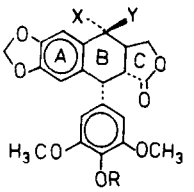
Tetrahedron Letters,Vol.27,No.27,pp 3099-3102,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

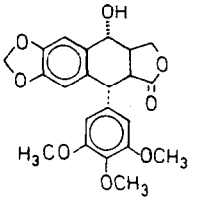
# TOTAL SYNTHESIS OF (+) EPIPODOPHYLLOTOXIN VIA A (3 + 2)-CYCLOADDITION STRATEGY

D.M. Vyas*, P.M. Skonezny, T.A. Jenks and T.W. Doyle
Bristol-Myers Company, Pharmaceutical Research and Development Division
5-Research Parkway, P.O. Box 5100
Wallingford, Connecticut 06492

Abstract: A total synthesis of racemic epipodophyllotoxin 1 from chalcone 6 has been developed employing a novel (3 + 2)-cycloaddition strategy to construct the correct substituent stereochemistry in aryltetralin ring B of 1.

Epipodophyllotoxin (1) and podophyllotoxin (2), two of several naturally occuring lignans[1] isolated from extract of roots of a variety of species of Podophyllum, have held a long standing interest among synthetic chemists, because of their utility in the synthesis of effective, glycosidic, clinical antitumor agents[2] etoposide (3) and teniposide (4).[2] The main synthetic obstacle to these lignan lactones has been the stereospecific construction of tetralin ring B. To date only two successful syntheses of epipodophyllotoxin (1) have been reported.[3] All prior syntheses[4] of 2[5] have proceeded via




5

1 X=H, Y=OH, R=$CH_3$

2 X=OH, Y=H, R=$CH_3$

3 X=H, Y=β-D-4,6-O-ethylidene glucose, R=H

4 X=H, Y=β-D-4,6-O-thienylidene glucose, R=H.

picropodophyllotoxin (5) using an epimerization sequence involving the Gensler enolate quenching procedure.[4a]

In our reterosynthetic analysis we envisioned epipodophyllotoxin 1 as ultimately being derivable from tetralone 8[4a] via key synthons 10, 11, and 14. The novel features of our approach are the use of a (3 + 2)-cycloaddition reaction (10 → 11) to achieve the correct stereochemical configuration at the four contiguous carbon centers in ring B and the formation of the highly strained trans-B/C ring junction in 1 by a diazotization sequence on aminoacid 14.

Our synthesis (Scheme 1) begins with the development of an improved synthetic methodo-

logy to prepare ketone 8. In 1982[6] Murphy and Wattanasin reported an improved three step synthesis of tetralone 8 from the readily available chalcone 6.[7] The elegant feature of their approach was the Lewis acid-catalyzed rearrangement of cyclopropyl ketone 7 to 8. However, for our purposes this methodology was not suitable since the rearrangement was slow (4 to 15 days), inefficient (< 60% yield), and afforded a mixture of products. Thus we modified their protocol by performing the rearrangement (7 → 8) in the presence of at least 2 equivalents of acetic anhydride.[8] Under our conditions ($BF_3Et_2O$, $CH_3NO_2$, $Ac_2O$, r.t.) the rearrangement afforded > 90% yield of tetralone 8 in less than one hour.

Having a good source of tetralone 8 in hand, we turned our attention to the preparation of cis-dihydronaphthalene ester 10. This was most effectively accomplished by conversion of 8 to 9 via the following reaction sequence: saponification (5% KOH/MeOH), reduction ($NaBH_4$/EtOH/$H_2O$/$CH_2Cl_2$), dehydration[9] (TsOH/toluene) and esterification ($Ph_2CH_2OH$/ TsOH/toluene). Epimerization of the trans-ester 9[10] by enolate quenching (LDA/THF -78°C → -40°C, HCl) afforded cis-ester 10 in ca. 70% isolated yield from 9. No detectable ($^1$HNMR) amount of the trans isomer 9 was found in the crude epimerized product 10.

The stereospecific assembly of the ring B substituents in 1 was initiated by a regiospecific (3+2)-cycloaddition of bromonitrile oxide,[11] generated in-situ ($Br_2CNOH$, $KHCO_3$, EtOAc, reflux), to cis-olefin 10 to yield cyclo-adduct 11 in 65% yield. This was followed by an acidic[12] ($CH_3NO_2$/HCl/MeOH) deprotection of the benzhydryl ester moiety to yield acid 12[13] in 75% yield. Reductive opening[14] of the isoxazoline ring in 12 to the hydroxynitrile 13 was effectively achieved by catalytic hydrogenation (RaNi or NiB/$H_2O$/MeOH/$CH_2Cl_2$, $H_2$, 40 psi).

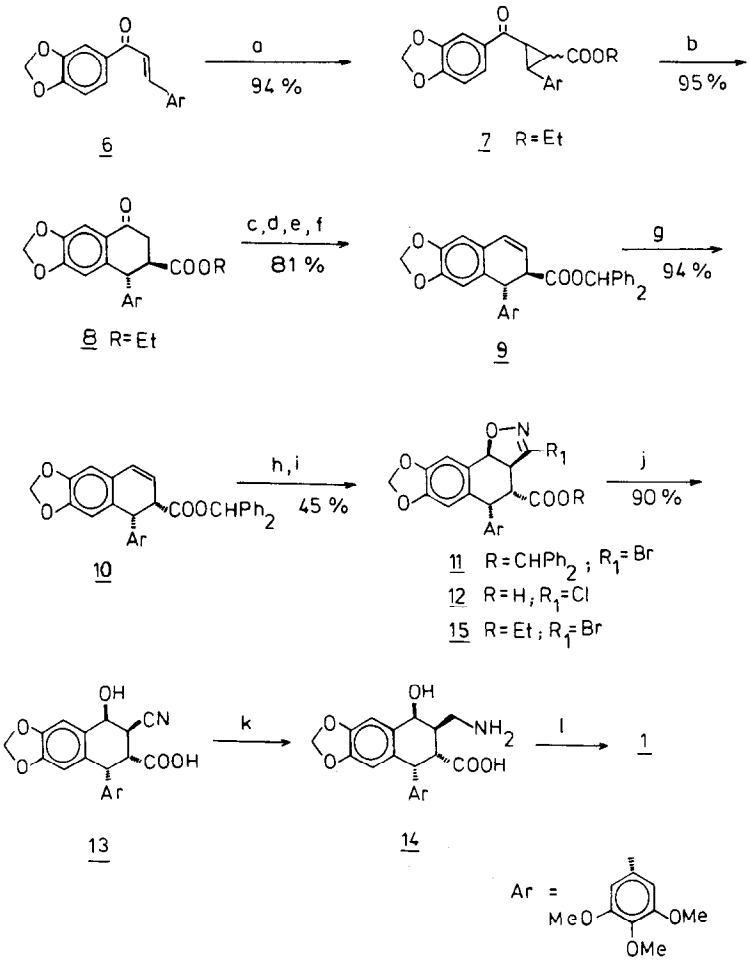
The final two chemical reactions leading to epipodophyllotoxin 1 were performed in one pot and involved lithium aluminium hydride reduction[15] of the nitrile 13 to the amino acid 14 followed by a diazotization[16] ($AcOH/H_2O/NaNO_2$) to yield the lactone 1 in a yield of 87% from 13. The 360 MHz NMR spectrum of synthetic (±) 1 was identical to that reported[17] for natural 1.

The reasonably simple stereospecific construction of the epipodophyllotoxin system (overall yield ca. 25%) we are reporting here should prove especially valuable for the synthesis of analogues and developing a commercial synthesis of clinical agents 3 and 4.

## REFERENCES AND NOTES

1. I. Jardine in 'Anticancer Agents Based on Natural Product Models', (J.M. Cassady and J.D. Douros, eds.) 1980, 319-351 (Academic Press) and references therein.

Scheme 1




a) Ref. 6; (b) $BF_3.Et_2O$ (1 equiv.), $CH_3NO_2$, $Ac_2O$ (2 equiv.), r.t, 1 hr; c) 5% KOH, MeOH; d) $NaBH_4$, $EtOH/CH_2Cl_2/H_2O$ (10:10:1), 40°C; c) TsOH, toluene, reflux; f) $Ph_2CHOH$ (1 equiv.), toluene, TsOH, reflux; g) LDA (1.2 equiv.), THF, -78°C→ -40°C, 35 min., HCl in THF quench h) $Br_2CNOH$ (3 equiv. portionwise addition), $KHCO_3$ (3 equiv.), EtOAc, reflux; i) 1N HCl ($CH_3COCl$ + MeOH) in $CH_3NO_2$, r.t; j) RaNi (1 microspatulla), $MeOH/H_2O/CH_2Cl_2$ (9:1:2), $H_2$, 40 psi, 6 hr; k) LAH (3.5 equiv.), THF, r.t., 16hr.; l)$NaNO_2$, $AcOH/THF/H_2O$, r.t. 1-2 hr..

2. T.W. Doyle in 'Etoposide (VP-16)', (B.F. Issell, F.M. Muggia and S.K. Carter, eds.), 1984, 15-32 (Academic Press).

3. (a) D. Rajapaksa, R. Rodrigo, J. Am. Chem. Soc., 1981, 103, 6208; R. Rodrigo, J. Org. Chem., 1980, 45, 4538; (b) J.V. Eycken, P. De Clercq, M. Vandewalle, Tetr. Lett., 1985, 32, 3871.

4. (a) W.J. Gensler, C.D. Gastonis, J. Org. Chem., 1966, 31, 4004; W.J. Gensler, C.D. Gastonis, J. Am. Chem. Soc., 1962, 84, 1748; (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.

5. 2 can be readily converted to 1. (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.

6. W.S. Murphy, S. Wattanasin, J.C.S. Perkin I 1982, 271.

7. S. Wattanasin, W.S. Murphy, Synthesis 1980, 621.

8. Presumably, the role of acetic anhydride in the rearrangement is to form a transient enol acetate and thus preclude the formation of an oxocarbonium ion intermediate which has been reported (ref. 6) to be responsible for the formation of side products.

9. During this step some lactone formation was also observed. However subsequent esterification reaction on the mixture of olefin and the lactone cleanly afforded ester 9 in high yield.

10. All new compounds were fully characterized spectroscopically and by elemental analysis.

11. D.M. Vyas, Y. Chiang, T.W. Doyle, Tetr. Lett. 1984, 25, 487.

12. In the case of ester 15 (R=Et, $R_1$=Br), base saponification proved to be problematic and consequently warranted preparation of acid sensitive ester 9.

13. Such a halogen exchange reaction was also observed in ref. 11. However, deprotection of 11 using trifluoroacetic acid circumvents this exchange.

14. S.K. Dubey, E.E. Kraus, J. Org. Chem., 1984, 49, 123 and reference therein.

15. The high selectivity for nitrile reduction over the carboxyl reduction may be attributed to steric factors.

16. Diazotization of glutamic acid to butyrolactone is well known. H. Plieninger, G. Ege, R. Fischer, W. Hoffman, Chem. Ber., 1961, 94, 2106.

17. C.F. Brewer, J.D. Loike, S.B. Horowitz, J. Med. Chem., 1979, 22, 215.

(Received in USA 14 March 1986)