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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

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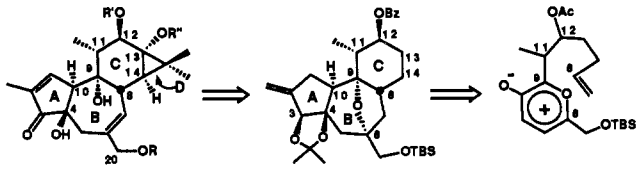
The phorbol esters (e.g., **1a**, Scheme I) have played a unique role in the evolution of our understanding of multistage carcinogenesis and have been found recently to function as high-affinity activators of protein kinase C, an ubiquitous enzyme of great biochemical interest.[2] In order to establish 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
1b: R =R'=R"=H
1c: R =R'=R"=Ac

2 **3**

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.

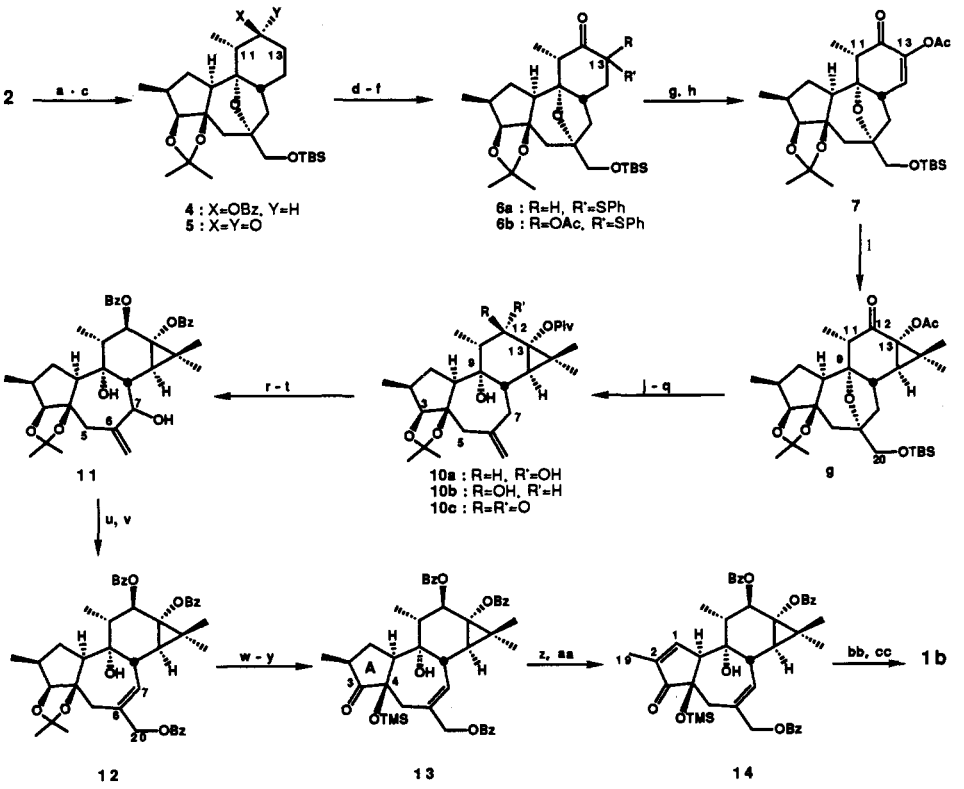
(12) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(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.

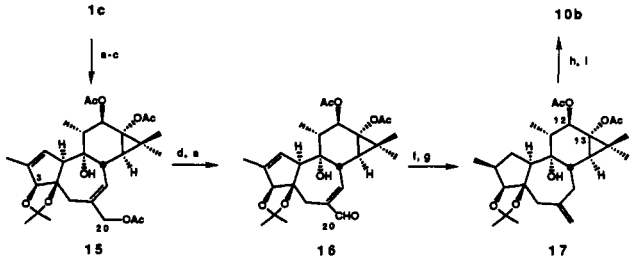
0002-7863/89/1511-8957$01.50/0

Scheme II[a]



[a](a) H_2 (1 atm), $RhCl(PPh_3)_3$, C_6H_6. (b) DIBAH, $PhCH_3$, −78 °C. (c) PCC, CH_2Cl_2. (d) LDA, THF; TMSCl. (e) PhSCl, CH_2Cl_2. (f) $Pb(OAc)_4$, C_6H_6. (g) *m*-CPBA, CH_2Cl_2. (h) 60 °C, $P(OEt)_3$, C_6H_6. (i) $Ph_2SC(CH_3)_2$ (8), −78 °C, THF, CH_2Cl_2. (j) DIBAH, $PhCH_3$. (k) $CO(Im)_2$, CH_2Cl_2. (l) TBAF, THF. (m) Tf_2O, Et_3N, CH_2Cl_2, pyr. (n) Bu_4NI, HMPA, 55 °C. (o) *t*-BuLi, Et_2O, −78 °C. (p) PCC, CH_2Cl_2. (q) $NaBH(OAc)_3$, THF, 60 °C. (r) DIBAH, $PhCH_3$. (s) Bz_2O, DMAP, pyr, CH_2Cl_2. (t) SeO_2, *t*-BuOOH, CH_2Cl_2, 0 °C. (u) $SOCl_2$, propylene oxide, Et_2O. (v) AgOBz, KOBz/TMEDA, CH_3CN. (w) $HClO_4$, MeOH, Montmorillonite clay (K10), $(CH_2OH)_2$. (x) SO_3·pyr·Et_3N, DMSO. (y) $CF_3CON(CH_3)TMS$, DMAP, CH_3CN. (z) $KN(TMS)_2$, −78 °C; TMSCl, −78 °C to room temperature; NBS, THF. (aa) $LiBr/Li_2CO_3$, DMF, 130 °C, 3 h. (bb) TsOH/MeOH. (cc) KCN/MeOH.

Scheme III[a]



[a](a) $NaBH_4$, $CeCl_3$, MeOH. (b) $(n\text{-}Bu)_4NF$, THF. (c) $CH_2C(OMe)CH_3$, PPTS, CH_2Cl_2. (d) $HClO_4$, MeOH. (e) MnO_2, CH_2Cl_2. (f) H_2 (1 atm), Pt/C, EtOAc. (g) ArSeCN, $(n\text{-}Bu)_3P$, THF, room temperature; mCPBA, CH_2Cl_2, −78 °C. (h) KCN, MeOH. (i) Me_3CCOCl, DMAP, CH_2Cl_2.

two-step chlorination (80%) and benzoate displacement (73%) sequence, which completed the B-ring functionalization. Elaboration of the A-ring functionality was then accomplished through a five-step sequence. Thus, the acetonide functionality of **12** was hydrolyzed,[15a] after which the C3 alcohol was oxidized (80%) and the C4 alcohol was selectively protected to give ketone **13** (91%). α-Bromination (65%) of this ketone followed by elimination[15b] provided phorbol triester **14** (72%). Hydrolysis of the latter afforded phorbol (**1b**) (86%).

In summary, this study has resulted in the first synthesis of phorbol (**1b**) as well as in the development of methodology for the rational synthesis of phorbol analogues, as required for the systematic study of these exciting chemotherapeutic leads. The problems posed by the eight stereogenic centers of phorbol and exacerbated by its congested and highly reactive functionality have each been selectively solved, with 93% overall stereoselectivity. This first test of a general strategy has additionally provided much needed experimental information pertinent to the manipulation of the highly reactive subunits of phorbol, which has already proven valuable in the completion of a simplified second-generation synthesis of phorbol[16] and in analogue synthesis.

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Registry No. 1b, 17673-25-5; **1c**, 19891-05-5; (±)-**2**, 123357-94-8; (±)-**4**, 123358-18-9; (±)-**5**, 123358-19-0; (±)-**6a**, 123358-17-8; (±)-**6b** isomer 1, 123358-20-3; (±)-**6b** isomer 2, 123409-74-5; (±)-**7**, 123358-21-4; **8**, 16601-43-7; (±)-9, 123358-22-5; (±)-**10a**, 123358-23-6; **10b**, 123409-75-6; (±)-**10b**, 123409-73-4; (±)-**10c**, 123358-27-0; **11**, 123380-74-5; **12**, 123358-24-7; **13**, 123358-25-8; **14**, 123358-26-9; **15**, 77573-27-4; **15** 3,4-diol, 77646-25-4; **15** 20-alcohol, 77573-38-7; **16**, 123358-28-1; **17**, 123358-29-2; SO_3·pyr·Et_3N, 123358-30-5.

Supplementary Material Available: NMR and IR data for compounds **7**, **9**, **10b**, and **12–14** (6 pages). Ordering information is given on any current masthead page.

(15) (a) At 51% conversion, the C3,C4 diol is obtained in 56% yield and a C3,C4,C20 triol is formed in 40%. The latter can be converted to the former by monobenzoylation. (b) For a similar transformation in the isoingenol series, see: Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192.

(16) Presented in part at the 197th National Meeting of the American Chemical Society, Dallas, TX, 1989; paper ORGN 61.