served.[3,13-16] As a result of this interaction, cluster III has only C_1 symmetry, with four Fe atoms at bonded distances to Mo. This may be relevant to the structure of FeMo-co, as the most recent EXAFS results on nitrogenase[17] suggest the presence of four Fe atoms as neighbors to Mo, and recent ENDOR studies[18] have been interpreted as favoring a low-symmetry structure for FeMo-co. (iii) The dimensions of the $MoFe_3S_4^{2+}$ cubane unit in III are anomalous compared to those of other clusters containing such units.[7a,19] The mean Mo–Fe and Fe–Fe distance are only 2.67 and 2.61 Å, respectively, which are 0.05 and 0.1 Å *shorter* than those observed in other single- and double-cubane clusters,[7a,19] while the mean Mo–S and Fe–S distances of 2.36 and 2.25 Å, respectively, are not unusual.[7a,19] (iv) The mean Mo–S distance in III (2.39 Å) is 0.06 Å shorter than that in I, consistent with a formal Mo oxidation state of ca. +3 and comparable to the value of 2.37 Å observed by EXAFS for FeMo-co.[17] This indicates that reaction of I with I_2 proceeds by oxidation of both the Fe and Mo sites. (v) The Fe atoms of the $MoFe_3S_4$ cubane are ligated by PEt_3 groups, with a mean Fe–P distance of 2.33 Å. This result is somewhat surprising, since no $MoFe_3S_4$ cubanes with phosphine ligands to Fe have been reported, although phosphines do bind at the Mo site.[19,20] High-nuclearity Fe–S–PR_3 clusters such as $[Fe_6S_8(PEt_3)_6]^{2+}$,[21a] $Fe_7S_6(PEt_3)_4Cl_3$,[21b] and $Fe_6S_6(PBu_3)_4Cl_2$[21c] have been reported, but there appears to be little correlation of Fe–P bond distances with formal Fe oxidation state.[21c]

Elemental analyses and IR spectra (CH_2Cl_2; ν(CO): (III) 2051 (s), 2012 (s), 1983 (m), 1967 (sh), 1946 (sh); (II) 2058 (s), 2020 (s), 1993 (m), 1976 (sh), 1963 (sh) are consistent with the presence of a similar "capped-cubane" structure in the iodide complex, II, as well. The stoichiometry, the blue shift of ca. 10 cm^{-1} in all CO stretching modes, and the comparative electronic properties of II vs III, however, make it clear that the $MoFe_5S_6(CO)_6$ core of II is one electron more oxidized than that in III and that the oxidation is centered on the $MoFe_3S_4$ cubane, which thus has a net 3+ charge (corresponding to the $MoFe_3S_4^{3+}$ or α core observed by Holm et al. in the single cubane clusters[7a,22]). Thus, variable temperature magnetic susceptibility measurements from 4 to 300 K are consistent with the presence of an $S = {}^3/_2$ ground state for II ($\mu_{eff} = 4.20 \pm 0.05\ \mu_B$ over the range 20–100 K), but with appreciable population of higher spin levels at $T > 100$ K (μ_{eff}, μ_B (T, K) = 4.43 (156), 4.67 (235), 4.93 (298)). The $MoFe_3S_4^{3+}$ core of the single cubane clusters exhibits room temperature magnetic properties due to an $S = {}^3/_2$ state,[7a,22] suggesting that the Mo–Fe interaction in the $MoS_2Fe_2(CO)_6$ unit results in the presence of low-lying excited states that are partially populated at room temperature. The EPR spectrum of II (ca. 1 mM in MeCN) at ca. 15 K exhibits g values of 4.34, 2.95, and 2.01, consistent with a rhombically distorted $S = {}^3/_2$ ground state. Similarly, magnetic data for III are consistent with an $S = 2$ ground state (as reported for the $MoFe_3S_4^{2+}$ or β core[22,23]) ($\mu_{eff} = 5.10 \pm 0.10\ \mu_B$ over the range 4–35 K, increasing to a value of 6.43 μ_B at room temperature), but as with III, population of higher spin excited states is appreciable at higher temperatures. The chemical shifts of the Et_3P ligands decrease with increasing temperature, consistent with the observed magnetic behavior (CD_3CN; isotropic shifts in ppm vs Et_3P diamagnetic reference (T, °C): (PCH_2CH_3) 16.69 (−30), 12.86 (45); (PCH_2CH_3) 2.66 (−30), 2.16 (45)). Electrochemical measurements show the expected[7a,24,25] one-electron-transfer process for the $[MoFe_5S_6(CO)_6]^{+/0}$ redox couples (cyclic voltammetry at Pt; 200 mV/s; potentials vs SSCE): (II) −0.77 V, reversible (50 mM $Et_4N^+I^-$/40 mM $Bu_4N^+PF_6^-$ in CH_3CN); (III) −1.09 V, quasi-reversible (50 mM $Bu_4N^+PF_6^-$ in THF)). In addition, III shows a quasi-reversible oxidation at +0.13 V. These values are in the range observed for the single cubane clusters[7a] and are consistent with localization of the reduction/oxidation on the $MoFe_3S_4$ subunit of the clusters.

Clusters II and III thus constitute members of a novel class of high-nuclearity Mo–Fe–S cluster. Their stoichiometry, their low symmetry, and the presence of an additional Mo–Fe bonding interaction external to the $MoFe_3S_4$ cubane unit immediately suggest that elaboration to more realistic FeMo-co models may be possible by further oxidative decarbonylation. Variations of the chemistry described above have been found to effect total decarbonylation of I–III and will be the subject of future communications.

Acknowledgment. We thank J. Ellena for assistance with the NMR measurements. This research was supported in part by the U.S. Department of Agriculture SEA/CRGO (Grant No. 86-CRCR-1-2033) and by the National Science Foundation (CHE-89-01474).

Supplementary Material Available: Tables of positional and thermal parameters and bond lengths and angles for III (10 pages); table of observed and calculated structure factors for III (17 pages). Ordering information is given on any current masthead page.

(13) Kovacs, J. A.; Bashkin, J. K.; Holm, R. H. *J. Am. Chem. Soc.* **1985**, *107*, 1784.
(14) Nametkin, N. S.; Tyurin, V. D.; Aleksandrov, G. G.; Kuz'min, O. V.; Nekhaev, A. I.; Andrianov, V. G.; Mavlonov, M.; Struchkov, Yu. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 1353.
(15) Chieh, C.; Seyferth, D.; Song, L.-C. *Organometallics* **1982**, *1*, 473.
(16) Barber, D. E.; Bose, K. S.; Lilley, G. L.; Bryan, R. F.; Sinn, E.; Averill, B. A., to be published.
(17) Conradson, S. D.; Burgess, B. K.; Newton, W. E.; Mortenson, L. E.; Hodgson, K. O. *J. Am. Chem. Soc.* **1987**, *109*, 7507.
(18) True, A. E.; Nelson, M. J.; Venters, R. A.; Orme-Johnson, W. H.; Hoffman, B. M. *J. Am. Chem. Soc.* **1988**, *110*, 1935.
(19) Zhang, Y.-P.; Bashkin, J. K.; Holm, R. H. *Inorg. Chem.* **1987**, *26*, 694.
(20) Palermo, R. E.; Holm, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 4310.
(21) (a) Agresti, A.; Bacci, M.; Cecconi, F.; Ghilardi, C. A.; Midollini, S. *Inorg. Chem.* **1985**, *24*, 689. (b) Noda, I.; Snyder, B. S.; Holm, R. H. *Inorg. Chem.* **1986**, *25*, 3851. (c) Snyder, B. S.; Holm, R. H. *Inorg. Chem.* **1988**, *27*, 2339.
(22) Mascharak, P. K.; Papaefthymiou, G. C.; Armstrong, W. H.; Foner, S.; Frankel, R. B.; Holm, R. H. *Inorg. Chem.* **1983**, *22*, 2851.
(23) Mizobe, Y.; Mascharak, P. K.; Palermo, R. E.; Holm, R. H. *Inorg. Chim. Acta* **1983**, *80*, L65.
(24) Armstrong, W. H.; Mascharak, P. K.; Holm, R. H. *Inorg. Chem.* **1982**, *21*, 1699.
(25) Mascharak, P. K.; Armstrong, W. H.; Mizobe, Y.; Holm, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 475.

Studies on Tumor Promoters. 7. The Synthesis of a Potentially General Precursor of the Tiglianes, Daphnanes, and Ingenanes[1]

Paul A. Wender,* Hee Yoon Lee, Robert S. Wilhelm, and Peter D. Williams

Department of Chemistry, Stanford University
Stanford, California 94305

Received June 26, 1989

The phorbol esters (e.g., **1a**, Scheme I) have been vigorously studied over the past half-century since the discovery that these *noncarcinogenic* compounds amplify the effect of certain carcinogens in animals.[2] Recent epidemiological studies[2a,3] and the

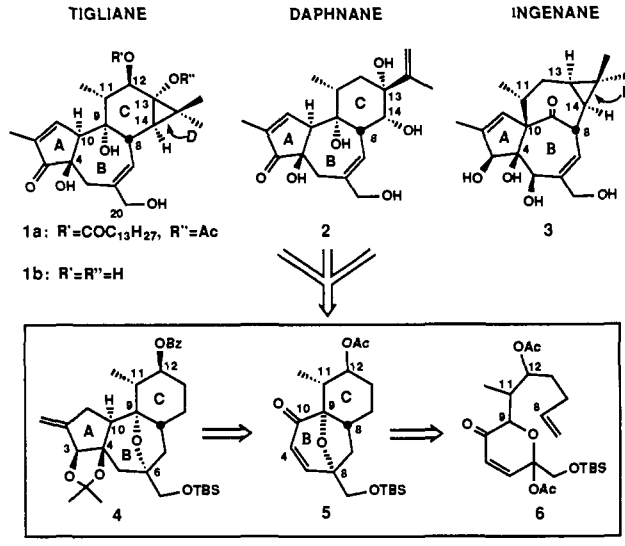
(1) (a) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, 1987; paper CHED 49. (b) Taken in part from the Ph.D. Dissertation of H.Y.L., Stanford University, 1988.
(2) For a recent comprehensive treatment of this subject and lead references, see: (a) *Naturally Occurring Phorbol Esters*; Evans, F. J., Ed.; CRC: Boca Raton, FL, 1986. (b) *Mechanism of Tumor Promotion*; Slaga, T. J., Ed.; CRC: Boca Raton, FL, 1984; Vols. I–IV. (c) Hecker, E.; Adolf, W.; Hergenhahn, M.; Schmidt, R.; Sorg, B. In *Cellular Interactions by Environmental Promoters*; Fujiki, H., et al, Eds.; Japan Science Society: Tokyo/VNU Science, Utrecht, 1984; pp 3–36. (d) Weinstein, I. B.; Galtoni-Celli, S.; Kirschmeier, P.; Lambert, M.; Hsiao, W. In *Biochem. Basis Chem. Carcinogenesis*; Greim, H. et al., Eds.; Raven: New York, 1984; p 193. (e) Hecker, E. *Arzneim.-Forsch.* **1985**, *35*(II), 12a, 1890. (f) Blumberg, P. M. *Cancer Res.* **1988**, *48*, 1. (g) A common but nonsystematic numbering system is used herein; for the Chemical Abstractions numbering, see: Tseng, S. S.; Van Duuren, B. L.; Solomon, J. J. *J. Org. Chem.* **1977**, *42*, 3645.

0002-7863/89/1511-8954$01.50/0

increasing number of new tumor promoters found in environmental and dietary sources[3,4] suggest that these compounds could also figure in human carcinogenesis. Efforts to elucidate the mode of action of these potential cancer risk factors have uncovered a complex biochemistry involving effects on cell proliferation and differentiation; ion transport; and DNA, RNA, and protein synthesis.[2] It is proposed that the phorbol ester promoters activate protein kinase C (PKC),[5,6] a key enzyme which mediates cellular signal transduction initiated by numerous effectors including hormones, neurotransmitters, growth factors, and oncogenes.[2,7] As a consequence, this pathway, PKC, and the phorbol esters have emerged as important leads in the formulation of a molecular mechanism for carcinogenesis as well as in the development of chemotherapeutic agents for cancer and other diseases, most notably including AIDS.[8] In order to establish a structural basis for such studies, we initiated a program aimed, in part, at the synthesis and modification of phorbol esters (**1a**) and structurally related promoters of the daphnane (**2**) and ingenane (**3**) families.[9,10] This communication describes the stereocontrolled synthesis of polycycle **4**, a general precursor to these three families and an intermediate in the first synthesis of phorbol (**1b**).[11]

The synthetic plan that guided this effort was predicated on the structural homology among the tigliane, daphnane, and ingenane promoters, suggesting that access to all three families could be realized from a common intermediate exemplified by polycycle **4**. This polycycle incorporates the ABC ring system of two of these families (**1** and **2**) and could be transformed into the third (**3**) through a biosynthetically modeled[2a] rearrangement (C11 to C10).[2g] Access to intermediate **4** was expected to arise through the annelation of **5**, during which the C6–C9 oxygen bridge would

Scheme I



internally protect the C9 hydroxyl group and conformationally and facially bias the otherwise flexible seven-membered B ring, as required for controlling stereogenesis at C10 and C4. Securing our commitment to this plan was the further recognition that intermediate **5** could be derived from **6** through an oxidopyrylium–alkene cycloaddition, a process that has been studied intermittently over the past four decades,[12] but was without relevant stereochemical precedent[13] at the outset of this investigation.

The first subgoal of this plan, preparation of cycloaddition precursor **6**, was accomplished in 52% overall yield for seven steps starting from furfuryl alcohol (Scheme II). Thus, **7** was converted to its silyl ether, which after lithiation and treatment with lithium propionate[14] afforded ketone **8**.[15] The enolate of **8** was then condensed with 4-pentenal to provide diastereomers **9a** (2:1 erythro:threo). Protection of the pro-C12 alcohol as an acetate, reduction of the ketone, and oxidation of the furan nucleus[16] gave pyranone **6a** as an inconsequential mixture of stereoisomers. This mixture was then converted to the acetates **6b**, which underwent smooth cycloaddition when heated at 150 °C (CH_3CN) or more conveniently when treated with DBU at ambient temperature, giving **5** as a 2:1 mixture of C12 epimers (92%).[17] As the first

(3) (a) Weber, J.; Hecker, E. *Experientia* **1978**, *34*, 679. (b) Hecker, E. J. *Z. Krebsforsch. Klin. Onkol.* **1981**, *99*, 103. (c) Hecker, E.; Lutz, D.; Weber, J.; Goerttler, K.; Morton, J. F. In *13th International Cancer Congress. Part B. Biology of Cancer*; Alan R. Liss: New York, 1983; p 219. (d) Berenblum, I. In *Risk Factors and Multiple Cancer*; Stoll, B., Ed.; John Wiley and Sons: New York, 1984.

(4) For examples, see: (a) Fujiki, H.; Mori, M.; Terada, M.; Suginura, T.; Moore, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 3872. (b) Horowitz, A. O.; Fujiki, H.; Weinstein, I. B.; Jeffrey, A.; Okin, E.; Moore, R. E.; Sugimura, T. *Cancer Res.* **1983**, *43*, 1529. (c) Nishio, Y.; Kakizoe, T.; Ohtani, M.; Sato, S.; Sugimura, T.; Fukushima, S. *Science* **1986**, *231*, 843.

(5) Blumberg, P. M.; Dunn, J. A.; Jaken, S.; Jeng, A. Y.; Leach, K. L.; Sharkey, N. A.; Yeh, E. In *Mechanisms of Tumor Promotion*; Slaga, T. J., Ed.; CRC: Boca Raton, FL, 1984; Vol. 3, pp 143–184.

(6) Nishizuka, Y. *Nature* **1984**, *308*, 693. Nishizuka, Y. *Science* **1986**, *233*, 305.

(7) For examples, see: Hsiao, W.-L. W.; Weinstein, I. B. *Mol. Cell. Biol.* **1986**, *6*, 1943.

(8) Harada, S.; Yamamoto, N.; Fujiki, H. *AIDS Res. Hum. Retroviruses* **1988**, *4*, 99. Poli, G.; Orenstein, J. M.; Kinter, A.; Folks, T. M.; Fauci, A. S. *Science* **1989**, *244*, 575.

(9) For previous work from this laboratory on divergent approaches to the tiglianes, ingenanes, and daphnanes, see: (a) Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205. (b) Wender, P. A.; Koehler, K. F.; Wilhelm, R. S.; Williams, P. D.; Keenan, R. M.; Lee, H. Y. In *New Synthetic Methodology and Funtionally Interesting Compounds*; Yoshida, Z.-I., Ed.; Elsevier: Amsterdam, 1986; pp 163–182. (c) Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390. (d) Wender, P. A.; Brighty, K. *Tetrahedron Lett.* **1988**, *29*, 6741. Other synthetic studies, primarily on ingenanes, include the following: (e) Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull. Jpn.* **1984**, *32*, 140. (f) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (g) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398. Rigby, J. H.; Kierkus, P. Ch. *J. Am. Chem. Soc.* **1989**, *111*, 4125. (h) Mehta, G.; Pathak, V. P. *J. Chem. Soc., Chem. Commun.* **1987**, 876. (i) Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192. (j) Winkler, J. D.; Henegar, K. E.; Williard, P. G. *J. Am. Chem. Soc.* **1987**, *109*, 2850. (k) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (l) Harwood, L. M.; Jones, G.; Pickard, J.; Thomas, R. M.; Watkin, D. *Tetrahedron Lett.* **1988**, *29*, 5825.

(10) For computer modeling studies on this subject, see: (a) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4214. (b) Wender, P. A.; Cribbs, C. M.; Koehler, K. F.; Sharkey, N. A.; Herald, C. L.; Kamano, Y.; Pettit, G. R.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7197. (c) Jeffrey, A. M.; Liskamp, R. M. J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 241. (d) Lotter, H.; Hecker, E. *Fresenius' Z. Anal. Chem.* **1985**, *321*, 639.

(11) See: Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.*, following paper in this issue.

(12) Pyrylium ion–alkene cycloadditions were unwittingly first studied in the fifties by L. L. Woods and by C. D. Hurd and co-workers as resolved in recent studies (Volkmann, R. A.; Weeks, P. D.; Kuhla, D. E.; Whipple, E. B.; Chmurny, G. N. *J. Org. Chem.* **1977**, *42*, 3976). E. F. Ullman and J. E. Milks (*J. Am. Chem. Soc.* **1962**, *84*, 1315) reported the first systematic study of this process. A related study was also provided by H. E. Zimmerman and R. D. Simkin (*Tetrahedron Lett.* **1964**, 1847). For more recent examples of related oxidopyrylium and carbonyl ylide cycloadditions, see: Griffin, G. *J. Am. Chem. Soc.* **1970**, *92*, 1402. Lown, J. W.; Matsumoto, K. *Can. J. Chem.* **1971**, *49*, 3443. Undheim, K.; Nilsen, B. P. *Acta. Chem. Scand., Ser. B* **1976**, *30*, 619. Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359. Shizuri, Y.; Nakamura, K.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1985**, 530. Potts, K. T.; Elliot, A. J.; Sõrm, M. *J. Org. Chem.* **1972**, *37*, 3838. Ibata, T.; Toyoda, J.; Sawada, M.; Takai, Y.; Tanaka, T. *Tetrahedron Lett.* **1988**, *29*, 317 and references cited therein. Taylor, K. G. *Tetrahedron* **1982**, *38*, 2151. Intramolecular examples include studies by the following: Garst, M. E.; McBride, B. J.; Douglass, J. G. *Tetrahedron Lett.* **1983**, *24*, 1675. Feldman, K. S. *Tetrahedron Lett.* **1983**, *24*, 5585. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817. Sammes and co-workers as reviewed in *Gazz. Chim. Ital.* **1986**, *116*, 109.

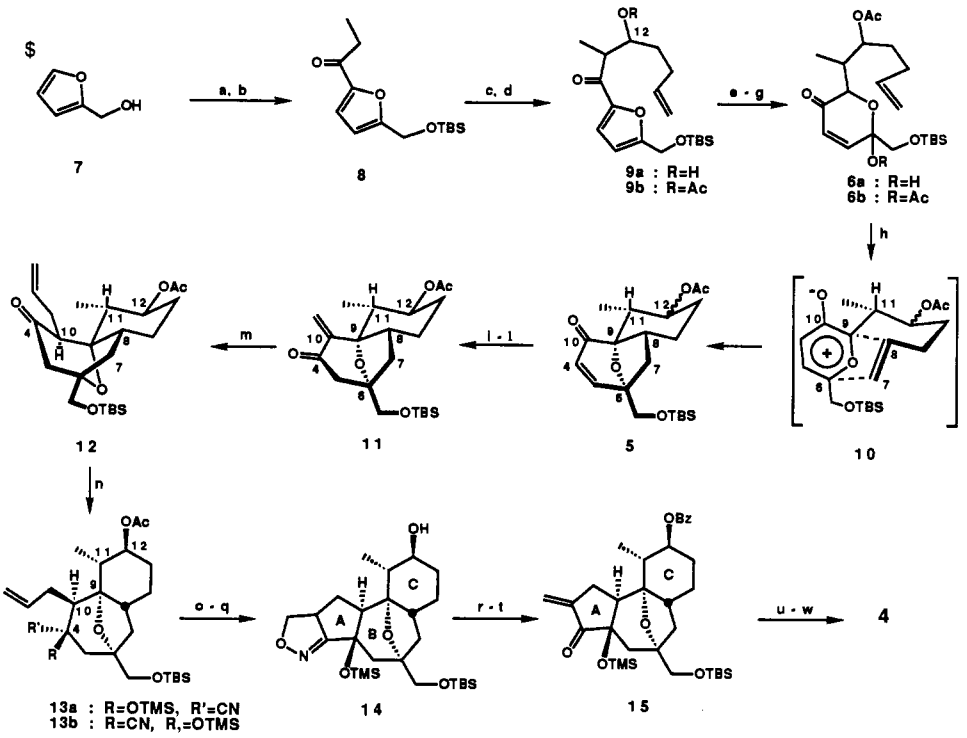
(13) The only other investigation of stereoinduction in these reactions that has appeared can be found in the elegant studies of P. G. Sammes and L. J. Street (*J. Chem. Soc., Chem. Commun.* **1983**, 666) in which a 5:1 diastereoselectivity was obtained in a cycloaddition involving an *allylic* stereogenic center in a *three-atom tether*.

(14) Heathcock, C. H.; Gulick, L. G.; Dehlinger, T. *J. Heterocycl. Chem.* **1969**, *6*, 141.

(15) Satisfactory NMR and IR spectra and combustion analyses or high-resolution mass spectra were obtained for all new compounds.

(16) Lefebvre, Y. *Tetrahedron Lett.* **1972**, 133. Williams, P. D.; Le Goff, E. *J. Org. Chem.* **1981**, *46*, 4143. For a recent application and lead references, see: Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588.

Scheme II[a]



[a](a) TBSCl, DMF. (b) *n*-BuLi; C_2H_5COOLi, THF. (c) $LiN(TMS)_2$, −78 °C, 15 h, THF; 4-pentenal. (d) AcCl, pyr, CH_2Cl_2. (e) $NaBH_4$, MeOH. (f) *m*-CPBA, THF. (g) Ac_2O, DMAP, pyr. (h) DBU, CH_2Cl_2, room temperature. (i) Separation (ref 17); H_2, Pd/C, EtOAc. (j) Ph_3PCH_2. (k) SeO_2, *t*-BuOOH, CH_2Cl_2. (l) MnO_2, CH_2Cl_2. (m) $(CH_2CH)_2CuCNLi_2$, THF. (n) TMSCN, ZnI_2. (o) DIBAH, $PhCH_3$. (p) NH_2OH, pyr. (q) NaOCl, THF. (r) H_2, Raney Ni/acetone/H_2O (4:1). (s) Bz_2O, CH_2Cl_2, DMAP, pyr. (t) DBU, THF. (u) $NaBH_4$, $CeCl_3$, MeOH. (v) TBAF, Et_2O. (w) 2-Methoxypropene, PPTS, CH_2Cl_2.

study of stereoinduction in four-atom-tethered oxidopyrylium–alkene cycloadditions,[13] it is noteworthy that this reaction proceeds with complete selectivity with respect to the relative stereochemistry at C8, C9, and C11. This result follows from an examination of the transition-state model **10**, in which the tether connecting the pyrylium and alkene moieties assumes a chair-like conformation with the C11 methyl group equatorially disposed in order to minimize steric interaction with the C10 oxygen. The sterically less demanding C12 acetate can presumably assume an axial or an equatorial orientation without overriding the C11 directing effect. The ratio of C12 epimers in **5**, therefore, simply reflects the diastereoselectivity of the aldol condensation (**8** to **9a**), which becomes irrelevant downstream as both epimers of **5** converge in the form of a C12 ketone.[17]

The next phase of our plan called for the attachment of the A ring to cycloadduct **5**. Since the diterpene targets possess or could be derived from a trans-fused AB ring system, this annelation requires that appendages be introduced at C10 and C4 in a trans relationship. Toward this end, the C10 appendage was introduced by generation of the methylene ketone **11** followed by conjugate addition of vinyl cuprate. The intended infuence of the C6–C9 oxygen bridge is manifested in this step by the sterically and stereoelectronically controlled α-face protonation of the intermediate enolate, which gives ketone **12** (78% yield over five steps). Influenced similarly by the stereochemical bias of its tricyclic subunit, ketone **12** was selectively converted[18] to nitriles **13a** and **13b** (15:1, respectively), the major isomer being derived from kinetic addition of cyanide to the less sterically encumbered face of the C4 carbonyl group.

With allyl and nitrile appendages appropriately positioned at C10 and C4, the stage was set for A-ring closure through an internal nitrile oxide cycloaddition.[19] Accordingly, nitrile **13a** was reduced with DIBAH and the resultant C4 carboxaldehyde was converted to an oxime. Oxidation of the latter with bleach produced the nitrile oxide, which underwent a 1,3-dipolar cycloaddition at ambient temperature, to furnish isoxazoline **14** (46% yield over four steps). Hydrogenolysis[20] of **14** gave a hydroxy ketone, which was dehydrated by benzoylation and DBU-catalyzed elimination, to provide methylene ketone **15**. In order to allow more flexibility over the selection of reagents and conditions projected for CD-ring elaboration,[11] the highly reactive A-ring functionality in **15** was stored at this point in the form of acetonide **4**, prepared in three steps by Luche reduction,[21] desilylation, and ketal formation. The overall yield through the six steps connecting **14** and **4** was 72%.

In summary, the synthesis of a general precursor (**4**) of the diterpene promoters from furfuryl alcohol (**7**) has been achieved through a 23-step sequence that proceeds in 10% overall yield (i.e., >90%/step) and with greater than 93% overall stereoselectivity. This study additionally provides an experimental reference point and a transition-state model for predicting stereoinduction in four-atom-tethered, oxidopyrylium–alkene cycloadditions, which should be of general value in further applications of this [5C + 2C] approach to seven-membered carbocycles. The following communication details the role of the diterpene precursor **4** in the first synthesis of phorbol (**1b**).[11]

Acknowledgment. The National Cancer Institute is gratefully acknowledged for their support of this work through Grant CA31841. Fellowship support to H.Y.L. from the Ministry of Education, Republic of Korea, and to R.S.W. (NRSA CA 07488) and P.D.W. (NRSA CA 07287) from the National Cancer Institute is also gratefully acknowledged. In addition, P.D.W.

(17) Both C12 epimers of **5** were independently carried through the synthesis to the point of convergence with comparable efficiency. For clarity, the graphical presentation is given for only the β isomer.

(18) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

(19) For a review, see: Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(20) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.

(21) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

received support from the Damon Runyon–walter Winchell Cancer Fund (DRG 589).

Supplementary Material Available: NMR and IR data for compounds **5** and **14** (2 pages). Ordering information is given on any current masthead page.

Studies on Tumor Promoters. 8. The Synthesis of Phorbol[1]

Paul A. Wender,* Hiroshi Kogen, Hee Yoon Lee, John D. Munger, Jr., Robert S. Wilhelm, and Peter D. Williams

Department of Chemistry, Stanford University Stanford, California 94305

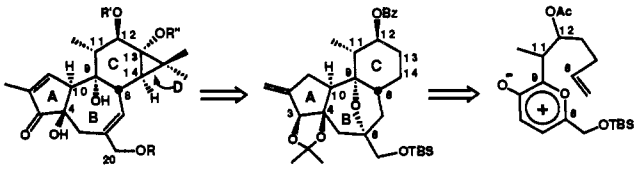
Received June 26, 1989

The phorbol esters (e.g., **1a**, Scheme I) have played a unique role in the evolution of our understanding of multistage carcinogenesis and have been found recently to function as high-affinity activators of protein kinase C, an ubiquitous enzyme of great biochemical interest.[2] In order to establish a structural basis for phorbol ester induced enzyme activation, an area rich with chemotherapeutic potential, access to systematically modified phorbol esters is required. Toward this end, we previously described[2] the synthesis of polycycle **2**. Herein we report the use of this key intermediate in the first synthesis of phorbol (**1b**).

In order to minimize problems arising from the hazardous properties of the phorbol esters[2] and from their notorious instability in the presence of acids, bases, air, and transition-metal oxidants,[3] our synthetic plan was sequenced to address the most reactive A-ring subunit last. Accordingly, the first subgoal of this study involved the attachment of the phorbol D ring to polycycle **2**, which in turn required that the C12 functionality of **2** be extended to a C13-oxygenated enone (Scheme II, **7**), in a fashion that would not epimerize the C11 center. Further complicating this task is the requirement that the C13-oxygenation take the form of a labile acyloxy group since model studies[4] indicate that the more stable α-alkoxy enones react with sulfur ylide reagents[5] to give spiro epoxides rather than the desired cyclopropanes.

To simplify the initial study of this plan, the double bond of **2** was first reduced with Wilkinson's catalyst to provide **4**[6] as a single stereoisomer (92%; Scheme II). Subsequent cleavage of the C12 benzoate and oxidation of the resultant alcohol gave ketone **5** in 94% overall yield. Kinetically controlled deprotonation of this ketone occurred exclusively at C13, thereby preserving C11 stereochemistry and allowing for the regiocontrolled formation of sulfide **6a** (77% for two steps).[7] Introduction of the C13 acyloxy group was then achieved through oxidation[8] of this sulfide, which gave acetate **6b** as a mixture of C13 isomers (78%). Upon further oxidation, **6b** underwent elimination, to furnish the acyloxy

Scheme I



1a: R = H, R'=$COC_{13}H_{27}$, R"=Ac **2** **3**
1b: R =R'=R"=H
1c: R =R'=R"=Ac

enone **7**. Gratifyingly, treatment of **7** with ylide **8**[5] occurred exclusively from the more accessible β-face to afford tigliane ketone **9** (85%), without previously encountered complications[4] involving C11 epimerization, acetyl migration, and spiro-epoxide formation.

A distant analogy[9] suggested that the next objective of this synthesis, introduction of the C12 stereocenter, could be achieved through simple reduction of the C12 ketone. However, since reaction of **9** with LAH or DIBAH gave predominantly (85% selectivity) the undesired C12 isomer, internal hydride delivery directed by a C9 alcohol was necessitated. For this purpose, the C12,C13 *cis*-diol obtained from the reduction of **9** was protected as a cyclic carbonate and the C20 ether was then converted to an iodide. Treatment of this iodide with *tert*-butyllithium resulted in the desired cleavage and in selective deprotection at C12 to provide **10a** in 45% yield for five steps. Oxidation of **10a** produced the C12 ketone **10c**, which still gave an isomeric mixture upon conventional reduction. However, when ketone **10c** was treated with sodium triacetoxyborohydride,[10] the desired C12 β-alcohol (**10b**) was finally obtained with complete stereocontrol in 92% yield.

The structure of **10b** was confirmed at this point through comparison with an enantiomerically pure sample obtained from phorbol[11] (Scheme III). Thus, phorbol triacetate **1c** was reduced[12] to 3β-hydroxyphorbol triacetate, from which acetonide **15** was formed by treatment with 2-methoxypropene. The C20 acetate was then hydrolyzed, and the resultant alcohol was oxidized to aldehyde **16**. Hydrogenation followed by alcohol elimination[13] gave alkene **17**, from which **10b** was derived through hydrolysis of the C12 and C13 acetates and acylation of the C13 alcohol. Due to its early availability, this phorbol-derived material was utilized in the final phase of the synthesis.

At this point, the synthetic plan called for B-ring functionalization through allylic oxidation of the exocyclic alkene in **10b**, a process that had been regioselectively accomplished with selenium dioxide in a related substrate.[14] While oxidation of the dibenzoate derived from **10b** did indeed provide exclusively the C7-oxidized product **11** (50%), subsequent studies revealed that this selectivity was due to the preferential destruction of the undesired C5-oxidized isomer. Comparison of these and previous studies[14] suggests that the regioselectivity of this oxidation could be improved by introduction of an α-oriented substituent at C3. This optimization study was deferred, however, in order to determine the utility of **11** as a precursor to phorbol. Accordingly, diol **11** was carried forward to allylic benzoate **12** through a

(1) (a) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, 1987; paper CHED 49. (b) Taken in part from the Ph.D. Dissertation of H.Y.L., Stanford University, 1988.

(2) Lead references and reviews on the isolation, structure, determination, biochemistry, and synthesis of phorbol and related diterpenes are given in the preceding communication: Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) For general reviews, see: Hecker, E.; Schmidt, R. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 377. Evans, F. J.; Taylor, S. E. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 1.

(4) Hillemann, C. L. Ph.D. Thesis, Harvard University, 1981.

(5) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912.

(6) Satisfactory NMR and IR spectra and combustion analyses or high-resolution mass spectra were obtained for all new compounds.

(7) Murai, S.; Kuroki, Y.; Hasegawa, K.; Tsutsumi, S. *J. Chem. Soc., Chem. Commun.* **1972**, 946.

(8) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.

(9) Acharya, S. P.; Brown, H. C. *J. Am. Chem. Soc.* **1967**, *89*, 1925.

(10) (a) Gribble, G. E.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (b) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287. (c) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (d) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449. (e) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (f) It was found best to stop this reaction at 58% conversion in order to facilitate product purification.

(11) Phorbol was obtained from croton oil (Sigma) through a modification of the Hecker procedure using KCN in place of $Ba(OH)_2$. For a related use of KCN, see: Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **1986**, *51*, 727.

(12) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(13) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(14) Wender, P. A.; Keenan, R. M.; Lee, H.-Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390.

0002-7863/89/1511-8957$01.50/0