An Intramolecular Diels–Alder Approach to Phorbols: Introduction of an Oxygenated Diene Using a Palladium Catalysed Coupling

Philip C. Bulman Page* and David C. Jennens
Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK

A synthesis of a carbotricycle related to the phorbol skeleton has been achieved in five steps hinging upon an unusual intramolecular Diels–Alder reaction; a usefully oxygenated diene subunit is introduced by a palladium catalysed coupling.

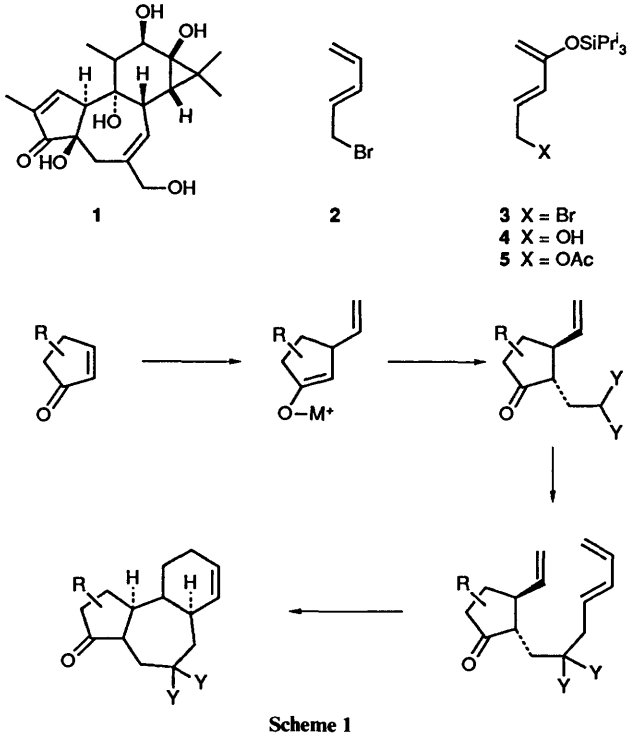
The daphnane and tigliane groups of natural products are diterpenes containing a tricyclo[9.3.0.0^{2,7}]tetradecane ring system as the major part of their carbon skeletons. Phorbol **1**[1] is a tetracyclic diterpene possessing a polyhydroxylated tigliane carbon skeleton; the molecule contains eight contiguous asymmetric carbon atoms, six of them sited around the six-membered C ring. Phorbol occurs naturally in the form of 12,13-diesters and 12,13,20-triesters, found in croton oil;[2] phorbol was isolated as an hydrolysis product of croton oil as early as 1935,[3] but the structure was not elucidated until 1967 by X-ray analysis of a derivative.[4]

The most important derivatives of phorbol are the 12,13-diesters, which are toxic and are potent tumour-promoting agents able to activate protein kinase C.[5] Phorbol esters also produce a wide variety of other biological responses and, as a consequence, have emerged as important lead compounds in the development of chemotherapeutic agents for a variety of diseases, most notably including AIDS.[8]

Despite their interesting biological activity, phorbol and its derivatives have received relatively little synthetical interest.[9,11] Our own approach to the tigliane/daphnane ring system is based around construction of the B and C rings using an intramolecular Diels–Alder (IMDA) reaction, coupled with a convergent synthesis of the cyclization precursor. The large number of total syntheses using an IMDA reaction as their key step amply illustrates the tremendous value to synthetic chemists of this strategy, no doubt because of the predictability and high degree of stereocontrol available at several asymmetric centres.[10] It is, therefore, particularly interesting that there are remarkably few examples in which the ring system produced is the C_{11} bicyclo[5.4.0]undecane, containing fused six- and seven-membered rings, as is found in phorbol.[11] For this reason such a strategy was attractive to us both as a general synthetic approach and as a probe for the degree of stereoselectivity available in this unusual category of IMDA reactions.

The approach we have devised, outlined in Scheme 1, involves conjugate addition of a suitable vinyl anion to a cyclopentenone followed by addition of the enolate to the C-2 position of a two-carbon unit able to sustain an anion at C-1. Coupling of such an anion with a pre-formed diene subunit provides the substrate for the crucial IMDA reaction which sets up most of the remaining asymmetric centres and which provides a usefully functionalized product of considerable synthetic potential. We have previously demonstrated the value of this approach for the rapid construction of a simple carbotricycle related to the daphnane and tigliane carbon skeletons (Scheme 2).[12] This short scheme requires no unusual techniques or special apparatus.

Introduction of oxygen substituents around the diene component might be expected to alter both the facility and stereoselectivity of the IMDA reaction. Here we report the successful

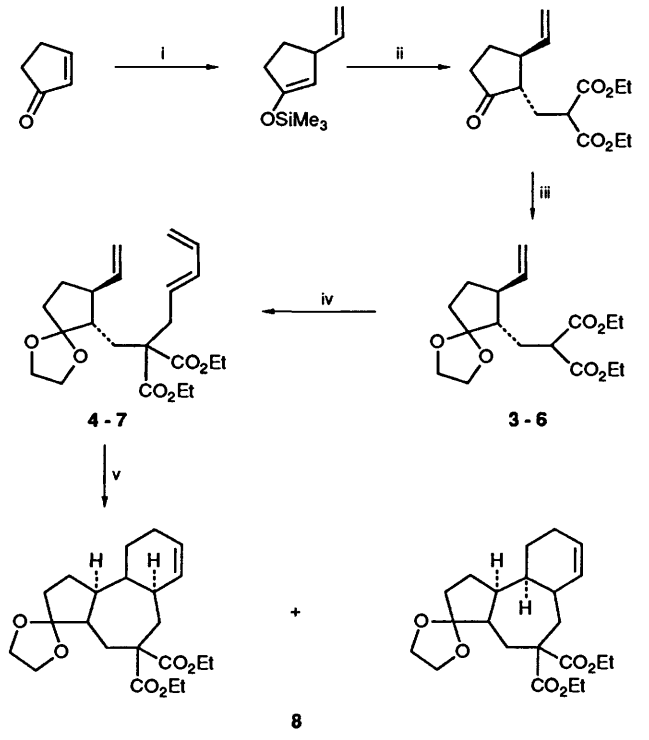


1 **2** **3** X = Br, **4** X = OH, **5** X = OAc

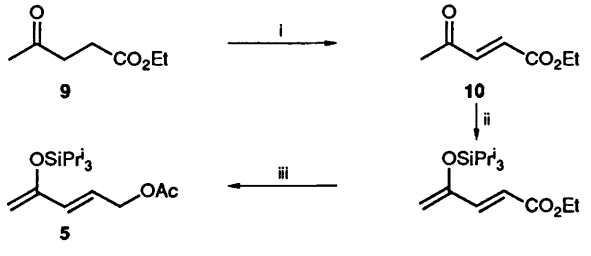
Scheme 1

introduction of an oxygenated diene unit prepared from ethyl laevulinate, and its utility in our synthetic approach to phorbols (Schemes 3 and 4). In our previous communication the diene component used was (*E*)-5-bromopenta-1,3-diene **2**;[13] coupling with the left hand segment **6**† to give the Diels–Alder substrate **7** was in that case readily accomplished by deprotonation of **6** at the malonate carbon atom using LDA followed by a simple displacement reaction of the allylic bromide unit of **2**. Accordingly, our initial approach to an oxygenated diene was to prepare **3**, an oxygenated analogue of the bromo diene **2**, for similar coupling with **6**. However, this C-2 oxygenated bromo diene proved difficult to isolate in reasonable yield, as did the corresponding mesylate and tosylate, also obvious candidates for S_N2 coupling. Mitsunobu coupling of **6** with C-2 oxygenated diene alcohol **4** gave the desired triene **11** in only 5% yield[14] and, as a result, we turned our attention to palladium-catalysed coupling of a carbonate or acetate derivative of **4** as a promising alternative. While we were not able easily to prepare the methyl carbonate,[15] the acetate derivative **5** proved a more amenable

† Isolated and used in all cases as a mixture of isomers (7.3:1, *anti*:*syn*, estimated by capillary gas chromatography and 400 MHz $^1H/^{13}C$ NMR spectroscopy); *anti* isomers shown for clarity.



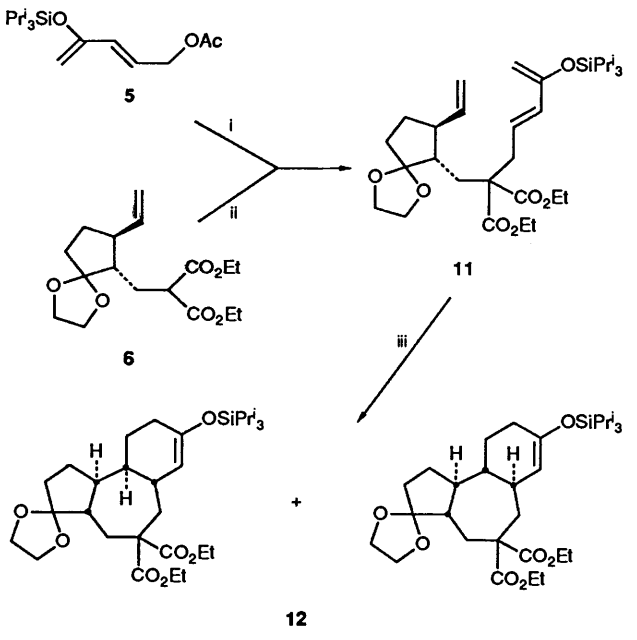
Scheme 2 *Reagents and conditions:* i, CH_2=CHMgBr/CuBr·DMS, Me_3SiCl, DMPU, Et_3N, THF, −78 °C, 94%; ii, diethyl methylenemalonate, $SnCl_4$, CH_2Cl_2, −78 °C, 77%; iii, ethylene glycol, TsOH, PhH, heat, 84%; iv, LDA, THF, −78 °C, 89%; **2**; v, toluene, sealed tube, 160 °C, 14 days, 70%



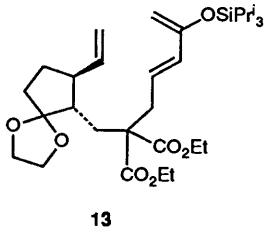
Scheme 3 *Reagents and conditions:* i, $Br_2/CHCl_3$; Et_3N, CH_2Cl_2, 95%; ii, TIPSOTf, Et_3N, Et_2O, 96%; iii, DIBAL, THF, 99%; Ac_2O, DMAP, Et_3N, CH_2Cl_2, 92%

target (Scheme 3). Bromination/dehydrobromination of ethyl laevulinate **9** afforded ethyl 4-oxopentenoate **10** in 95% yield. Treatment with triisopropyl triflate (TIPSOTf) in the presence of triethylamine gave the corresponding enol ether (96%), the ester moiety of which was reduced to the alcohol using DIBAL (99%). Conversion into the acetate with acetic anhydride in the presence of *N,N*-dimethylaminopyridine (DMAP) completed the sequence to give **8** in 92% yield.

A palladium π-complex was prepared from the diene acetate **5** by treatment with tetrakistriphenylphosphinepalladium(0) (4 mol%), formed *in situ* by reaction of trisdibenzylideneacetonedipalladium chloroform solvate $[Pd_2(dba)_3·CHCl_3]$ with



Scheme 4 *Reagents and conditions:* i, $[Pd_2(dba)_3·CHCl_3]$, $CHCl_3$, Ph_3P, THF; iii, LHMDS, THF; iii, toluene, sealed tube, 150–160 °C, 3 days



triphenylphosphine.[16] Coupling of this palladium π-complex with the left hand subunit **6** to give **11** was accomplished in up to 77% yield by addition to the lithium anion derived from **6** by deprotonation using LDA or LHMDS.[12,17]

Gratifyingly, the triene **11** when heated at 150–160 °C for 3 days in a base-washed (HMDS) resealable tube in dry degassed toluene solution afforded the desired IMDA cycloadducts **12** as an inseparable mixture of isomers in 45% isolated yield together with unchanged **11** and deprotected enone **13** (93% yield of **12** based on recovered material).*

Interestingly, the corresponding IMDA reaction of the simpler triene **7** required 14 days at 160 °C under similar conditions to produce a 70% yield of the cycloadducts **8**, confirming the expected increased reactivity of the oxygenated system. The relative ease of the IMDA reaction in the oxygenated system coupled with the rapid construction of the tricyclic daphnane/tigliane framework suitably functionalized for further synthetic transformations augurs well for the application of this approach to phorbol synthesis.

Acknowledgements

This investigation has enjoyed the support of the SERC (D. C. J.: quota studentship).

References

1 F. J. Evans and C. J. Soper, *Lloydia*, 1978, **41**, 193; E. Hecker and R. J. Schmidt, *Fortschr. Chem. Org. Naturst.*, 1974, **31**, 377; A. S. Kraft and W. B. Anderson, *Nature*, 1983, **301**, 621; *Naturally Occurring Phorbol Esters*, ed. F. J. Evans, CRC, Boca Raton, 1986.

* 45% **12**, 11% **11**, 30% **13**. Isolated **12** appears to contain principally two isomers, assigned as the products of *exo* cycloaddition by analogy with the IMDA reaction of **7**, and by correlation of ^1H and ^{13}C NMR data with that of **8**, the structure of which was confirmed by X-ray analysis. Both the triene **11** and the cycloadduct **12** are unstable to gas chromatography. Examination of molecular models for IMDA reactions of both **7** and **11** suggest that transition states for *endo* cycloaddition are more crowded than for *exo* cycloaddition, and particularly so in the case of **11**.

2 The oil expressed from the seeds of the purging croton, the leafy shrub *Croton tiglium* (Euphorbiaceae), native to South-East Asia.[1] The oil and the seeds, formerly known as molucca grains, were in common use in Europe from the sixteenth century as a purgative and emmenagogue, having been introduced from China by the Dutch. W. Ainslie, quoted by J. Lindley, in *A Natural System of Botany*, Longman, Rees, Orme, Brown, Green and Longman, London, 1836 (senior author's collection); G. Graves and J. D. Morries, *Hortus Medicus*, Adam & Charles Black, Edinburgh, 1834.
3 R. Bohm, B. Flaschenträger and L. Lendle, *Arch. Exp. Pathol. Pharmakol.*, 1935, **177**, 212.
4 W. Hoppe, F. Brandl, I. Strell, M. Röhl, I. Gassmann, E. Hecker, H. Bartsch, G. Kreibich and C. V. Szczepanski, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 809; E. Hecker, H. Bartsch, H. Bresch, M. G. Schwendt, E. Härle, G. Kreibich, H. Kubinyi, H. U. Schairer, C. V. Szczepanski and H. W. Thielmann, *Tetrahedron Lett.*, 1967, 3165; R. C. Petterson, G. Ferguson, L. Crombie, M. L. Games, D. J. Pointer, *J. Chem. Soc., Chem. Commun.*, 1967, 716.
5 E. Hecker, in *Methods of Cancer Research*, vol. 6, ed. H. Busch, Academic Press, London, 1971; R. K. Bontwell, *ibid.*, 1974, **2**, 419; V. Armuth and I. Z. Berenblum, *Krebsforsch. Klin. Oncol.*, 1976, **85**, 79; L. Diamond, T. G. O'Brien and W. M. Baird, *Adv. Cancer Res.*, 1980, **32**, 1; P. M. Blumberg, *C.R.C. Crit. Rev. Toxicol.*, 1981, **8**, 199; E. Hecker, *J. Cancer Res. Clin. Oncol.*, 1981, **99**, 103; S. E. Taylor, M. A. Gafur, A. K. Choudhury and F. J. Evans, *Phytochemistry*, 1981, **20**, 2749; P. M. Blumberg, in *Mechanisms of Tumour Promotion*, vol. 3, ed. T. J. Slaga, CRC, Boca Raton, 1984, pp. 143–184; Y. Nishizuka, *Nature*, 1984, **308**, 693; Y. Nishizuka, *Science*, 1986, **233**, 305; A. P. Kozikowski, K. Sato, A. Basu and J. S. Lazo, *J. Am. Chem. Soc.*, 1989, **111**, 8954. The most potent of the diesters is phorbol myristate acetate (PMA, TPA); paradoxically one 12,13-diester has been shown to exhibit antitumour activity,[6] and the parent molecule phorbol is neither a carcinogen nor a cocarcinogen.[7]
6 S. M. Kipchon, I. Uchida, A. R. Braifman, R. G. Dailey and B. Y. Fei, *Science*, 1976, **191**, 571.
7 C. J. Soper and F. J. Evans, *Cancer Res.*, 1977, **37**, 2487.
8 S. Harada, N. Yamamoto and H. Fujiki, *AIDS Res. Hum. Retroviruses*, 1988, **4**, 99; G. Poli, J. Orenstein, A. Kinter, T. M. Foks and A. S. Fauci, *Science*, 1989, **244**, 575.
9 S. J. Burrell, A. E. Derome, M. S. Edenborough, L. M. Harwood, S. A. Leeming and N. S. Isaacs, *Tetrahedron Lett.*, 1985, **26**, 2229; L. M. Harwood, S. A. Leeming, N. S. Isaacs, G. Jones, J. Pickard, R. M. Thomas and D. Watkin, *Tetrahedron Lett.*, 1988, **29**, 5017; L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas and D. Watkin, *Tetrahedron Lett.*, 1988, **29**, 5825; L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas and D. Watkin, *J. Chem. Soc., Chem. Commun.*, 1990, 605; L. M. Harwood, B. Jackson, G. Jones, K. Prout, R. M. Thomas and F. J. Witt, *J. Chem. Soc., Chem. Commun.*, 1990, 608; L. M. Harwood, T. Ishikawa, H. Phillips and D. Watkin, *J. Chem. Soc., Chem. Commun.*, 1991, 527; P. A. Wender, H. Y. Lee, R. S. Wilhelm and P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8957; P. A. Wender and F. E. McDonald, *J. Am. Chem. Soc.*, 1990, **112**, 4956; P. A. Wender, J. L. Mascareñas, *J. Org. Chem.*, 1991, **56**, 6267; J. H. Rigby, P. C. Kierkus and D. Head, *Tetrahedron Lett.*, 1989, **30**, 5073; J. I. McLoughlin, R. Brahma, O. Canpopiano and R. D. Little, *Tetrahedron Lett.*, 1990, **31**, 1377; L. A. Paquette, R. J. Ross and Y.-J. Shi, *J. Org. Chem.*, 1990, **55**, 1589; K. Shigeno, K. Ohne, T. Yamaguchi, H. Sasai and M. Shibasaki, *Heterocycles*, 1992, **33**, 161.
10 G. Brieger and J. N. Bennett, *Chem. Rev.*, 1980, **80**, 63; D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, 1990; F. Fringuelli and A. Taticchi, *Dienes in the Diels–Alder Reaction*, Wiley, New York, 1990.
11 W. Oppolzer and R. L. Snowden, *Helv. Chim. Acta*, 1981, **64**, 2592; D. A. Smith, K. Sakan and K. N. Houk, *Tetrahedron Lett.*, 1986, **27**, 4877; P. A. Wender, R. M. Keenan and H. Y. Lee, *J. Am. Chem. Soc.*, 1987, **109**, 4390; K. J. Shea, K. S. Zandi, A. J. Stuab and R. Carr, *Tetrahedron Lett.*, 1990, **31**, 5885; D. Craig and J. C. Reader, *Tetrahedron Lett.*, 1990, **31**, 6585; D. A. Smith and K. N. Houk, *Tetrahedron Lett.*, 1991, **32**, 1549.
12 P. C. B. Page and D. C. Jennens, *Synlett*, 1991, 472.
13 K. Mori, *Tetrahedron*, 1974, **30**, 3807.
14 O. Mitsunobu, *Synthesis*, 1981, 1.
15 M. Matzner, R. P. Kurkjy and R. J. Cotter, *Chem. Rev.*, 1964, **64**, 645.
16 T. Ukai, H. Kawazura and Y. Ishii, *J. Organomet. Chem.*, 1974, **65**, 253.
17 B. M. Trost, *Chemtracts*, 1988, **1**, 415.

Paper 2/04398J
Received 13*th August* 1992
Accepted 1*st September* 1992