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THE SYNTHESIS OF 2-AZAPODOPHYLLOTOXINS

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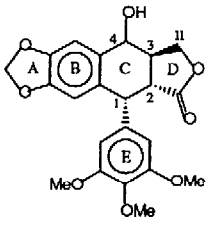
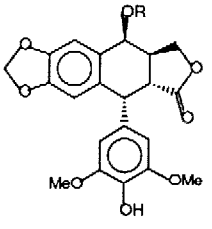
Abstract : 2-Azapodophyllotoxins, tetrahydroisoquinoline analogues of podophyllotoxin have been synthesized. They constitute a new class of highly potent anti-tumor agents.

Podophyllotoxin **1,** a lignan lactone isolated from several plant species like Podophyllum peltatum is a potent cytotoxic agent.[1] Two derivatives of the also naturally occuring epipodophyllotoxin **2**, namely etoposide **3** and teniposide **4** have been developed in the sixties and are currently in use for the treatment of several human tumors[2,3]. Both **1** and **2** received considerable attention as targets for total synthesis[4] since Gensler's first report in 1966[4a].

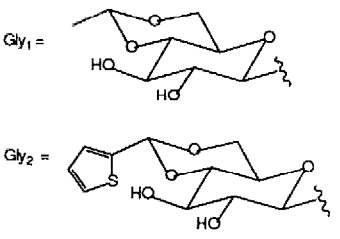
A few years ago we decided to investigate the synthesis and the biological properties of the isosteric 2-aza analogues of **1** and **2**.[5,6] A recent publication[7] of the Lilly Research Laboratories prompts us to disclose part of our work. In the preceding Letter we reported the synthesis of the 4-desoxy-2-azapodophyllotoxins[12]. Presently we want to describe the synthesis of the tetrahydroisoquinoline skeleton carrying a 4-hydroxy group. In the carbocyclic series (**1, 2, 3** and **4**) it has been shown that the 1,2-cis-2,3-trans configuration is of critical importance for the antitumor activity. This structural feature is furthermore a severe obstacle for the total synthesis of **1** and **2**. It seemed to us that the 2-aza analogues could be more readily accessible and that the synthesis of all four geometrical isomers would be highly desirable for evaluation of the biological activities. Several routes based on the Pictet-Spengler and Bischler-Napieralski methodology for construction of the title compounds have been studied. Results obtained via the latter method are presented and involve the prior obtention of threo and erythro acyclic precursors **10** and **24**.



1 4α
2 4β

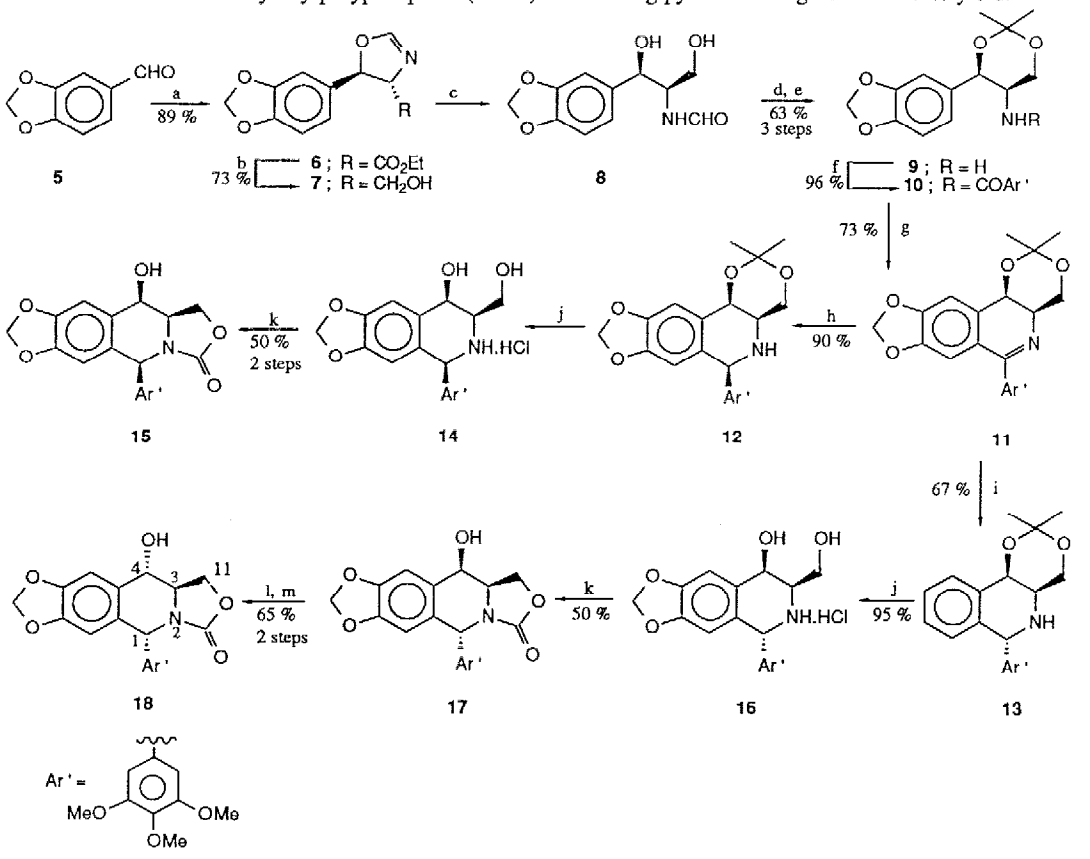


3 R = Gly_1
4 R = Gly_2



The threo isomer **10**, the precursor for the 4-epi series of the target molecules, was obtained by Schöllkopf's method[8] (scheme 1). Condensation of **5** with ethyl isocyanoacetate led under thermodynamic conditions to trans **6**. Reduction of the ester function to **7** and hydrolytic cleavage of the oxazoline nucleus afforded **8**, after which the diol was protected as the acetonide. Removal of the formyl group was found to be difficult; eventually the best results

were obtained with hydrazine[9] in an overall yield from **7** to **9** of 63 %. The Bischler-Napieralski reaction on **10**, under the usual Lewis-acid conditions, invariably led to isoquinolines via elimination of the 4-oxy group. Although a cumbersome process[10], treatment of **10** with P_2O_5 in pyridine gave the expected **11** in 60 %. The best method involved the use of trimethylsilylpolyphosphate (PPSE) in refluxing pyridine[11] to give **11** in 73 % yield.



a) CN-CH_2COOEt, NaCN, EtOH, 15°C, 2.5 h; b) $NaBH_4$, i.PrOH, rt, 24 h; c) Et_3N, H_2O/EtOH (1:1), reflux, 1.5 h; d) 2,2-dimethoxypropane, Me_2CO, 1 M HBr in MeOH, rt, 1 h; e) $N_2H_4.H_2O$ 85 % aq, reflux, 2 h; f) Ar'COCl,-Pyr, DMAP, 0°C - rt, 1.5 h; g) PPSE (in CH_2Cl_2), Pyr, reflux, 18 h; h) AlH_3, THF, -30°C - -10°C, 2 h; i) $AlMe_3$, THF, rt, 20 min, then LAH, rt, 30 min; j) HCl, p.dioxane, water, 25°C, 4 h; k) $COCl_2$, CH_2Cl_2, Et_3N, O°C, 4 h; l) PCC, CH_2Cl_2, rt, 5 h; m) Zn $(BH_4)_2$, Et_2O, rt, 1 h.

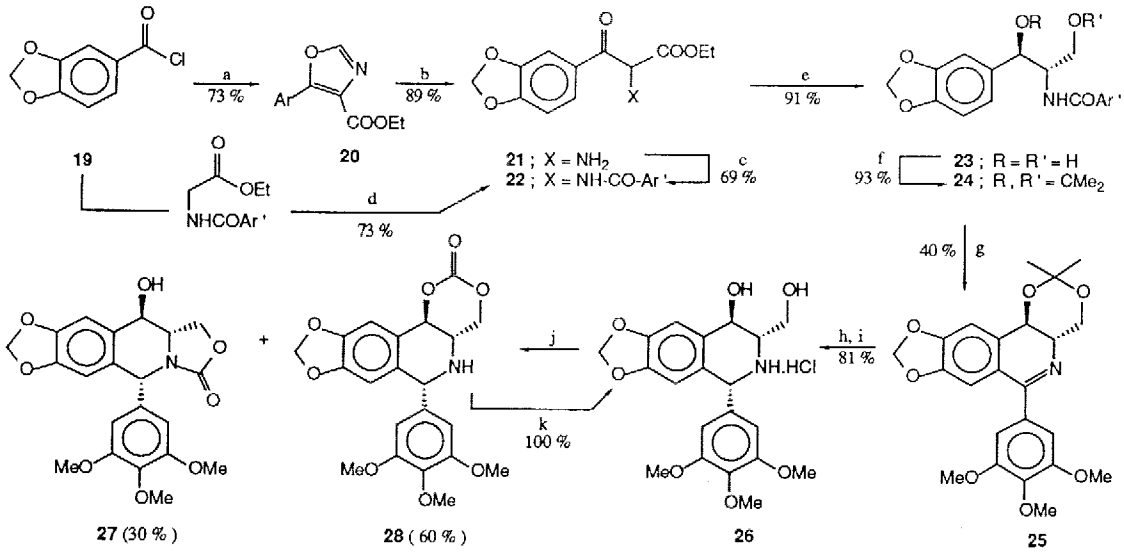
Scheme 1

With **11** in hand we turned our attention to its reduction to both the 1,3-cis and 1,3-trans tetrahydroisoquinolines **12** and **13**. As described for the 4-desoxy analogues[12], AlH_3 reduction solely led to the cis isomer **12**. On the other hand, after complexation[13] of the imine with $AlMe_3$, $LiAlH_4$ reduction afforded the trans isomer as the main product (ratio **13**:**12** = 3:1, 90 % total yield). This result could be due to the fact that in the iminium salt, the 3-substituent is forced to take an axial orientation, thus releaving the A-1,2-strain. As a consequence, hydride attack from the axial direction at C-1, thus leading to a chair-like intermediate,[14] occurs from the β-site. Finally after hydrolysis of the acetonide protective group, the D ring was formed upon treatment of **14** and **16** with phosgene; **15** and **17** were obtained in 50 % yield. The isomer **17**, which is the analogue of

epipodophyllotoxin **2**, was subsequently transformed into **18**, the analogue of podophyllotoxin **1**, via an oxidation-reduction procedure similar to the transformation of **2** into **1**.[15]

For the erythro-series at first an approach via **20**[16] has been explored. Although β-keto-ester **21** could be obtained in high yield, subsequent reduction of the keto-function gave irreproducible results. Optimization has until now met with limited success. On the other hand, reduction of the corresponding amide **22** led, in line with Felkin's rule[17], to the erythro-intermediate **23**.

Alternatively β-keto-ester **22** could be obtained directly upon reaction of **19** with the lithium-enolate anion of ethyl N-(3,4,5-trimethoxybenzoyl)-glycinate in 73 % yield. Ketalization of **23** and Bischler-Napieralski reaction[10] gave **25** which was stereoselectively reduced, leading to the 1,3-cis isomer **26** after removal of the protective group. Treatment of the amino-diol with phosgene led to a mixture of the desired product **27** (30 % unoptimized yield; m.p. 221-226° decomp.) next to 60 % of the presumed cyclic carbonate **28**. The latter could be hydrolyzed back to the diol **26** in virtually quantitative yield.



a) $CN\text{-}CH_2COOEt$, Et_3N (3 eq), THF, O°C - rt, 48 h; b) HCl conc., EtOH, 55°C, 3 h; c) $3,4,5\text{-}(MeO)_3C_6H_2COCl$, NEt_3, CH_2Cl_2, 0°C - rt, 90 min; d) LDA, HMPA, -70°C; e) $LiBH_4$, DME, rt, 12 h; f) Me_2CO, DMP, pTSA, rt, 18 h; g) P_2O_5, Pyr, sand, 110°C, 2.5 h; h) AlH_3, THF, -30°C - rt, 2 h; i) 1 N HCl, THF, rt, 16 h; j) $COCl_2$, NEt_3, CH_2Cl_2, 0°C, 2 h; k) 50 % NaOH, H_2O, rt.

Scheme 2

The four isomers **15**, **17**, **18** and **27**[18] and some other D ring modified analogues are presently screened in several human tumor cell lines. Details of the physiological activity will be published elsewhere, together with forthcoming chemical results.

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References and Notes

1. Hartwell, J.L.; Schrecker, A.W.; Fortschr. Chem. Org. Naturst., **1958**, *15*, 83.
2. Keller-Juslén, C.; Kuhn, M.; von Wartburg, A.; Stähelin, H.; J. Med. Chem., **1971**, *14*(10), 936;
3. Jardine, I.; Med. Chem., **1980**, 16, 319.
4. (a) Gensler, W.J.; Gatsonis, C.D.; J. Org. Chem., **1966**, *31*, 4004; (b) Kende, A.S.; King, M.L.; Curran, *D.P.; J. Org. Chem.*, **1981**, *46*, *2826; (c) Murphy, W.S., Wattanasin, S.; J. Chem. Soc., Chem.* Commun., **1980**, 262; Tetrahedron Lett., **1980**, *21*, 3517; (d) Rajapaksa, D.; Rodrigo, R.; J. Am. Chem. Soc., **1981**, *103*, 6208; (e) Van der Eycken, J.; De Clercq, P.; Vandewalle, M.; Tetrahedron, **1986**, *42*(15), 4285 and 4297; (f) MacDonald, D.I.; Durst, T.; J. Org. Chem., **1986**, *51*, 4749; (g) Jones, D.W., Thompson, A.M.; J. Chem. Soc., Chem. Commun., **1987**, 1797; (h) Kaneko, T.; Wong, H.; Tetrahedron Lett., **1987**, *28*, 517; (i) Andrews, R.C.; Teague, S.J.; Meyers, A.I.; J. Am. Chem. Soc., **1988**, *110*, 7854 and references cited in these publications.
5. Vandewalle, M.; Van der Eycken, J.; Van Wijngaarden, I.; Van Hes, R.; Hulkenberg, A.; Keet, C.; Patent appl. A 87 C 73.149 EP 251.361; JP 87.283.960 and Annual Drug Data report **1988,** *10*, 510.
6. Hulkenberg, A. Van Hes, R.; Vandewalle, M.; Van der Eycken, J.; Van Wijngaarden, I.; Xth Int. Symp. Med. Chem., Aug 15-19, Budapest **1988**, 26; Annual Drug Data Report **1988**, *10*, 850.
7. Pearce, H.L.; Bach, N.J.; Cramer, T.L.; Tetrahedron Lett.; **1989**, *30*(8), 907; no reference to ref. 5 and 6 is given.
8. Schöllkopf, U.; Scheunemann, K.-H.; Liebigs Ann. Chem., **1980**, *30*(8), 1348.
9. Nordin, I.C.; Thomas, J.A.; Tetrahedron Lett., **1984**, *25* (50), 5723.
10. *Itoh, N.; Sugasawa, S.; Tetrahedron*, **1959**, *6*, *16.*
11. Yokoyama, M.; Yoshida, S.; Imamoto, T.; Synthesis **1982**, 591.
12. Van der Eycken, J.; Bosmans, J.-P.; Van Haver, D.; Vandewalle, M.; Hulkenberg, A.; Veerman, W.; Nieuwenhuizen, R.; this Journal, preceeding publication.
13. Maruoka, K.; Yamamoto, H.; Angew. Chem., **1985**, *97*, 670.
14. Deslongchamps, P.; "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, Oxford, **1983**, Series Editor : Baldwin, J.E.; pp. 211-221.
15. Gensler, W.J.; Johnson, F.; Sloan, A.D.B.; J. Am. Chem. Soc., **1960**, *82*, 6074.
16. a) Suzuki, M.; Iwasaki, T.; Matsunoto, K.; Okunura, K.; Synth. Comm., **1972**, *2*(4), 237; b) Suzuki, M.; Iwasaki, T.; Matsunoto, K.; Okunura, K.; Niyoshi, M.; J. Org. Chem., **1973**, *38*, 3571; c) Suzuki, M.; Iwasaki, T.; Matsunoto, K.; Okunura, K.; Chem. Ind., **1973**, 228.
17. Chérest, M., Felkin, H.; Prudent, N.; Tetrahedron Lett., **1968**, 2199; Ahn, N.T.; Eisenstein, O.; Nouv. J. Chim., **1977**, *1*, 61.

18. Relevant ^1H NMR data of the 4 isomers (360 MHz, Bruker WH-360) :

	H-1	H-3	H-4	H-11
15 (CD_2Cl_2)	5.42 (s,1)	4.15 (ddd, 1, J=2.1, 10.6, 8.0 Hz)	4.66 (d(bs), 1, J=2.1 Hz)	4.51 (dd, 1, J=10.6 Hz, ^{2}J=8.1 Hz) 4.42 (dd(t), 1, J=8.0 Hz, ^{2}J=8.1 Hz)
17 ($CDCl_3$)	5.86 (s,1)	4.09 (ddd, 1, J=2.3, 4.4, 9.0 Hz)	4.49 (d(bs), 1, J=2.3 Hz)	4.69 (dd, 1, J=4.4 Hz, ^{2}J=8.4 Hz) 4.39 (dd(t), 1, J=9.0 Hz, ^{2}J=8.4 Hz)
18 ($CDCl_3$)	5.82 (s,1)	3.76 (ddd, 1, J=9.1, 3.7, 7.9 Hz)	4.62 (d, 1, J=9.1 Hz)	4.51 (dd, 1, J=7.9 Hz, ^{2}J=9.1 Hz) 4.45 (dd, 1, J=3.7 Hz, ^{2}J=9.1 Hz)
27 ($CDCl_3$)	5.46 (s,1)	3.86 (ddd(m), 1, J=9.2, 7.6, 10.3 Hz)	4.90 (d, 1, J=9.2 Hz)	4.69 (dd, 1, J=7.6 Hz, ^{2}J=8.6 Hz) 4.30 (dd, 1, J=10.3 Hz, ^{2}J=8.6 Hz)

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