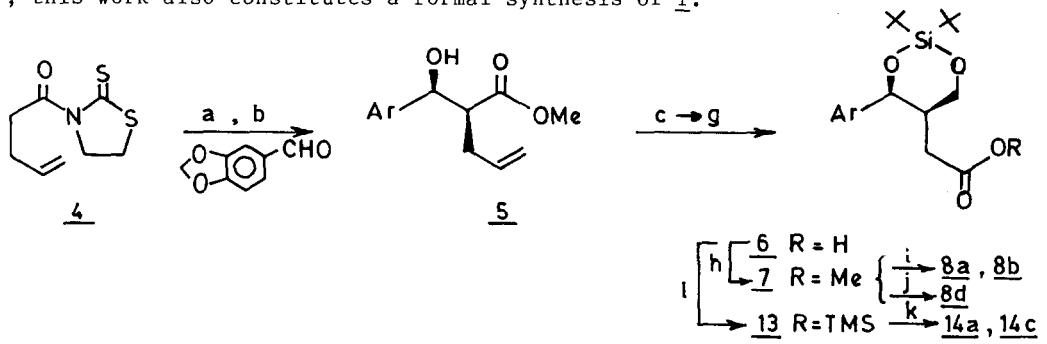
Study of the electrophilic ring closure of the different isomers 8 was now undertaken. Treatment with a variety of acid catalysts (TFA, $SnCl_4$, ZnI_2) failed to produce the desired tetraline 9. Instead, dihydronaphtalenes 10 (arising from SE-reaction of a 4-carbenium ion on ring D) and tetrahydrofurans 11 (from internal displacement at C-4) were invariably formed. This indicates that in this case, when one of the oxygens of the silylene ether is benzylic, this protective group is not stable towards Lewis acid-catalyzed intramolecular displacement reactions.[17]

In order to ensure regioselective formation of a C-1 carbenium ion, we decided to replace the hydroxyl function in 8 with a sulfide group[18], via the mesylate. Much to our surprise, treatment of 8a with mesylchloride (NEt_3, CH_2Cl_2, -10°C) afforded directly, in 90% yield, tetraline 9 , with the correct stereochemistry at all centers. Under the same conditions, 8c produced the C-1 epimer of 9, thus indicating a neat SN_2-type displacement at C-11[9]. However, 8b and 8d gave rise to mixtures of 10 and 11, showing that inversion of the configuration of C-2 has severe implications for the ring closure reaction, inhibiting the reacting centers C-1 and C-8a to approach in the desired rotameric form.

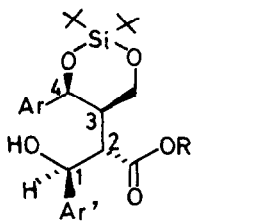
Transformation of 9 into 2 requires hydrolysis of the methyl ester prior to deprotection of the 1,3-diol, in order to prevent epimerization at C-2 [6a]. Attempts to hydrolyze ester 9 invariably led to the neopodophyllotoxin derivative 12 [21] via internal nucleophilic displacement at C-4.

This problem was circumvented by performing the aldol condensation on the trimethylsilylester 13 , which led to a different product distribution: 14a and 14c were obtained in a 4:5 ratio (45%)[21]. Selective in situ protection of the acid function in 14a with a trimethylsilyl group, subsequent treatment with mesyl chloride (NEt_3, CH_2Cl_2, -10°C) and aqueous work-up afforded the desired acid 15 (45%)[22]. Cleavage of the silyl

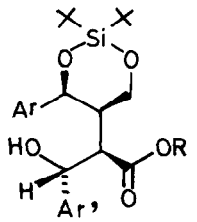
protective group (TBAF, THF, r.t., 16 h) and lactonization (DCC, DMAP, CH_2Cl_2, r.t., 16 h) gave (±)-2, identical, except for rotation, with a sample of natural (-)-epipodophyllotoxin (2)[23]. Since 2 has previously been converted to podophyllotoxin (1)[7a], this work also constitutes a formal synthesis of 1.



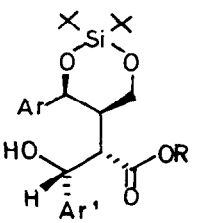
a) $Sn(OSO_2CF_3)_2$ (1.25 eq.), N-Et-piperidine, CH_2Cl_2, -78 °C; b) K_2CO_3, MeOH, r.t., 10 min; c) $LiAlH_4$, (1.5 moleq.), THF, 0°C, 1 h; d) $(t.Bu)_2Si(OSO_2CF_3)_2$ (1.2 eq.), 2,6-lutidine (3 eq.), CH_2Cl_2, 0°C, 2 h; e) OsO_4, (1 mol %), NMMO (1 eq.), acetone-water (3 : 1), r.t., 16 h; f) $NaIO_4$ (3.3 eq.), acetone-water (3 : 1), r.t., 2 h; g) $NaClO_2$ (1.25 eq.), 2-Me-2-butene (10 eq.), t.BuOH-water (5 : 1), pH 3 (NaH_2PO_4-buffer), r.t., 30 min; h) CH_2N_2, ether, 0°C; i) LDA (2 eq.), -78°C to -40°C, ether, 90 min.; Ar'CHO (1.2 eq.), -100°C, 1 min; 10 % HOAc in ether, -100 °C (inverse quench); j) LDA (2 eq.), THF, -78°C to -40°C, 90 min; Ar'CHO (1.2 eq.) , -30°C to 10°C, 90 min; NH_4Cl; k) LDA (3 eq.), -78°C to -40°C, THF, 90 min; Ar'CHO (1.2 eq.), -78°C, 3 min; 10 % HOAc in ether, -78°C (inverse quench); l) TMSCl (1.1 eq.), NEt_3 (1.1 eq.), THF, 0°C, 15 min.



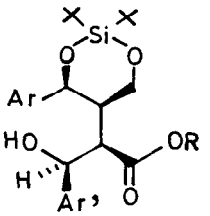
8a R = Me
14a R = H



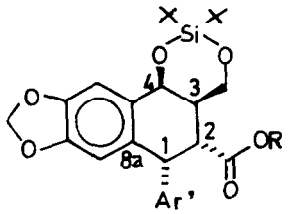
8b R = Me



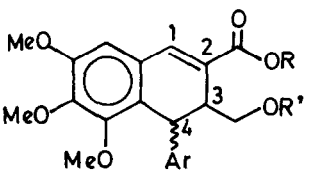
8c R = Me
14c R = H



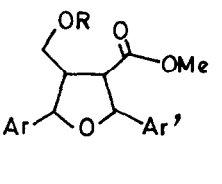
8d R = Me



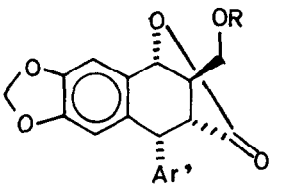
9 R = Me
15 R = H



10 R = Me ; R' = H or TFA



11 R = $(t.Bu)_2SiOH$



12

With the valuable information that only diastereomer 8a leads to the desired relative configuration present in the target molecules, a stereoselective synthesis of 8a is presently studied. Also an asymmetric synthesis of 1 and 2 is in progress.

Acknowledgements - We thank the "N.F.W.O." and the "Ministerie voor Wetenschapsbeleid" for financial support to the laboratory.

REFERENCES AND NOTES

1. Research fellow of the "Nationaal Fonds voor Wetenschappelijk Onderzoek".
2. Senior Research Associate of the "Nationaal Fonds voor Wetenschappelijk Onderzoek".
3. (a) J.L. Hartwell, A.W. Schrecker, Fortschr. Chem. Org. Naturst., **1958**, 15, 83; (b) R.S. Ward, Chem. Soc. Rev., **1982**, 11 (2), 75-125.
4. (a) G.R. Pettit, "Biosynthetic Products for Cancer Chemotherapy", Plenum Press, New-York/London, vol. 1 (1977), pp.97-104; (b) I. Jardine, Med. Chem., **1980**, 16, 319.
5. (a) W.J. Gensler, C.D. Gatsonis, J. Org. Chem., **1966**, 31, 4004; (b) W.J. Gensler, C.D. Gatsonis, J. Am. Chem. Soc., **1962**, 84, 1748.
6. (a) D. Rajapaksa, R. Rodrigo, J. Am. Chem. Soc., **1981**, 103, 6208; R. Rodrigo, J. Org. Chem., **1980**, 45, 4538; (b) A.S. Kende, L.S. Liebeskind, J.E. Mills, P.S. Rutledge, D.P. Curran, J. Am. Chem. Soc., **1977**, 99, 7082; A.S. Kende, M.L. King, D.P. Curran, J. Org. Chem., **1981**, 46, 2826.
7. (a) W.J. Gensler, F. Johnson, A.D.B. Sloan, J. Am. Chem. Soc., **1960**, 82, 6074; (b) J.L. Hartwell, A.W. Schrecker, J. Am. Chem. Soc., **1951**, 73, 2909.
8. F.E. Ziegler, J.A. Schwartz, J. Org. Chem., **1978**, 43, 985.
9. A detailed account will be given elsewhere.
10. T. Mukaiyama, N. Iwasawa, R.W. Stevens, T. Haga, Tetr., **1984**, 40 (8), 1381.
11. Y. Nagao, K. Seno, K. Kawabata, T. Miyasaka, S. Takao, E. Fujita, Tetr. Lett., **1980**, 21, 841.
12. B.M. Trost, C.G. Caldwell, Tetr. Lett., **1981**, 22, 4999.
13. E.J. Corey, P.B. Hopkins, Tetr. Lett., **1982**, 23, 4871.
14. V. Van Rheenen, R.C. Kelly, D.Y. Cha, Tetr. Lett., **1976**, 17, 1973.
15. B.O. Lindgren, T. Hilsson, Acta Chem. Scand., **1973**, 27, 888; for a detailed procedure see e.g. G.A. Kraus, B. Roth, J. Org. Chem., **1980**, 45, 4825.
16. The configuration of compounds 8 was deduced by comparing ^{1}H-NMR-data with those of a related dioxane, whose structure was established by single crystal X-ray analysis: C. Piccinni-Leopardi, J.P. Declercq, G. Germain, M. Van Meerssche, J. Van der Eycken, P. De Clercq, M. Vandewalle, Bull. Soc. Chim. Belge, **1984**, 93 (12), 1047.
17. This protective group was chosen because its stability towards Lewis acid conditions has been claimed.[12]
18. A. Pelter, R.S. Ward, P. Satyanarayana, P. Collins, J. Chem. Soc., Perk. Trans. I, **1983**, 643.
19. Treatment of 8a and 8c with Burgess' reagent[20] led to the same compound 9 and its C-2 epimer respectively.
20. E.M. Burgess, H.R. Penton, E.A. Taylor, J. Org. Chem., **1973**, 38, 26.
21. This compound has been converted to podophyllotoxin (1): J. Renz, M. Kuhn, A. von Wartburg, Liebigs Ann. Chem., **1965**, 681, 207.
22. yield not optimized.
23. (-)-2 was prepared from commercial (-)-podophyllotoxin (1) (Aldrich, technical grade) via conversion to epipodophyllotoxin chloride and subsequent hydrolysis, analogous to the procedure described by E. Schreier, Helv. Chim. Acta, **1964**, 47 (6), 1529; see also ref. 7b.

(Received in UK 11 June 1985)