Synthesis of the Unusual Diterpenoid Tropones Hainanolidol and Harringtonolide

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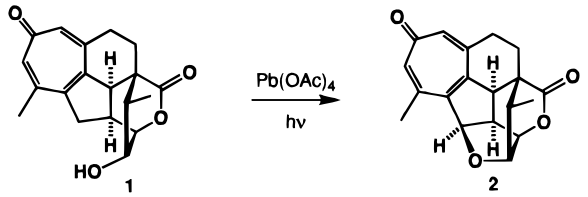
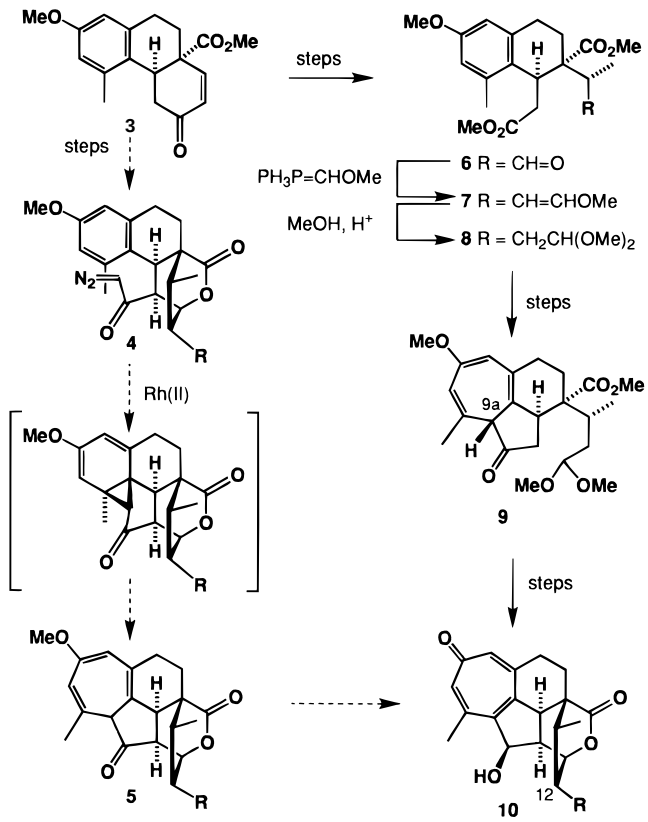
The diterpenoid tropone, harringtonolide (**2**), was first isolated in North America from seeds of *Cephalotaxus harringtonia* (Taxaceae), and its structure was established by X-ray crystallography.[1] It was shown to be an inhibitor of plant growth in tobacco and beans, also causing necrosis under some conditions. At about the same time, **2** was independently discovered in the bark of the related Chinese species *Cephalotaxus hainanensis*, given the name hainanolide,[2] and found to have antineoplastic and antiviral properties.[3,4] In *C. hainanensis*, **2** was accompanied by the closely related, but biologically inactive carbinol, hainanolidol (**1**), the structure of which was established by conversion into **2** by transannular oxidation with lead tetraacetate (Scheme 1).[5] To explore the chemistry and therapeutic potential of these unusual compounds, we have embarked upon a program of total synthesis. Retrosynthetic analysis led logically to the initial proposition that we should base our approach on the sequence **3** → **4** → **5** → **10** → **2** (Scheme 2), the pivotal arene cyclopropanation reaction **4** → **5** being based on the precedents provided by the studies of McKervey and co-workers in simpler systems.[6] Our attempts to prepare **4**, however, were frustrated by the severe steric constraints that prevailed in the "bay" region of the phenanthrene precursors; therefore, we adapted the basic strategy to a more open system, in which the assembly of the lactone group took place after the cyclopropanation stage of the synthesis. The feasibility of this alternative approach was first demonstrated with the preparation of carbinol **10** (R = H) as outlined in Scheme 2,[7] and now we describe how this sequence may be modified to incorporate an additional hydroxyl in the side chain, thereby allowing completion of the syntheses of hainanolidol (**1**) and harringtonolide (**2**) (the latter in a formal sense).

Enol ether **7**, was oxidized with *m*-chloroperoxybenzoic acid in methanol to afford a 3:1 mixture of hydroxy acetal **12** with γ-lactone **11** (Scheme 3). A NOE experiment indicated that the methyl and acetal groups attached to the lactone ring in **11** possessed a trans relationship; thus, the relative stereochemistry of the major product must be as indicated in structure **12**. In this latter case, lactonization was presumably inhibited by the requirement for the methyl and acetal groups to adopt an eclipsed conformation in the transition state leading to the cis isomer corresponding to **11**. Following protection[8] of **12** as its *tert*-butyldimethylsilyl (TBDMS) ether,[9] selective hydrolysis of the primary methyl ester function in this intermediate proved to be routine, but preparation of diazoketone **13a** was troublesome. The diazoketone precursor to **9** had been prepared using the mixed carbonate anhydride method so as to cater for the lability of the acetal function toward acid,[7] but the equivalent anhydride in the present series failed to react with diazomethane. The acid chloride was therefore prepared by treating the sodium carboxylate with Vilsmeier reagent and adding the reaction mixture directly to an excess of diazomethane,[10] affording **13a** in 80% overall yield from **12**. Cyclopropanation catalyzed by rhodium mandelate[11] then furnished an unstable adduct that was immediately treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[12] to give the less labile cycloheptatriene **14a** (84% overall yield).

Scheme 1



Scheme 2



(1) Buta, J. G.; Flippen, J. L.; Lusby, W. R. *J. Org. Chem.* **1978**, *49*, 1002−1003.

(2) Sun, N.; Xue, Z.; Liang, X.; Huang, L. *Acta Pharm. Sin.* **1979**, *14*, 39−43.

(3) Harringtonolide is active against Lewis lung carcinoma, Walker carcinoma, Sarcoma-180, and L-1210, L-615, and P-388 leukemias. It also shows in vitro activity against influenza type A, Newcastle disease, Japanese B encephalitis, and vaccinia viruses.

(4) Kang, S.; Cai, S.; Teng, L. *Acta Pharm. Sin.* **1981**, *16*, 867−868.

(5) Xue, X.; Sun, N.; Liang, X. *Acta Pharm. Sin.* **1982**, *17*, 236−237.

(6) McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129−131. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.

(7) Rogers, D. H.; Morris, J. C.; Roden, F. S.; Frey, B.; King, G. R.; Russkamp, F.-W.; Bell, R. A.; Mander, L. N. *Pure Appl. Chem.* **1996**, *68*, 515−522.

(8) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1985**, *22*, 3455−3458.

(9) Formation of silyl ethers was effected in all cases using silyl triflates, cf.: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz., A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1−26.

(10) The mixed anhydride method is normally satisfactory for primary acids, but less so for more hindered systems. The present procedure ensures that intermediates are not exposed to the traces of adventitious HCl that are likely to accompany the isolation of the acyl chloride and has proved to be generally effective for very acid-sensitive substrates.

(11) (a) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1028−1030. (b) Agaskar, P. A.; Cotton, F. A.; Falvello, L. R.; Hahn, S. *J. Am. Chem. Soc.* **1986**, *108*, 1214−1223.

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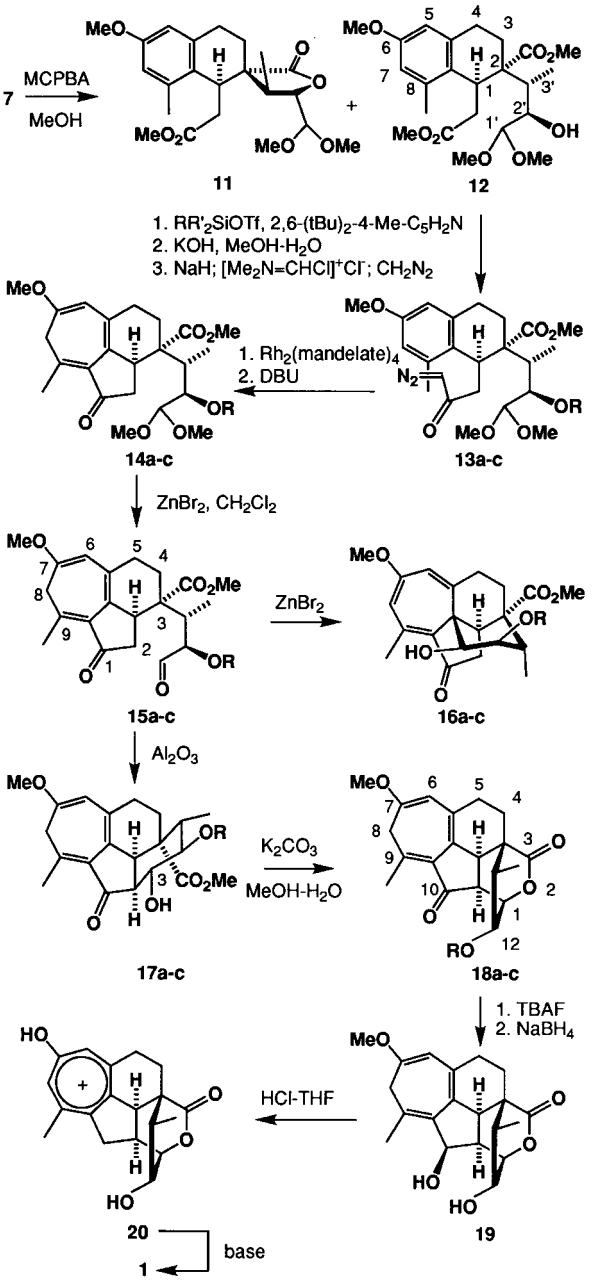
Scheme 3[a]



[a] Key for structures **12**−**18**: **a**, R = tBu(Me)$_2$Si; **b**, R = iPr(Me)$_2$Si; **c**, R = iPr(Et)$_2$Si.

In the expectation that chelation between the silyl ether and acetal functions might assist in the liberation of the aldehyde function from the dimethyl acetal, **14a** was treated with $ZnBr_2$. Initial experiments with this reagent afforded **16a**[13] via a Mukaiyama-like aldol process,[14] but with more carefully controlled conditions, aldehyde **15a** could be obtained as the major product (61% net), and subsequent exposure to basic alumina gave the desired aldol **17a** (76%).[15] Treatment with K_2CO_3 in aqueous methanol then furnished lactone **18a** in 33% yield (65% based on recovered **17a**). As a consequence of the lactonization step, however, the TBDMS function is folded into a very hindered environment, and subsequent difficulties with desilylation prompted us to examine the more labile isopropyldimethylsilyl[16] and diethylisopropylsilyl (DEIPS)[17] protecting groups, of which the latter ultimately proved to be the more satisfactory.[18] Yields previously obtained with the TBDMS group could be reproduced for the sequence **13c** → **18c** and then desilylation was effected smoothly with tetrabutylammonium fluoride (TBAF). The resulting ketone[19] was reduced with sodium borohydride to diol **19**[21] which, when briefly exposed to acid, afforded in >50% overall yield a product with ^{1}H NMR and mass spectral data matching those reported[2] for hainanolidol (**1**).[23] The formation of the tropone moiety, coupled with deletion of the C(10) functionality in this way, depends very much on the stability of the tropylium moiety which provides a "thermodynamic sink" for the possible reaction processes. Thus, the allylic hydroxyl in **19** presumably undergoes ionization on exposure to acid to form various double-bond isomers which then rearrange to form **20**. The process has been successfully duplicated in a number of other hydroxy cycloheptatrienes and therefore provides a new general method for tropone synthesis.

In view of the conversion outlined in Scheme 1, the preparation of **1** also constitutes a formal synthesis of harringtonolide (**2**).[24] These syntheses demonstrate yet again the utility and rich potential afforded by benzenoid synthons for the construction of polycyclic natural products.[25]

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Supporting Information Available: Experimental and ^{1}H and ^{13}C NMR spectral data for compounds **1**, **11**−**19**, and synthetic intermediates (34 pages). See any current masthead page for ordering information and Web access instructions.

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(12) Consideration of the geometry of the alternative transition states indicates that cyclopropanation on the β-face of the aryl ring should be clearly preferred over α-face addition; therefore, the primary adduct may be presumed to have the same relative stereochemistry as **9**, although this is of no consequence to the final objective. More importantly, because H(9a) is flanked by two double bonds and the C(1) carbonyl group, it appears especially vulnerable to attack by adventitious O_2. Conjugation of the Δ^8 alkene bond (DBU) to give **14** improves stability to a certain extent.

(13) This structure was determined by single-crystal X-ray crystallography, details of which will be published elsewhere.

(14) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331.

(15) Only the equatorial 3α-epimer ($\delta_{3\beta H}$ 3.14, $J_{3,2}$ = 8.7 Hz, $J_{3,3a}$ = 10.2 Hz, $J_{3,OH}$ = 2.1 Hz) was detected, suggesting that the aldol process is under thermodynamic control. Cf.: White, J. M.; Rogers, D. H.; Mander, L. N. *Acta Crystallogr.* **1991**, *C47*, 2254−2256.

(16) Corey, E. J.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 7319−7320.

(17) Toshima, K.; Mukaiyama, S.; Kinoshita, M.; Tatsuta, K. *Tetrahedron Lett.* **1989**, *30*, 6413−6416.

(18) For the sequence **12** → **18**, the isopropyldimethylsilyl derivatives gave similar outcomes to those obtained with the TBDMS group except for the hydrolysis of the dimethyl acetal function in **14b**, which furnished only a 20% yield of **15b**.

(19) There was the prospect that this ketone might cyclize to the corresponding hemiacetal, which could then be deoxygenated[20] to afford an immediate precursor to harringtonolide, but there was no indication of acetal formation.

(20) (a) Barton, D. H. R.; Hartwig, W.; Motherwell, R. S. H.; Motherwell, W. B.; Stang, A. *Tetrahedron Lett.* **1982**, *23*, 2019−2022. (b) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.

(21) Steric shielding of the upper face of the cyclopentanone ring steers the approach of reagents to the lower face. Attempts to reverse the stereochemical outcome by means of a directed reduction using $[Me_4N]^+[(AcO)_3BH]^-$ and obtain the preferred 10α-epimer (which would allow ether formation by an S_N2 process) were unproductive.[22]

(22) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578. (b) Bhaskar, K. V.; Mander, L. N. *Tetrahedron Lett.* **1996**, *37*, 719−722.

(23) It has not been possible to obtain a sample of natural hainanolidol for direct comparison.

(24) Continuing studies are being directed towards an alternative route to **2** via the 12-epimer of **19**, from which it should be feasible to form the ether ring by an S_N2 process. Subsequent oxidation of the triene system with $Hg(NO_3)_2$, as already established in model systems and in the preparation of tropone **10**,[7] should then afford **2**. Preliminary experiments have shown that with due care, lactone **11** may be converted into 2′-*epi*-**12** and its derived TBDMS ether. Although **11** is the minor product from dihydroxylation of **7**, dihydroxylation of the simple vinyl 8-desmethyl analogue of **7** has been shown to afford a single hydroxymethyl lactone (85% yield) with the same relative stereochemistry as **11**.

(25) (a) Mander, L. N. *Synlett* **1991**, 134−144. (b) King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C.; Zhang, H. *J. Am. Chem. Soc.* **1997**, *119*, 3828−3829.