A Unified Entry into the Ingenane, Tigliane, and Taxane Ring Systems

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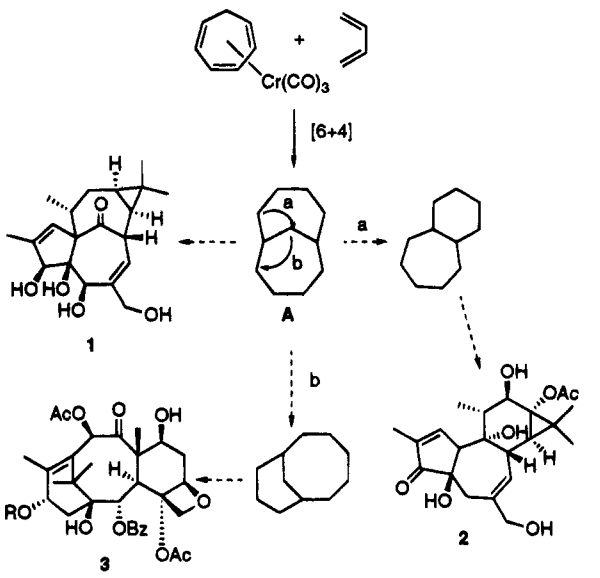
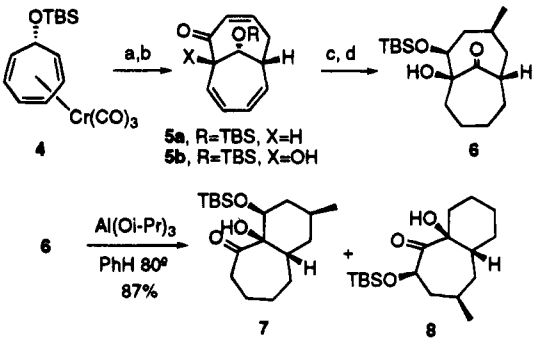
The diterpenes ingenol (**1**), phorbol (tigliane) (**2**), and taxol (**3**) have elicited intense scrutiny recently by virtue of their profound biological activities as well as their structural complexities. Derivatives of compounds **1** and **2** are known to be potent tumor promoters,[1] and taxol (**3**) is one of the most promising anticancer agents currently available for clinical use.[2] Considerable synthetic effort has been devoted to all three classes of compounds,[3,4] which has culminated in the total syntheses of phorbol[5] and taxol.[6] The close structural relationship between the ingenane and tigliane systems has been noted previously,[7] and synthetic strategies that exploit these similarities have frequently been sought, but few have been brought to practice.[3] We now disclose a novel strategy based on transition metal-promoted [6π + 4π] cycloaddition chemistry that can deliver key ring system components of the ingenane, tigliane, and taxane diterpenes from essentially a common bicyclo[4.4.1]undecane precursor (Scheme 1).

The bicyclo[4.4.1]undecane system represented by generic intermediate **A** can be effectively assembled by employing chromium(0)-promoted [6π + 4π] cycloaddition chemistry.[8] The versatility of this process is such that a wide variety of substitution and functionality patterns on the resultant bicyclic products can be accessed quickly and efficiently. In the current study, conversion of these species into the target compounds rests on the recognition of certain structural relationships between the bicyclo[4.4.1]undecane system and the diterpenes of interest. For example, a direct correlation between **A** and the BC substructure of ingenol (**1**) is clearly evident, and several approaches have been reported from our laboratory[9] as well as from others[3] for elaborating the ingenane skeleton

Scheme 1



Scheme 2[a]



[a] Key: (a) (i) CH_2=CHCH=CHOAc, *hv*; (ii) triton-B, MeOH, rt; (iii) Swern Ox. (65%); (b) KHMDS, THF, Davis reagent, −78 °C (82%); (c) i) Me_2CuLi, Et_2O, −78 °C; (ii) $NaBH_4$, $CeCl_3$ $7H_2O$ MeOH 0 °C; (iii) Ag_2O, MeCN, reflux (45%), (d) (i) H_2/PtO_2, MeOH; (ii) Dess–Martin, CH_2Cl_2 (76%).

from a bicyclo[4.4.1]undecane precursor. Implementation of the less obvious transformations of **A** into the BC rings of phorbol (**2**) and the AB moiety of taxol (**3**), which is the subject of this investigation, can be envisioned to proceed through a series of bond reorganizations designated in Scheme 1 as a and b, respectively.

Access to the tigliane (phorbol) BC ring system via pathway a could be achieved from an appropriate precursor employing either a pinacol or an α-ketol type rearrangement, and it is noteworthy that Hecker has reported a related interconversion in the natural series.[7b] Photocycloaddition of readily available complex **4**[10,11] with excess 1-acetoxybutadiene followed by routine functional group manipulation afforded enone **5a** (Scheme 2).[11] Exposure of the well-behaved bridgehead enolate[12] derived from this material to the Davis oxaziridine reagent[13] provided the key α-ketol **5b**[11] in good yield. After some experimentation, it was determined that the projected α-ketol rearrangement to the desired bicyclo[5.4.0]-undecane was best executed on the fully reduced carbon

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(1) (a) Rando, R. R.; Kishi, Y. In *Protein Kinase: Current Concepts and Future Perspectives*; Lester, D. J., Epand, R. M., Eds.; Ellis Horwood: New York, 1992; p 41. (b) Nishizuka, Y. *Cancer* **1989**, *63*, 1892. (c) Nishizuka, Y. *Science* **1986**, *233*, 305.

(2) (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (b) Schiff, P. B., Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(3) For an overview of approaches to the ingenanes and tiglianes, see: Rigby, J. H. In *Studies in Natural Products Chemistry*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1993; Vol. 12 (Part H), pp 233–74.

(4) For a recent review of taxol synthetic studies, consult: Swindell, C. S. In *Studies in Natural Products Chemistry*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1993; Vol. 12 (Part H), pp 179–231.

(5) (a) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *Ibid.* **1989**, *111*, 8957. (c) Wender, P. A.; McDonald, F. E. *Ibid.* **1990**, *112*, 4956.

(6) (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597, 1599. (b) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. (c) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723.

(7) (a) Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205. (b) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423.

(8) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579.

(9) Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286.

(10) Pauson, P. L.; Todd, K. H. *J. Chem. Soc. C* **1970**, 2315.

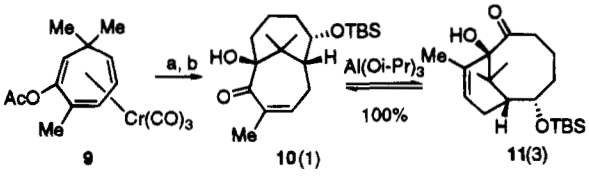
(11) This compound exhibited (^{1}H NMR, ^{13}C NMR, IR) and analytical (combustion analysis and/or HRMS) data fully consistent with the assigned structure.

(12) Rigby, J. H.; Moore, T. L. *J. Org. Chem.* **1990**, *55*, 2959.

(13) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774.

0022-3263/95/1960-7720$09.00/0

Scheme 3[a]



9 10(1) 11(3)

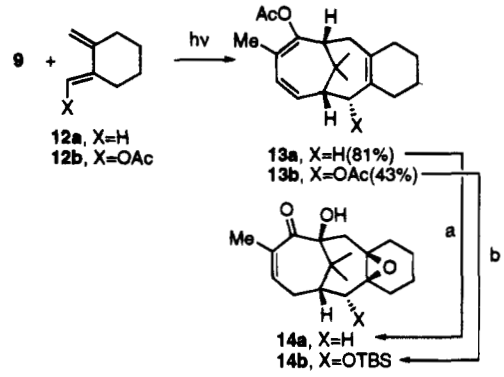
[a] Key: (a) (i) CH_2=CHCH=CHOTMS, *hν*; (ii) K_2CO_3/MeOH, rt; (iii) H_2/Pd–C; (iv) TBSCl, imid., DMF, rt (78%); (b) LDA, THF, Davis reagent; −78 °C (70%).

skeleton. Consequently, reduced α-ketol **6**[11] was prepared in good yield and subjected to Al(O-*i*-Pr)$_3$ in refluxing benzene to afford a 1:1 mixture of isomeric products **7**[11] and **8**,[11] both of which display the basic BC ring system of phorbol in a form amenable to subsequent A-ring introduction.[5] Modifications of this sequence designed to control the regioselectivity of the rearrangement and for accessing the natural trans-fused system from an "in, out" bicyclo[4.4.1]undecane precursor (trans interbridgehead stereochemistry) will be reported in due time. It is noteworthy that our rearrangement proceeded smoothly to the fused bicyclic product without the benefit of ring strain release that characterized Hecker's earlier work with the highly strained ingenol system itself.[7b]

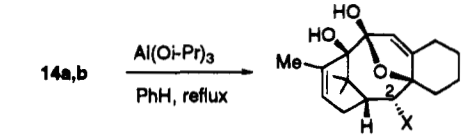
The taxane AB substructure could be envisioned to arise from a related bicyclo[4.4.1]undecane intermediate via pathway b. In this case, a readily available triene complex derived from eucarvone[14] was selected for study because it would permit facile introduction of most of the taxane A ring substitution directly during the cycloaddition event. Thus, complex **9**[11] underwent *quantitative* photocycloaddition with 1-[(trimethylsilyl)oxy]butadiene to afford, after routine functional group manipulation, α-ketol **10**[11] in 55% overall yield (Scheme 3). Heating **10** with Al(O-*i*-Pr)$_3$ in benzene yielded an equilibrium mixture consisting of the desired bicyclo[5.3.1]undecane **11**[11,15] and starting material in a 3:1 ratio, respectively.[16]

With the basic elements of the cycloaddition–rearrangement protocol established, this approach was extended to the assembly of the tricyclo[9.3.1.0^{3,8}]pentadecane system characteristic of the taxanes by introducing an intact C-ring unit during cycloaddition. The successful implementation of this plan is clearly indicative of the power and versatility of the metal-promoted cycloaddition technology in the context of complex synthesis. In the event, photocycloaddition of complex **9** with dienes **12a**[17] and **12b**[18] afforded adducts **13a**[11] and **13b**[11] in 81% and 43% yields, respectively. Routine functional group manipulation of these compounds followed to give the α-ketol epoxides **14a,b**, respectively, in good overall

Scheme 4[a]



[a] Key: (a) (i) K_2CO_3, MeOH, rt; (ii) *m*-ClPBA, CH_2Cl_2, 0 °C; (iii) LiN(C_5H_{10}), THF, Davis reagent −78 °C (46%); (b) (i) K_2CO_3, MeOH, rt; (ii) TBSCl, imid., DMF, rt; (iii) m-ClPBA, CH_2Cl_2, 0 °C; (iv) LiN(C_5H_{10}), THF, Davis reagent, −78 °C (54%).



15a, X=H (81%)
15b, X=OTBS (65%)

yields (Scheme 4). The epoxide positioned at the BC ring fusion in these species was incorporated in an attempt to drive the α-ketol rearrangement to completion via a β-elimination of the initially formed keto-epoxide, as well as to enhance the level of functionalization in the C-ring region of the resultant products.[19] Treatment of **14a** and **14b** with Al(O-*i*-Pr)$_3$ in refluxing benzene once again afforded good yields of the desired tricyclic products **15a**[11,15] and **15b**,[11] both of which possess a functionalized taxane ABC ring system. Furthermore, the latter compound also exhibits a configurationally correct oxygen function at C-2 (taxane numbering). It is also interesting to note that a transannular acetal formed spontaneously in both cases, which results in conformationally rigid and facially biased products that can be amenable to subsequent stereoselective manipulation.

In conclusion, these model studies illustrate that bicyclo[4.4.1]undecane intermediates, easily prepared from metal-promoted higher-order cycloaddition, can be transformed into key elements of the related ingenane and tigliane diterpene families. Extension of this concept to include the rapid assembly of the structurally unrelated taxane system has also been achieved.

Acknowledgment. The authors wish to thank the National Institutes of Health for their generous support of this investigation.

Supporting Information Available: Experimental procedures and complete spectroscopic data for compounds **5a,b**, **6–11**, **13a,b**, **14a,b**, and **15a,b** (21 pages).

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(14) Eucarvone is readily available from carvone via a two-step sequence: Ayer, W. A.; Browne, L. M. *Can. J. Chem.* **1974**, 1352.

(15) The structure of this compound was confirmed by single-crystal X-ray analysis.

(16) Access to the taxane system via a different α-ketol rearrangement has been reported: Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772.

(17) Block, E.; Aslam, M. *Org. Synth.* **1987**, *65*, 90.

(18) Jacquier, R.; Petrus, C.; Petrus, F.; Valentin, M. *Bull. Soc. Chim. Fr.* **1970**, 2678. An improved procedure for the preparation of this diene will be reported in due time.

(19) The epoxide function also served to preclude other undesirable rearrangement pathways that prevailed under certain circumstances in its absence.