substituents but are not yet predictable for aliphatic amino acids, except that high pH seems to favor dealdolation through stronger base catalysis. The situation is complicated by the electronic requirements of the leaving group. In any case high alkalinity precludes γ-decarboxylation, which is restricted to a relatively low pH range, in both the presence and absence of metal ions.

Acknowledgment. This work was supported by a grant, No. AM-11694, from the National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health.

Communications to the Editor

A Stereocontrolled Synthesis of Antineoplastic Podophyllum Lignans

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Received April 27, 1981

Podophyllotoxin (**1**) with its four contiguous chiral centers, its rigid and strained trans B/C ring fusion, and its axially locked C-1 aryl substituent, has long been a challenging target for stereocontrolled synthesis. Kinetic reprotonation of the C-2 enolate of 4-*O*-(tetrahydropyranyl)picropodophyllin (**3**), accomplished with 38% C-2 epimerization and 51% recovery of picropodophyllin (**2**), was reported 15 years ago by Gensler and Gatsonis[1] as the culminating step of their synthesis of **1**. Subsequent refinements[2] of structural aspects of the synthetic problem have led to picropodophyllin again, but no method has yet been devised for avoiding the formidable thermodynamic hurdle of the Gensler epimerization. Consequently, no practical synthesis of **1**, **4**, or **8** yet exists. The renowned antineoplastic activity[3] of **1** and **4** and the recent clinical application[4] of two glycosides VM-26 (**5**) and VP-16-213 (**6**) in the treatment of lung and bladder cancer are other urgent reasons for solving the stereochemical problem. In a partial solution, illustrated with a recent synthesis[5] of (±)-deoxypodophyllotoxin (**7**), we disclosed strategies for stereocontrol at three chiral centers (C_1–C_3). We now present a comprehensive solution with syntheses of (±)-epipodophyllotoxin (**4**), (±)-neopodophyllotoxin (**8**), and (±)-podophyllotoxin (**1**). Moreover, since clinical agents **5** and **6** have been previously prepared[6] from natural podophyllotoxin, our current endeavors also constitute a formal synthesis of these materials.

The bicyclo precursor **9**[5] hydrogenolyzed with freshly prepared W-2 Raney nickel[7] gave a 77% yield of the tetralin **10** which was converted to the acetonide **11** by standard methods.[8,9] This reaction is not a mere protection of the diol system; it also transforms a tetralin (**10**) into what is essentially a benzo-*cis*-decalin (**11**) with stereochemically fruitful consequences. Basic hydrolysis of the methyl ester moiety of **11** now takes place *without* inversion[10] at C-2 to provide the acid **12**. We advance a thermodynamic argument for this remarkable resistance of the C-2 ester to epimerization.[11] Of the two chair conformers possible for the flexible acetonide, **11a** is severely destabilized by interactions involving both the C-1 aryl substitutent and the axial methyl group of the acetonide; epimerization of its axial ester moiety does little to alleviate such sources of strain. The overwhelming preponderance of conformer **11**, with its equatorially disposed C-2 ester group, is evident in the large diaxial coupling ($J_{2,3}$) and the "normal" chemical shifts of the acetonide methyl groups. Thus the simple expedient of ketalization is employed here to alter the thermodynamic properties of the system and thereby maintain[12] stereochemical integrity at a remote site (C-2).

Removal of the acetonide with very dilute acid in aqueous dioxane at room temperature was interesting. After 24 h epipodophyllic acid (**13**) can be crystallized.[13] Exposure of **12** to the same conditions for 48 h. produces (±)-neopodophyllotoxin (**8**) in 95% yield.[14] Since the latter has been previously converted[14] to podophyllotoxin (**1**) (two steps, 63% overall[16]), this concludes a synthesis of **1** with the final element of stereocontrol (at C-4). Lactonization of **13** with dicyclohexylcarbodiimide (DCC) proceeded uneventfully to yield[15] epipodophyllotoxin (**4**).

(1) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004.

(2) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99* 6082. Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Chem. Commun.* **1980**, 262.

(3) For a recent review see: Jardine, I. *Med. Chem.* **1980**, *16*, 319.

(4) Radice, P. A.; Bunn, P. A.; Ihde, D. C.; *Cancer Treat. Rep.* **1979**, *63* 1231.

(5) Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538.

(6) Keller-Juslen, C.; Kuhn, M.; von Wartburg; A., Stähelin, H. *J. Med. Chem.* **1971**, *14*, 936. Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1969**, *52*, 948. Kuhn, M.; Keller-Juslen, C.; von Wartburg, A. *Ibid.* **1969**, *52*, 944. These conversions were carried out with natural podophyllotoxin. Our product is racemic, of course, but we are attempting resolution at some suitable stage in the synthesis.

(7) Mozingo, R. "Organic Syntheses, Collect. Vol. 111"; Wiley: New York, 1955; 181. We have observed that yields decrease, and some inversion at C-1 results if aged samples of the catalyst are used. Diol **10** has been fully characterized previously. See ref 5 for data.

(8) ^{1}H NMR spectra were run at 80 or 400 MHz in the FT mode and are reported for the C-3a dideuterio derivatives. Coupling constants for H-1, H-2 and/or H-3, and H-4 are obtained directly from the spectra and used to monitor the stereochemistry of reactants and products. Assignments were confirmed by decoupling. The entire synthesis was repeated with the protonated analogues.

(9) With 2,2-dimethoxypropane and *p*-toluenesulfonic acid [yield 81%; m.p. 175 °C; δ ($CDCl_3$) 4.95 (d, H-4, $J_{3,4}$ = 3.71 Hz), 4.46 (d, H-1, $J_{1,2}$ = 6.05 Hz) 2.31 (q, H-3, $J_{2,3}$ = 12.2 Hz) 1.6 and 1.3 (s, 3 H each, CMe_2). H-2 was obscured by OMe at 3.5–3.8].

(10) Dilute sodium hydroxide in aqeueous dioxane at reflux for 6 h. [**12**, 82% yield; m.p. 190 °C; δ ($CDCl_3$) 4.95 (d, H-4, $J_{3,4}$ = 3.90 Hz), 4.49 (d, H-1, $J_{1,2}$ = 5.86 Hz), 2.27 (q, H-3, $J_{2,3}$ = 12.2 Hz). Deuterium incorporation at C-2 is observed under the same conditions (NaOD, D_2O).

(11) Under identical conditions the unprotected tetralin **10** was hydrolzed with complete inversion of C-2 to yield epipicropodophyllic acid (C-2 epimer of **13** [$\nu C{=}O^{KBr}$ 1700 cm^{-1}; δ (methanol-d_4) 4.90 (d, H-4, $J_{3,4}$ = 4.4. Hz), 4.43 (d, H-1, $J_{1,2}$ = 6.25 Hz), 3.12 (q, H-2, $J_{2,3}$ = 3.51 Hz), 2.49 br t, H-3)].

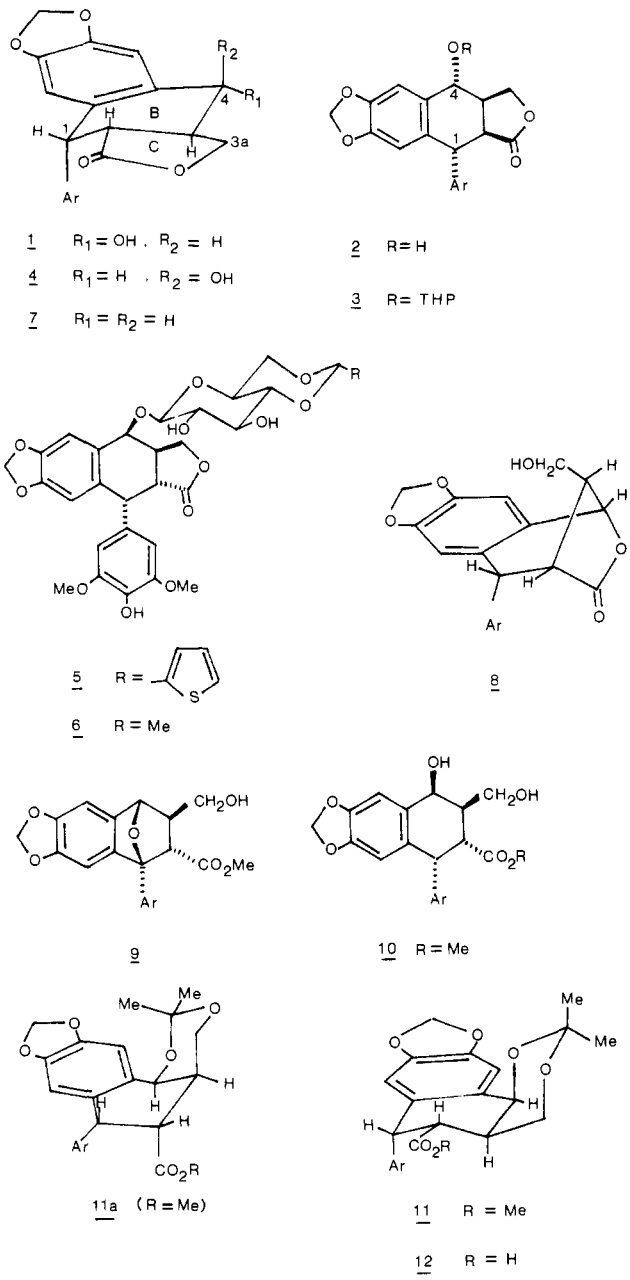
(12) The possibility that this method can be used not merely to maintain but to invert an unfavorable configuration at C-2 (e. g., in the C-2 epimer of **11**) has not escaped us. We are endeavoring to prepare such a compound.

(13) [**13**, 45% yield; m.p. 186 °C; δ (methanol-d_4) 4.93 (d, H-4, $J_{3,4}$ = 3,52 Hz), 4.46 (d, H-1, $J_{1,2}$ = 6.2 Hz), 2.33 (q, H-3, $J_{2,3}$ = 12.5 Hz) H-2 is obscured by residual methanol; $\nu_{C=O}^{KBr}$ 1690 cm^{-1}).

(14) Renz, J.; Kuhn, M.; von Wartburg, A *Liebigs Ann. Chem.* **1965**, *681*, 207. The infrared and ^{1}H NMR spectra of 8 were identical with spectra reproduced in this paper. Monitoring (TLC) of the reaction indicates that **13** is the initial product of hydrolysis. It presumably equilibrates to the C-4 epimer podophyllic acid which is irreversibly lactonized to **8**. A slow buildup of **8** is evident on TLC. No podophyllic acid was detected in admixture with **13** or in the recovered starting material.

0002-7863/81/1503-6208$01.25/0

Chart I



The entire sequence from bromopiperonal can be completed in 2 weeks and requires no chromatography except for a filtration column to remove dicyclohexylurea after the DCC lactonization. Practical stereocontrolled syntheses of **1** (9.4%, 12 steps[16]), **4** (6%, 11 steps), and **8** (14.9%, 10 steps) have thus been achieved.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work. The 400-MHz spectra were obtained at the South-Western Ontario NMR Centre Funded by a major installation grant from NSERC, Canada.

(15) **4**; 85% yield; m.p. 211 °C; $\nu_{C=O}^{CHCl_3}$ 1780 cm^{-1}. The ^{1}H NMR spectrum of **4** was identical with a published trace (Brewer, C. F.; Loike, J. D.; Horowitz, S. B.; Sternlicht, H.; Gensler, W. J. *J. Med. Chem.* **1979**, *22*, 215).

(16) The figure of 63% is based on the crude yield (78%) of podophyllic acid obtained from the saponification of **8** by the previous authors. Purification of the crude product provided podophyllic acid in only 29% yield[14] which reduces the overall yield for the two steps to 24%. Our overall yield of 9.4% for **1** is based on the higher figure.

Photoassisted Reduction of Molecular Oxygen to Hydrogen Peroxide Catalyzed by Oxoalkoxomolybdenum(V) Porphyrin

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Received March 27, 1981

In the last few years much attention has been focused on the photochemistry of metalloporphyrins as these complexes exhibit very intense absorptions in the visible region.[1] This makes them choice candidates in the design of light-harvesting systems for solar energy conversion. However, very few examples of the photochemistry of porphyrins with a redox-active central metal have been described.[2] Recently we reported on the photolysis of a diperoxomolybdenum(VI) porphyrin $(O_2)_2Mo(TPP)$ which affords the related *cis*-dioxo complex $O_2Mo(TPP)$.[3-5] The paucity of such a photoejection of a dioxygen ligand from a transition-metal complex[6,7] led us to study the photochemical behavior of molybdenum porphyrins containing Mo-O bonds.[8]

When $O{=}Mo^{V}(TPP){-}OCH_3$[9] (**1**) was aerobically irradiated (100-W tungsten lamp) in a benzene solution containing 5% v/v methanol, a clean evolution of the UV-visible spectrum was observed as shown in Figure 1, affording a new absorbance at λ 431 nm in the Soret region, characteristic of $O{=}Mo^{IV}$ TPP) (**2**).[10] When this solution was left in the dark, the spectra of **1** was fully restored. The dependence of the wavelength of irradiation on the reaction was examined by using a monochromatic light source.[11] No noticeable decomposition of **1** was observed when a benzene solution (1.4×10^{-6} M) was irradiated in a 5-cm pathlength cell at λ 620 or 575 nm near the maximum of absorption, respectively, of the α and β bands. However a rapid evolution to **2** was obtained when this solution was irradiated in the Soret region. The quantum yield for the reaction, determined by using the ferrioxalate ac-

(1) Hopf, F. R.; Whitten, D. G. In "Porphyrins and Metalloporphyrins"; Smith, K. M., Ed., Elsevier Scientific Publishing Company: Amsterdam, 1975; Chapter 16, pp 667-700. Hopf, F. R.; Whitten, D. G. *Porphyrins* **1978**, *2*, 161-195. Horsey, B. E.; Hopf, F. R.; Schmehl, R. H.; Whitten, D. G. In "Porphyrin Chemistry Advances"; Longo, F. R., Ed., Ann Arbor Science Publishers Inc.: Ann Arbor, 1979; Chapter 3, pp 17-28.

(2) Bartocci, C.; Scandola, F.; Ferri, A.; Carassitti, V. *J. Am. Chem. Soc.* **1980**, *102*, 7067-7072 and references therein. Inaki, Y.; Takahashi, M.; Kameo, Y.; Takemoto, K. *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 399-406. Hatano, K.; Usui, K.; Shida, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 413-420.

(3) Abbreviations used: *meso*-tetraphenylporphyrinato, TPP; *meso*-tetra(*p*-tolyl)porphyrinato, TTP; octaethylporphyrinato, OEP; electron paramagnetic resonance, EPR.

(4) Ledon, H.; Bonnet, M.; Lallemand, J.-Y. *J. Chem. Soc., Chem. Commun.* **1979**, 702-704.

(5) Mentzen, B. F.; Bonnet, M. C.; Ledon, H. J. *Inorg. Chem.* **1980**, *19* 2061-2066.

(6) Geoffroy, G. L.; Hammond, G. S.; Gray, H. B. *J. Am. Chem. Soc.* **1975**, *97*, 3933-3936.

(7) Boreham, C. J.; Latour, J. M.; Marchon, J. C. *Inorg. Chim. Acta* **1980**, *45*, L 69-L 71.

(8) A preliminary account of this work has been presented at the XXI International Conference in Coordination Chemistry, Toulouse, France, July 7-11, 1980. Ledon, H.; Bonnet, M.; Varescon, F. Abstracts of Papers, No. 101.

(9) Ledon, H. J.; Bonnet, M. C.; Brigandat, Y.; Varescon, F. *Inorg. Chem.* **1980**, *19*, 3488-3491.

(10) $O{=}Mo^{IV}$(TPP) was prepared as described for $O{=}Mo^{IV}$(TTP): Diebold, T.; Chevrier, B.; Weiss, R. *Inorg. Chem.* **1979**, *18*, 1193-1200.

(11) 150-W xenon lamp OSRAM XBO and Bausch and Lomb monochromator were used. Slides were adjusted to provide a spectral band width of about 10 nm. Filters M.T.O. J 351, Kodak W 4, and Kodak W 25 were, respectively, used for irradiations at 454, 575, and 620 nm.

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