The First Formal Asymmetric Synthesis of Phorbol

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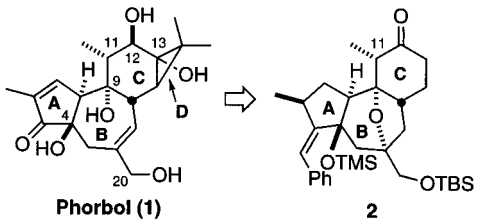
Received February 26, 1997

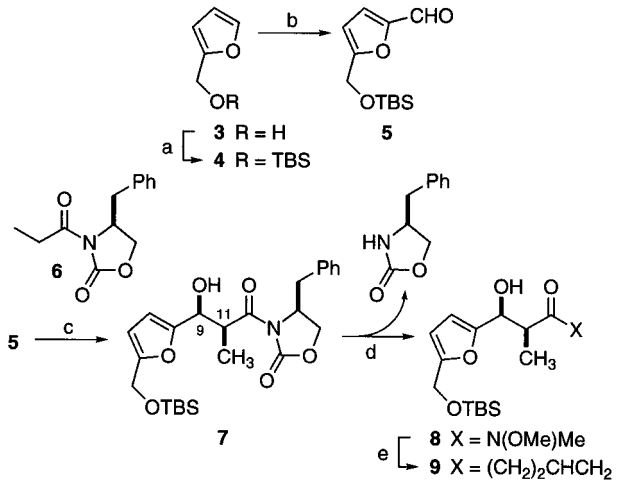
Phorbol (**1**) is a tigliane diterpene whose 12,13-diesters play a principal role in efforts to understand a range of cellular processes at the molecular level, including most notably carcinogenesis and signal transduction.[1] The highly potent biological activity of phorbol esters is attributed to their ability to avidly bind to and activate isozymes of the protein kinase C (PKC) family.[2] Although many such 12,13-diesters are potent tumor promoters, other derivatives possessing the phorbol skeleton hold promise as chemotherapeutic leads due to their antitumor and anti-HIV activity.[3] In 1989, we reported the first synthesis of phorbol in racemic form.[4,5] To identify therapeutic targets in the PKC signaling pathway and to elucidate the structural basis for their biological activity, we have now developed an efficient asymmetric synthesis of **2** (Scheme 1), a highly flexible synthetic precursor to phorbol analogues possessing the ABC-ring skeleton. The utility of this intermediate is further demonstrated by its transformation to phorbol in racemic form, thereby establishing the first formal asymmetric synthesis of phorbol.

Our approach to the phorbol BC-ring system was designed around an intramolecular oxidopyrylium−alkene [5 + 2] cycloaddition (**12** to **13**).[6] As a consequence, the control of absolute stereochemistry rested on stereocontrolled installation of the pro-C(11) center in the sequence leading to the cycloaddition precursor (**12**). This was achieved through a chiral oxazolidinone-based asymmetric aldol reaction[7] between aldehyde **5**, prepared in two steps from furfuryl alcohol **3** by silylation (99%)[4a] and formylation of the corresponding furyl lithium (75%), and *N*-propionyl oxazolidinone **6**[7b] (Scheme 2). The aldol reaction occurred with high diastereoselectivity (98% de) to provide upon column chromatography alcohol **7** as a single diastereomer in 96% yield. Introduction of the alkene subunit into the tether was accomplished through transamination of **7** to provide Weinreb amide **8** (86%) along with recovered chiral auxiliary (88%). Addition of 3-butenylmagnesium bromide (4 equiv) to **8** afforded hydroxy ketone **9** (82%). Reduction of **9** with DIBAL gave diol **10** (Scheme 3) in 85% yield and high diastereoselectivity (30.6/1), consistent with formation of a six-membered aluminum chelate.[8] Initial attempts to perform a ring expansion of the furan at this stage were unsatisfactory.[9] Therefore, selective acetylation of the potentially interfering C(12) hydroxyl was conducted by treatment of **10** with trimethylsilylimidazole to first effect silylation of the more reactive furfuryl alcohol[9a] followed by in situ acetylation. Subsequent deprotection of the transient trimethylsilyl ether afforded **11** in 82% yield. Oxidative ring expansion of **11** with VO(acac)$_2$/*t*-BuOOH followed by acetylation of the

Scheme 1

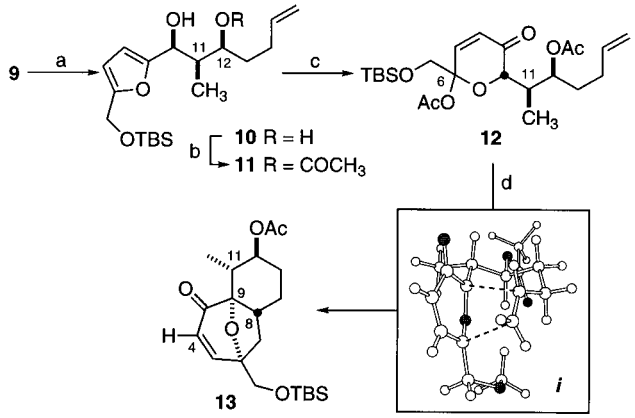


Scheme 2



(a) TBDMSCl, imidazole, DMF. (b) *n*-BuLi, THF; DMF; H_3O^+. (c) Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C. (d) Me_3Al, Me(MeO)NH-HCl, CH_2Cl_2. (e) 3-butenylMgBr, THF, 60 °C.

Scheme 3



(a) DIBAL, THF, -78 °C. (b) TMS-imidazole, THF; AcCl, pyr., DMAP; citric acid, MeOH. (c) VO(acac)$_2$, *t*-BuOOH, CH_2Cl_2; Ac_2O, pyr., DMAP. (d) DBU, CH_3CN.

† National Institutes of Health Postdoctoral Fellow.

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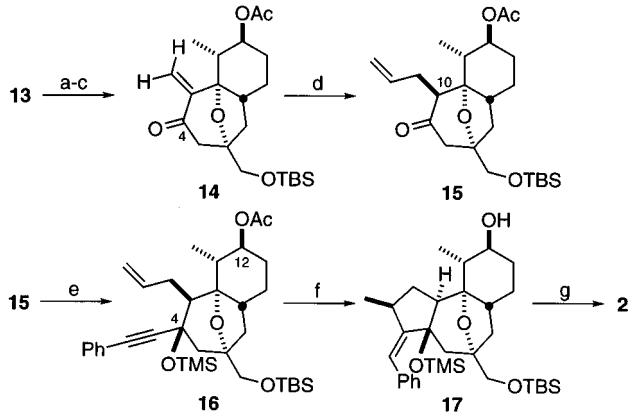
S0002-7863(97)00625-2 CCC: $14.00

Scheme 4



(a) H_2, Pd/C, EtOAc. (b) KO*t*-Bu, Ph_3PCH_3Br, toluene. (c) SeO_2, *t*-BuOOH, CH_2Cl_2; MnO_2, CH_2Cl_2. (d) $(CH_2CH)_2Cu(CN)Li_2$, Et_2O. (e) PhCCLi, LiBr, THF; HMPA, TMSCl. (f) Cp_2ZrCl_2, *n*-BuLi, THF; HOAc. (g) PCC, NaOAc, CH_2Cl_2.

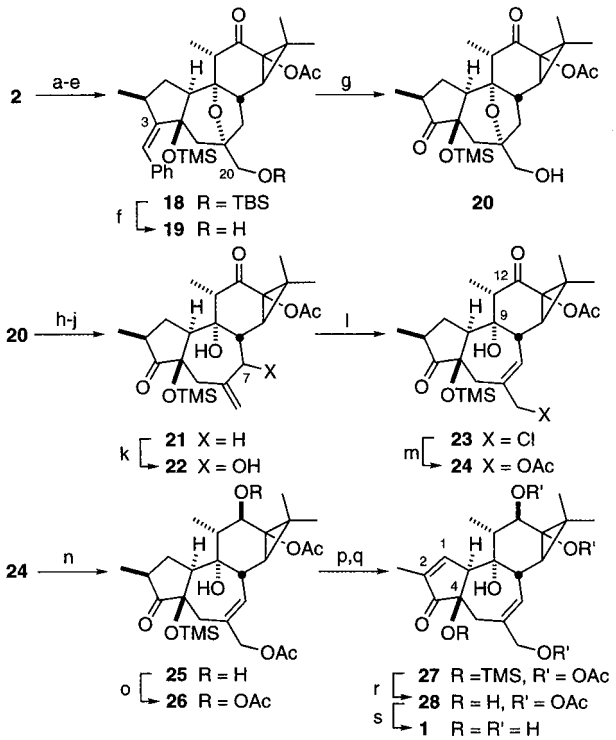
crude hydroxy pyranones afforded **12** in 88% yield as an inconsequential mixture (2/1) of C(6) epimers.

Intramolecular oxidopyrylium−alkene cycloaddition occurred upon treatment of an acetonitrile solution of epimers **12** with DBU (2.0 equiv), affording cycloadduct **13** in 79% yield as a single diastereomer. The high stereoselectivity of this transformation can be rationalized by the PM3 semiempirical representation of the proposed transition state (***i***), in which the tether between the reactive subunits adopts a chair-like conformation with the C(11) methyl group equatorially disposed to minimize steric interactions with the pyranone carbonyl. Thus, the chirality installed at C(11) effectively controls stereogenesis at C(8) and C(9).

Elaboration of cycloadduct **13** to intermediate **2** (Scheme 4) next required C(4) oxygenation and annelation of the A ring through zirconocene-mediated enyne cyclization. For this purpose, the cycloadduct was first hydrogenated to afford the corresponding ketone (95%), which underwent subsequent Wittig olefination (79%) and allylic oxygenation (89%) to afford enone **14**. Conjugate addition of vinyl cuprate to **14** followed by stereoselective (axial) protonation of the intermediate enolate afforded **15** as a single diastereomer in 83% yield. The addition of lithium phenylacetylide to **15** in the presence of lithium bromide followed by HMPA (6 equiv)[10] and TMSCl gave exclusively the β-addition product **16** in 75% yield, thus establishing the required trans A/B ring fusion. Zirconocene-mediated enyne cyclization[11] proceeded with fortuitous deprotection of the C(12) acetate to afford alcohol **17** (93%). Subsequent PCC oxidation (94%) provided the desired *ent*-**2** in 16 steps (9.0% yield) overall from furfuryl alcohol **3**.

The selection of **2** as a target in the above studies was based on the demonstration as described below that *rac*-**2**[4d] serves as an effective precursor of *rac*-**1** (Scheme 5). This new sequence provides a more concise and efficient solution to previously encountered problems[4] attending elaboration of the C,D-ring system, B-ring ether cleavage, and introduction of the A-ring. This sequence started with phenyl sulfenylation of the kinetically generated silyl enol ether of **2** (96%) followed by oxidation with lead tetraacetate[12] to provide a diastereomeric mixture of C(13) acetoxy phenyl sulfides (84%). Further oxidation and thermal sulfoxide elimination afforded the corresponding 13-acetoxy enone (88%). Diphenylisopropylsulfonium ylide addition occurred with β-face stereoselectivity, thereby introducing the

Scheme 5



(a) LDA, THF, -78 °C; TMSCl; PhSCl, CH_2Cl_2, -78 °C. (b) $Pb(OAc)_4$, benzene. (c) *m*-CPBA, CH_2Cl_2, -20 °C. (d) $P(OEt)_3$, benzene. (e) $Ph_2SC(CH_3)_2$, CH_2Cl_2, THF, -78 °C. (f) 49% HF, CH_3CN, 0 °C. (g) O_3, CH_2Cl_2/MeOH, -78 °C; $(NH_2)_2CS$. (h) Tf_2O, pyr., CH_2Cl_2, 0 °C. (i) *n*-Bu_4NI, CH_3CN. (j) Zn, EtOH, 80 °C. (k) SeO_2, *t*-BuOOH, CH_2Cl_2. (l) $SOCl_2$, pyr., Et_2O, 0 °C. (m) KOAc, 18-Crown-6, AgOAc, CH_3CN. (n) $NaBH(OAc)_3$, THF. (o) Ac_2O, DMAP, pyr., CH_2Cl_2. (p) MSTFA, DMAP, DABCO, CH_3CN, 100 °C; NBS, THF. (q) Li_2CO_3, LiBr, DMF, 130 °C. (r) TBAF, THF, -20 °C. (s) $Ba(OH)_2$, MeOH.

D-ring and providing tigliane **18** in 80% yield. Deprotection of the C(20) silyl ether (96%) followed by ozonolysis of the benzylidene (89%) unmasked the C(3) carbonyl to provide diketone **20**. Cleavage of the ether bridge was accomplished by conversion of **20** to the corresponding iodide (67%), which underwent elimination in the presence of activated zinc to afford alkene **21** (61%). Allylic oxidation of **21** occurred preferentially at the C(7) carbon to afford allylic alcohol **22** (54%). Subsequent treatment with thionyl chloride followed by silver-assisted nucleophilic substitution gave diacetate **24** (71%, 2 steps). Hydroxyl (C(9)) directed reduction of the C(12) ketone with sodium triacetoxyborohydride provided the desired β-alcohol **25** in 92% yield, which was subsequently acetylated to provide triacetate **26** (89%). Installation of the C1,2 olefin was achieved in a two-step sequence by bromination of the corresponding silyl enol ether of **26** (63%) followed by endocyclic halide elimination of the resulting bromide to provide the desired α,β-unsaturated ketone **27** in 56% yield. Finally, deprotection of the C(4) silyl ether (88%) and exhaustive acetate hydrolysis (62%) afforded racemic phorbol in 17 steps from the intermediate *rac*-**2**. Current efforts are directed at utilizing **2** as a cornerstone intermediate to prepare phorbol and daphnane derivatives as required to explore and exploit these novel families of highly potent biological probes and therapeutic leads.

Acknowledgment. Support of this research by the National Cancer Institute through grant CA31841 is gratefully acknowledged. M.E.S. thanks the National Institutes of Health for a Postdoctoral Fellowship (GM17351-02).

Supporting Information Available: Experimental details, full characterization data for **1**, **2**, **5**, and **7**−**28**, and the synthesis of *rac*-**2** (40 pages). See any current masthead page for ordering and Internet access instructions.

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(10) The use of HMPA as additive was found to be essential for efficient trapping of the intermediate alkoxide.

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