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Inter- and Intramolecular Reductive Coupling Reactions: An Approach to the Phorbol Skeleton

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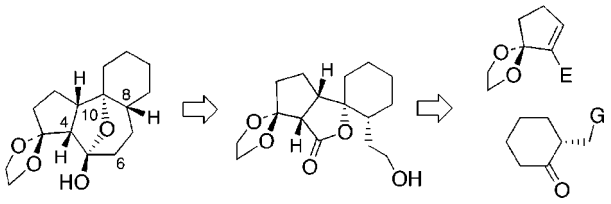
ABSTRACT



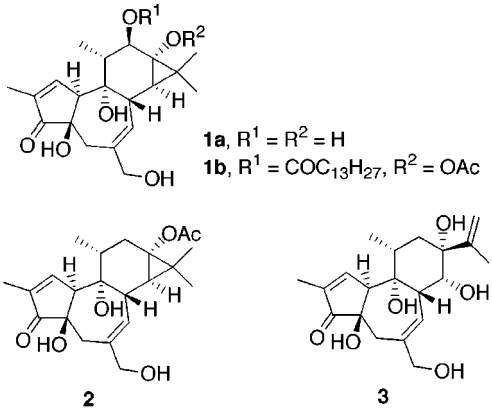
An expeditious convergent route to the ABC-tricyclic core of the phorbol esters is described. The chemistry capitalizes upon both inter- and intramolecular reductive coupling processes promoted electrochemically and via the use of samarium diiodide.

The phorbol esters **1b** are well-known for their tumor-promoting properties.[1] Studies have also established that the closely related materials **2** and **3** display phorbol inhibitory or *anti*-tumor properties.[2] This fine line between two extremes of biological activity for such similar materials adds to their attractiveness as synthetic targets and potential sources of new bioactive materials. Phorbol (**1a**) has been synthesized, most recently in an enantiopure state, by Wender and co-workers (Scheme 1).[3] In addition to their pioneering efforts, those of others have led to the development of a number of ingenious routes to the tigliane, daphnane, and ingenane class of naturally occurring substances.[4]

In this paper we report our recent studies directed toward construction of the tricyclic core of the phorbols. The route (Scheme 2) features the use of both inter- and intramolecular reductive coupling strategies to form the C_5-C_6, C_8-C_9, and C_9-C_{10} bonds and provides an exceptionally rapid access to the framework. We selected **4** as a target structure, and compounds **5**, **6**, and **7** as key subgoals.

We first elected to synthesize **7** (as **10** and **11**), and did so in the following manner. In each case, an electroreductive

Scheme 1



(1) *Naturally Occurring Phorbol Esters*; Evans, F. J., Ed.; CRC Press: Boca Raton, FL, 1986. (b) Berenblum, I. In *Risk Factors and Multiple Cancer*; Stoll, B., Ed.; John Wiley and Sons: New York, 1984. (c) 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.

(2) (a) Szallasii, Z.; Krsmanovic, L. Blumberg, P. M. *Cancer Res.* **1993**, *53*, 2507. (b) Yoshida, M.; Feng, W. J.; Saijo, N.; Ikekawa, T. *Int. J. Cancer* **1996**, *66*, 268.

(3) (a) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956. (b) Wender, P. A.; Mascareñas, J. L. *J. Org. Chem.* **1991**, *56*, 6267. (c) Wender, P. A.; Rice, K. D.; Schnute, M. *J. Am. Chem. Soc.* **1997**, *119*, 7897.

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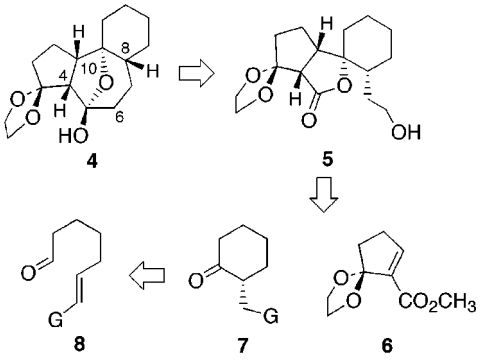
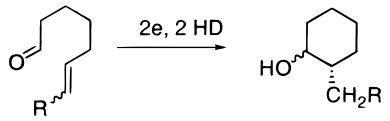
Scheme 2



cyclization was used.[5] Ester **9b** and lactone **9c** were constructed from enoate **8b**; nitrile **9a** was derived from **8a**. Voltammetric studies (cyclic voltammetry [CV]) of **8a** and **8b** show an irreversible reduction wave indicative of the existence of a rapid reaction on the time scale of the CV scan, following the electron transfer step. Our previous mechanistic studies have shown that process to be a rate-determining protonation of the initially formed radical anion.[6] This is followed by the addition of a second electron and cyclization of the resulting carbanion. Reactions were carried out at a controlled potential, in the presence of a variety of proton donors, solvents, electrode materials, supporting electrolytes, and additives. As illustrated in Table 1 (entry 1), the best results were obtained using a mercury cathode with dimethyl malonate as the proton source. Recent studies have shown that malononitrile is often preferable, however,

Table 1. Electroreductive Cyclization



8a, R = CN
8b, R = CO_2Me

9a, R = CN
9b, R = CO_2Me
9c, lactone form[b]

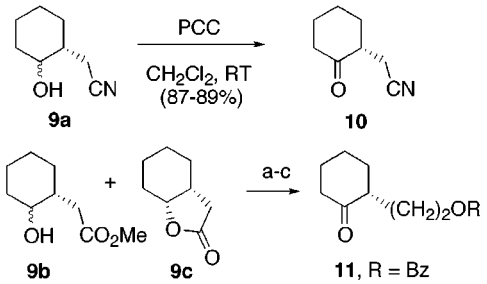
entry[a]	solvent	electrolyte	voltage	proton donor	product yield (%)[c] R=CN	product yield (%)[c] R=CO_2Me
1	CH_3CN	Bu_4NBr	-2.4 V	malonate	85-89	88-92
2	CH_3CN	Bu_4NBr	-2.6 V	H_2O	53	—
3	CH_3CN	Bu_4NBr	-2.6 V	t-butanol	46	—
4	DMF	Bu_4NBr	-2.2 V	malonate	74	78
5	DMF	$LiClO_4$	-2.6 V	t-butanol	49	—
6	CH_3CN	Bu_4NBr	-2.6 V	malonate	45	—
7	DMF	Bu_4NBr	-2.2 V	t-butanol	28	—

a, mercury pool electrode, entries 1-5; graphite electrode, entry 6; lead electrode, entry 7. b, Complete lactonization of the *cis*-hydroxy ester occurs over silica gel during purification. c, *trans* to *cis* ratios are typically in the range of 1.4:1 to 1.2:1.

as it can more readily be removed by extraction into the aqueous layer during workup.

Keto nitrile **10** and ketone **11** were examined as candidates for the proposed intermolecular reductive coupling with enoate **6**. For the hydroxynitrile **9a**, produced from the electroreductive cyclization of **8a**, this simply required oxidation with PCC. For **9b** and **9c**, reduction with LAH converted each to a mixture of diols (Scheme 3). Although

Scheme 3

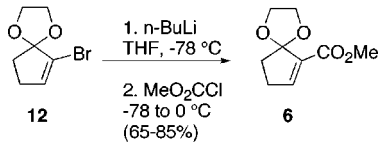


a, LAH, Et_2O, reflux (69-78%); b, BzCl, TEA, CH_2Cl_2 (89%); c, PCC, CH_2Cl_2, room temp (90-95%).

selective oxidation of the 2° alcohol to the desired keto-alcohol could be accomplished with NaOCl, rapid formation of the internal hemi-ketal made further transformations problematic. Consequently, selective protection as the primary benzoate was required prior to oxidation. PCC oxidation provided the α-substituted ketobenzoate **11** in high yield.

With **10** and **11** in hand, we were positioned to examine the samarium diiodide promoted intermolecular reductive coupling to enoate **6**.[7] The latter was conveniently synthesized from vinyl bromide **12** via lithium−halogen exchange and subsequent treatment with methyl chloroformate (Scheme 4).[8] Coupling of **6** and ketobenzoate **11** occurred with modest

Scheme 4



efficiency to afford hydroxy ester **15** as a single stereoisomer. We presume the stereoselectivity reflects the role of samarium in both complexing to and holding the coupling

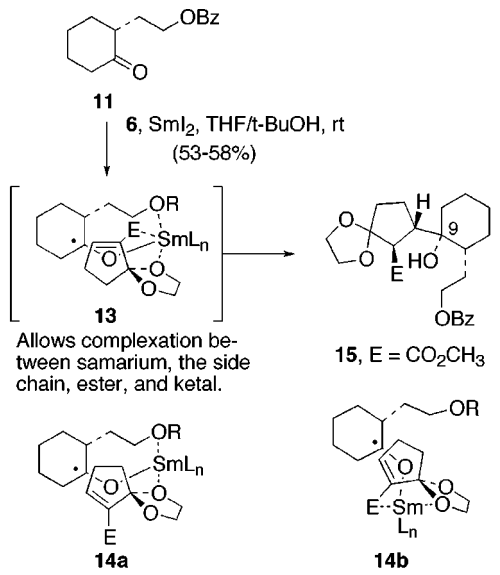
(4) For example, see: (a) Lee, K.; Cha, J. K. *Org. Lett.* **1999**, *1*, 523. (b) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976. (c) Shigeno, K.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 4937. (d) Sugita, K. Neville, C.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 1067. (e) Rigby, J.; Keirkus, P. *Tetrahedron Lett.* **1989**, *30*, 5073.

(5) (a) Little, R. D. *Chem. Rev.* **1996**, *96*, 93. (b) Little, R. D.; Schwaebe, M. K. Reductive Cyclizations at the Cathode. In *Electroorganic Synthesis: Bond Formation at Anode and Cathode*; Steckhan, E., Ed.; Topics in Current Chemistry 185; Springer: Berlin, 1997; pp 1−48.

(6) Fry, A. J.; Little, R. D.; Leonetti, J. *J. Org. Chem.* **1994**, *59*, 5017.

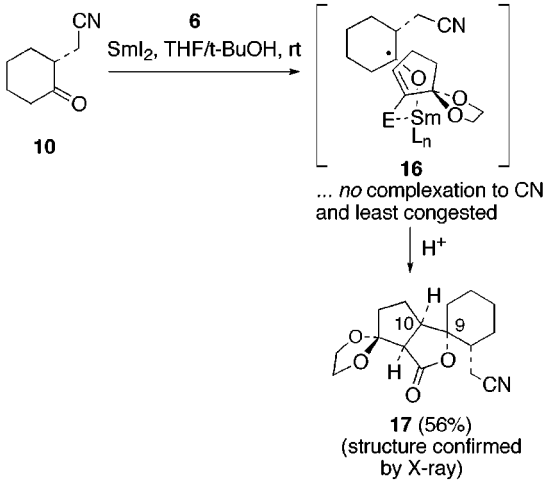
partners in the manner portrayed by **13** (Scheme 5). While it is more sterically demanding than the alternative formulations **14a** and **b**, the former maximizes the opportunity for complexation between samarium and each of the oxophilic sites located on both of the reacting partners.

Scheme 5



Interestingly, when the oxophilic benzoyloxyethyl side chain of **11** is replaced by a cyanomethyl substituent (see **10**), the stereochemical outcome at the pro-C_{10} carbon is *reversed* (Scheme 6). This is consistent with a picture where the coupling partners, in this case **6** and **10**, approach one another in the sterically least demanding manner. Since coordination of samarium to the nitrile is not expected to occur, the trajectory portrayed by **16** allows optimal interaction between the samarium ketyl and the ester unit of the enoate and also minimizes steric interactions. Unlike the chemistry shown in Scheme 5 where the stereochemistry at the pro C_{10} carbon is *opposite* to that needed to access the natural products, the coupling between **10** and **6** leads to the desired stereochemical outcome at the pro C_8, C_9, *and* C_{10} carbons.[9]

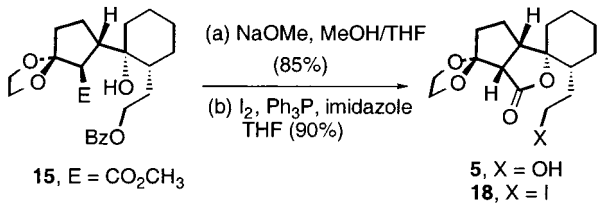
Scheme 6



The preceding examples (Schemes 5 and 6) illustrate that it is possible to obtain *either* stereochemical outcome at C_{10} simply by making the appropriate choice of substituents appended to the coupling partners. That obtained in the case of ketonitrile **10** is the outcome needed for natural product synthesis. In the discussion that follows, we focus attention upon **15**, however, since the nitrile proved difficult to manipulate in subsequent transformations.[10] Furthermore, our goal at this point was to determine whether the methodology portrayed in Scheme 2 could be used to gain access to the basic *skeleton* of the natural products.

In preparation for cyclization leading to the formation of the pro C_5-C_6 bond and the assembly of the seven-membered ring, we treated **15** with sodium methoxide in methanol/THF. This led to removal of the benzoate, epimerization α to the methyl ester, *and* lactonization, affording **5** in an 85% yield. Conversion of **5** to the iodide using I_2, PPh_3, and imidazole in THF provided iodo lactone **18** in yields of 90% (Scheme 7).

Scheme 7



The best method for reductive cyclization of **18** used samarium diiodide. The initial reaction was clean but required 5−7 h to reach completion and occurred with variable yields (43−68%). Upon the addition of catalytic nickel(II) iodide, the reaction reached completion within 1 h and yields improved to 82−88%.[11] A single isomer was isolated and established to be the hemiketal **4**; the presence of the

(7) (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (c) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, Shizuyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669. (d) Fukuzawa, S.; Seki, K.; Tasuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482. (e) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, Shizuyoshi, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920. (f) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, Shizuyoshi, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624.

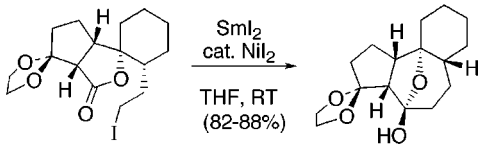
(8) Smith, A. B., III.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.

(9) Yields for this transformation ranged from 68 to 74%. The major product, consistently isolated in a 56% yield, was compound **17**. The remainder of the mass consisted of a mixture of open hydroxy ester and lactonized forms.

(10) Selective manipulation of the nitrile in the presence of the lactone proved problematic. Thus, while the use of 1 equiv of DIBAL did result in the formation of the desired lactol, further reductions proved unselective. Acid or base hydrolysis procedures also proved problematic and require further investigation before they can be used reliably.

hemiketal was evident by the absence of a carbonyl signal in both the IR and ^{13}C NMR spectra (Scheme 8).

Scheme 8



18 **4**

This material provided a single crystal from which X-ray data was acquired. The structure was solved and the stereochemical outcome was determined unambiguously. The pro C_4, C_8, and C_9 stereocenters match those of the phorbol skeleton. The stereochemistry at C_{10} is consistent with the intermolecular coupling model portrayed in Scheme 5 but is opposite to that of the natural materials. It is important to reiterate that we are able to control the stereochemistry, thereby making the appropriate choice of the side chain substituent appended to the ketone coupling partner (compare Schemes 5 and 6).

We have described a rapid and direct means to assemble the basic skeleton of the phorbol esters. The chemistry more clearly establishes the utility of both inter- and intramolecular reductive coupling methods in synthesis. Efforts to use it to synthesize functionally more elaborate bioactive phorbol analogues are in progress.

Acknowledgment. We thank the National Science Foundation for supporting this research and Dr. X. Bu for the X-ray structural determination of **4** and **17**.

Supporting Information Available: Spectral data for **6**, **8a**, **8b**, **9a**, **9b**, **9c**, **10**, **11**, **15**, **17**, **5**, **18**, and **4**. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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