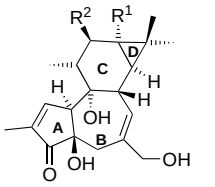
Diastereocontrol in the Synthesis of Models of Rings C and D of Phorbol: Directing Effect of an Ether Substituent on Lithium Carbenoid Mediated Cyclopropanation**

Michael G. B. Drew, Laurence M. Harwood,*
Antonio J. Macías-Sánchez, Richard Scott,
R. M. Thomas, and Daniel Uguen

Phorbol esters is a term used collectively to describe a family of structurally related, biologically active tetracyclic diterpenes.[1] Phorbol (**1**), the parent compound of this class of diterpenes, was first isolated in 1934 by Bohm et al.[2] as a hydrolysis product of *Croton tiglium* oil. Its core structure was elucidated by X-ray crystallography by Hecker and co-workers in 1967.[3] Probably the most important physiological property of the phorbol esters is their capacity to act as tumor promoters;[4] for example, tetradodecanoyl phorbol acetate (TPA; **2**) is the most potent tumor promoter known to man, being active at levels of 0.02 μmol.[5] The origin of such activity was identified in 1982 when Castagna et al.[6] showed TPA (**2**) bound to the ubiquitous enzyme protein kinase C.

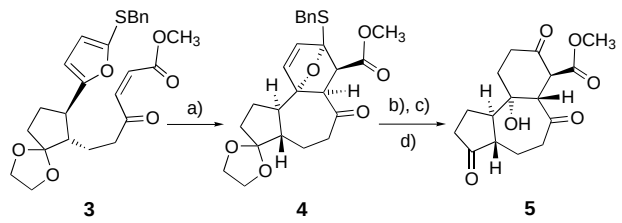


1 $R^1 = R^2 = OH$
2 $R^1 = OCO(CH_2)_{12}CH_3$, $R^2 = OAc$

The complex polycyclic structure of phorbol, together with an intense interest in structure–activity relationship studies to map the basis of the tumor-promotion activity have fueled extensive efforts towards establishing efficient synthetic routes to phorbol (**1**) and its derivatives.[7]

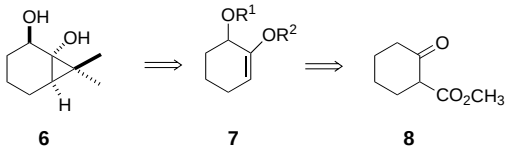
The approach adopted by our group has involved the intramolecular Diels–Alder reaction of **3**, which bears a furan system and a suitable dienophile fragment. In one step, we obtained the ABC tricyclic core **4**, which possessed strategically situated functionality for further elaboration.[8] Additional transformations of the cycloadduct led to a β-ketoester functionality on ring C (compound **5**),[9] which allows us to tackle the construction of the bicyclo[4.1.0]heptane moiety of rings C and D in phorbol (**1**; Scheme 1).

Herein we report the synthesis of 1*S*(*R*),2*R*(*S*)-dihydroxy-7,7-dimethyl-(6*R*(*S*))-bicyclo[4.1.0]heptane (**6**), as a model of rings C and D of phorbol (**1**), by means of a stereoselective cyclopropanation of an intermediate enol ether **7**, which in turn would be obtained from methyl 2-oxocyclohexanecarboxylate (**8**) (Scheme 2).



3 **4** **5**

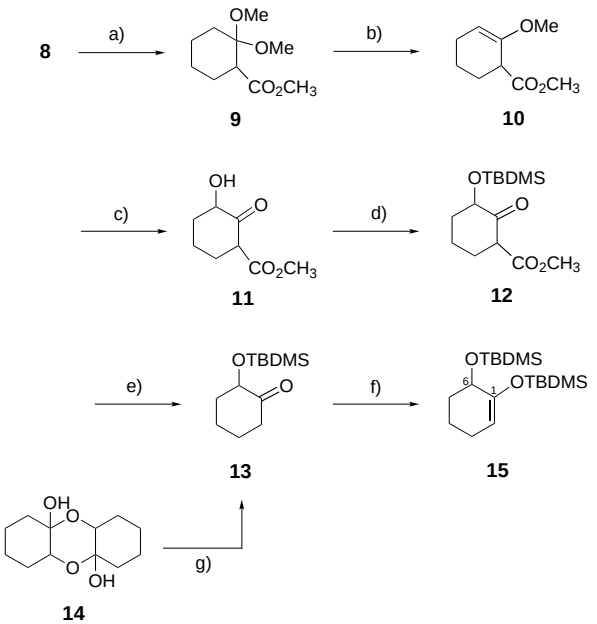
Scheme 1. Reagents and conditions: a) 1900 MPa, CH_2Cl_2, 15 h, 65%; b) H_2 (1.5 MPa), EtOAc, $Pd/BaSO_4$, 83%; c) NaOMe cat., MeOH, room temperature, 84%; d) $HgCl_2$, aq. CH_3CN, 50 °C, 8 days, 58%.



6 **7** **8**

Scheme 2. Retrosynthetic analysis of the synthesis of model compound **6** from methyl 2-oxocyclohexanecarboxylate (**8**).

In the initial part of the study, β-ketoester **8** was treated with trimethyl orthoformate and 10-camphorsulfonic acid (10-CSA) in MeOH, and heated at reflux for 16 h to furnish the dimethyl acetal **9**. This compound was transformed into the methyl enol ether **10** under kinetic conditions by treatment of compound **9** with two equivalents of lithium diisopropylamide (LDA) in THF at −40 °C (Scheme 3).



8 **9** **10** **11** **12** **13** **14** **15**

Scheme 3. Synthesis of enol ether **15** from either β-ketoester **8** or adipoin (**14**). Reagents and conditions: a) $HC(OMe)_3$, 10-CSA, MeOH, reflux, 16 h, 99%; b) LDA (2 equiv), THF, −40 °C, 1 h, 92%; c) 1. DMDO (0.1M solution in acetone), CH_2Cl_2, 10 min; 2. 10-CSA, acetone, 30 min, 70%; d) TBDMSCl, imidazole, DMAP (cat.), CH_2Cl_2, room temperature, 2 h, 91%; e) dimethyl sulfoxide, H_2O, NaCl, 130 °C, 30 min, quant.; f) TBDMSOTf, Et_3N, CH_2Cl_2, room temperature, 3 h, 83%; g) TBDMSCl, imidazole, DMAP (cat.), CH_2Cl_2, room temperature, 2 h, quant.

[*] Prof. L. M. Harwood, Prof. M. G. B. Drew, Dr. A. J. Macías-Sánchez, Dr. R. Scott
Department of Chemistry, University of Reading
Whiteknights, Reading RG6 6AD (UK)
Fax: (+44) 1189-316-782
E-mail: l.m.harwood@reading.ac.uk

Prof. D. Uguen
École de Chimie, des Polymères et des Matérieaux
Laboratoire de Synthèse Organique
25 rue Becquerel, 67087 Strasbourg (France)

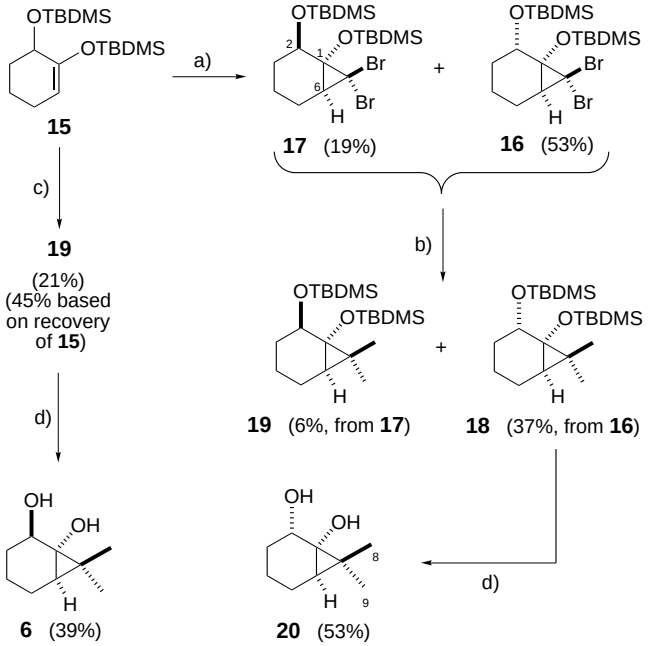
Dr. R. M. Thomas
Astra-Zeneca
Silk Road Business Park
Macclesfield SK102NA (UK)

[**] We thank Mr. A. W. Jahans for technical assistance. A.J.M.-S. thanks the Secretaria de Estado de Universidades, Investigacion y Desarrollo (SEUID; Spanish funding body) for a postdoctoral fellowship. R.S. thanks Astra–Zeneca for a research studentship.

To accomplish the incorporation of the secondary hydroxy group, a consecutive two-step sequence was conceived in which an epoxidation of the enol ether **10** with dimethyldioxirane (DMDO)[10] was followed by an acidic workup to allow the formation of the α-hydroxyketone **11**. Subsequently, the secondary hydroxy group was protected by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl), imidazole, and a catalytic amount of 4-dimethylaminopyridine (DMAP), to yield compound **12** (Scheme 3).

The β-ketoester function in **12** was decarboxylated by the application of a variation of the procedure of Krapcho,[11] to give compound **13**. An alternative and convenient short route to **13** was subsequently employed from this point. Treatment of the commercially available 2-hydroxycyclohexanone dimer (adipoin; **14**) with TBDMSCl, imidazole, and a catalytic amount of DMAP in CH_2Cl_2 at room temperature, provided the protected hydroxyketone **13** in a quantitative yield. To proceed to the critical cyclopropanation step, compound **13** was transformed into the TBDMS enol ether **15** by treatment with TBDMSOTf (OTf = trifluoromethanesulfonate) and triethylamine at room temperature in dichloromethane for three hours (Scheme 3).[12]

Initially, the construction of the dimethylcyclopropane moiety was addressed by reaction of compound **15** with dibromocarbene[13] and further transformation of the resulting dibromocompound with a homocuprate,[14] to yield the dimethylated compounds **18** and **19**. Thus, when one equivalent of bromoform was added dropwise for one hour to a stirred slurry of compound **15** and potassium *tert*-butoxide in anhydrous pentane at $-10\,^{\circ}C$, dibromo compounds **16** and **17** were obtained (Scheme 4). Both compounds showed analogous patterns in their ^1H and ^{13}C NMR spectra, but the signals



Scheme 4. Synthesis of the epimeric diols **6** and **20** from the enol ether **15**. Reagents and conditions: a) $CHBr_3$ (1 equiv, dropwise over 1 h), *t*BuOK, pentane, $-10\,^{\circ}C \rightarrow$room temperature, 3 h; b) Me_2CuLi (4 equiv), Et_2O, $-23\,^{\circ}C$, 3 h, then MeI, $-63\,^{\circ}C$, 1 h; c) $(CH_3)_2CBr_2$, *n*BuLi, pentane, $-78\,^{\circ}C$ (3 h), $-78\,^{\circ}C \rightarrow$room temperature (14 h); d) nBu_4NF, THF, reflux, 2 h.

at $\delta = 4.07$ (dd, $J = 4.3$ Hz, 11.5 Hz, 1H; C*H*OTBDMS) in compound **16** and at $\delta = 4.13$ (t, $J = 9.1$ Hz, 1H; C*H*OTBDMS) in compound **17** suggested that they were epimers at C2. Compound **16** proved to be thermally unstable and after one week at room temperature was completely degraded. Nevertheless, compound **17** was stable under the same conditions. This permitted a pure sample of compound **17** to be obtained, a difficult task by chromatography. Compound **17** furnished crystals suitable for X-ray crystallographic analysis,[15] which established the structure of compound **17** as 7,7-dibromo-1*S*(*R*),2*S*(*R*)-di-*tert*-butyldimethylsilyloxy-(6*R*(*S*))-bicyclo[4.1.0]heptane. Therefore, the major compound **16** was concluded to be the epimeric 7,7-dibromo-1*S*(*R*),2*R*(*S*)-di-*tert*-butyldimethylsilyloxy-(6*R*(*S*))-bicyclo[4.1.0]heptane.

Treatment of a mixture of **16** and **17** with four equivalents of lithium dimethylcuprate at $-23\,^{\circ}C$, and then with MeI at $-63\,^{\circ}C$, yielded the corresponding *gem*-dimethyl compounds **18** and **19** (Scheme 4). The stereochemistry in compound **18** was established by NOE analysis, which in turn served to confirm the stereochemistry of the major dibromo adduct **16**.

An alternative and direct route to compound **19** was found when the enol ether **15** was treated with the lithium carbenoid generated from *n*BuLi and 2,2-dibromopropane[16] in pentane at $-78\,^{\circ}C$.[17] Compound **19** was furnished as the sole adduct. The separate treatment of **19** and **18** with tetra-*n*-butyl ammonium fluoride in THF yielded the epimeric diols **6** and **20** in yields of 39% and 53%, respectively.

The behavior of the dibromocarbene and that of the lithium carbenoid derived from 2,2-dibromopropane are different. For dibromocarbene, steric hindrance seems to play a major role in determining the course of the approach of the reagent to the double bond, to yield **16**, with a cyclopropane ring *trans* to the secondary silyl ether group, as the major product. On the other hand, the reaction with the lithium carbenoid only yields a single product, compound **19**, whose cyclopropane ring is *cis* to the secondary silyl ether group. This suggests a directing effect from the oxygen in the ether functionality on the cyclopropanation reaction. This kind of effect has been reported previously in Simmons–Smith type reactions,[18] but, to our knowledge, has not been described previously for lithium carbenoids.

In summary, we have converted a β-ketoester into a hydroxydimethylcyclopropane derivative with diastereocontrol, by means of a protocol that may be applied in our synthetic strategy towards phorbol derivatives. We have also shown an interesting diastereocomplementarity of halocarbenes and alkylcarbenes in this process.

Experimental Section

Selected spectroscopic data: **20**: ^1H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.89$ (m, 1H; C*H*OTBDMS), 2.90–2.70 (2H; -OH) 1.98–1.83 (1H; 5-H), 1.69–1.42 (4H; 3-H, 3′-H, 4-H, 4′-H), 1.39–1.05 (m, 1H; 5′-H), 1.21 (s, 3H; CH_3), 1.00 (s, 3H; CH_3), 0.81 (dd, $J = 2.5$, 9.5 Hz, 1H; CH); ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 65.20$, 60.65, 31.22, 27.78, 23.38, 22.75, 19.14, 18.64, 16.04. **6**: ^1H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.38$ (dd, $J = 7.9$, 10.6 Hz, 1H; C*H*OTBDMS), 2.18–1.89 (2H; 3-H, 5-H) 1.55 (m, 1H; 4-H), 1.28–1.13 (3H; 3′-H, 4′-H, 5′-H), 1.23 (s, 3H; CH_3), 1.17 (s, 3H; CH_3), 0.98 (dd, $J = 3.3$, 10.0 Hz, 1H; CH); ^{13}C NMR

  0044-8249/01/11312-2374 $ 17.50+.50/0 *Angew. Chem.* **2001**, *113*, Nr. 12

(62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 76.31, 62.70, 31.84, 31.58, 25.65, 24.17, 22.71, 19.04, 16.37$.

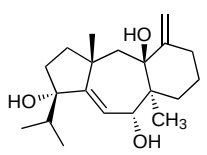
Received: December 18, 2000 [Z16294]

[1] F. J. Evans, C. J. Soper, *Lloydia* **1978**, *41*, 193.
[2] R. Bohm, B. Flaschenträger, L. Lendle, *Arch. Exp. Pathol. Pharmakol.* **1935**, *177*, 212.
[3] a) W. Hoppe, F. Brandl, I. Strell, M. Röhrl, I. Gassman, E. Hecker, H. Bartsch, G. Kreibich, C. V. Szczepanski, *Angew. Chem.* **1967**, *79*, 824; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 809; b) E. Hecker, H. Bartsch, H. Bresch, M. G. Schmendt, E. Härle, G. Kreibach, H. Kubinyi, H. U. Shairer, C. V. Szczepanski, H. W. Thielman, *Tetrahedron Lett.* **1967**, 3165.
[4] E. Hecker, R. Schmidt, *Fortschr. Chem. Org. Naturst.* **1974**, 377.
[5] J. G. Kidd, P. Rous, *J. Exp. Med.* **1938**, *68*, 529.
[6] M. Castagna, Y. Takai, K. Kaibuchi, S. Komihiko, U. Kikkawa, Y. Nishizuka, *J. Biol. Chem.* **1982**, *257*, 7847.
[7] L. M. Harwood, A. C. Brickwood, V. Morrison, J. Robertson, S. Swallow, *J. Heterocycl. Chem.* **1999**, *36*, 1391, and references therein.
[8] a) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, D. Watkin, *J. Chem. Soc. Chem. Commun.* **1990**, 605; b) L. M. Harwood, B. Jackson, G. Jones, K. Prout, R. M. Thomas, F. J. Witt, *J. Chem. Soc. Chem. Commun.* **1990**, 608; c) L. M. Harwood, T. Ishikawa, H. Phillips, D. Watkin, *J. Chem. Soc. Chem. Commun.* **1991**, 527.
[9] A. C. Brickwood, M. G. B. Drew, L. M. Harwood, T. Ishikawa, P. Marais, V. Morisson, *J. Chem. Soc. Perkin Trans. 1* **1999**, 913.
[10] W. Adam, Y.-Y. Chan, D. Cremer, J. Gauss, D. Scheutzow, M. Scindler, *J. Org. Chem.* **1987**, *52*, 2800.
[11] P. A. Krapcho, *Synthesis* **1982**, 893.
[12] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1984**, *25*, 5953.
[13] P. Amice, L. Blanco, J. M. Conia, *Synthesis* **1976**, 196.
[14] A. Speicher, T. Eicher, *Synthesis* **1995**, 998.
[15] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152923. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[16] P. Fischer, G. Schaefer, *Angew. Chem.* **1981**, *93*, 895; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 863.
[17] This reaction failed to proceed when it was attempted using Et_2O as a solvent, and only starting material was recovered.
[18] a) Zn-mediated: J. H.-H. Chan, B. Rickborn, *J. Am. Chem. Soc.* **1968**, *90*, 6406; F. Mohamadi, W. C. Still, *Tetrahedron Lett.* **1986**, *27*, 893, and references therein; b) Sm-mediated: G. A. Molander, L. S. Harring, *J. Org. Chem.* **1989**, *54*, 3525; M. Lautens, P. H. M. Delanghe, *J. Org. Chem.* **1992**, *57*, 798; c) Al-mediated: K. Maruoka, Y. Fukutani, H. Yamamoto, *J. Org. Chem.* **1985**, *50*, 4412; d) Mg-mediated: C. Bolm, D. Pupowicz, *Tetrahedron Lett.* **1997**, *38*, 7349.

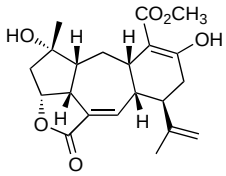
Constructing Tricyclic Compounds Containing a Seven-Membered Ring by Ruthenium-Catalyzed Intramolecular [5+2] Cycloaddition**

Barry M. Trost* and Hong C. Shen

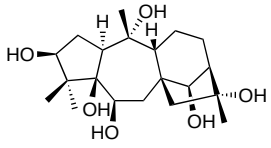
Polycyclic natural products that contain an embedded polyhydroazulene subunit, for example, dilatriol[1a] (**1a**), rameswaralide[1b] (**1b**), grayanotoxin[1c] (**1c**), and phorbol[1d] (**1d**), possess a diversity of biological activities. As such, they



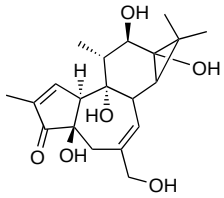
1a



1b



1c



1d

represent interesting yet demanding synthetic challenges and stimulate the development of new methodologies. The ability to increase molecular complexity rapidly by cycloaddition reactions should prove to be particularly interesting in offering short, atom-economical routes to such targets. Among these reactions, Rh-[2] and Ru-catalyzed[3] [5+2] cycloaddition reactions that involve cyclopropyl enynes have been discovered by the Wender group and by our group, respectively. We have shown that the Ru^{II} catalyst **2** can catalyze this process under very mild conditions[3] (room temperature in acetone within a few hours). This fact encouraged us to examine the applicability of this strategy to complex targets represented by **1a**–**d**, which raises a number of reactivity and selectivity issues that are addressed herein.

The sensitivity of the Ru-catalyzed reactions to steric hindrance immediately led us to test the ability of 1,2,3-trisubstituted cyclopropanes to participate in these reactions.

[*] Prof. B. M. Trost, H. C. Shen
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@leland.stanford.edu

[**] We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. H.S. is a Stanford Graduate Fellow. Mass spectra were provided by the Mass Spectrometry Facility of the University of California, San Francisco, which is supported by the NIH Division of Research Resources.