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STUDIES ON TUMOR PROMOTERS. 10.[1] SYNTHESIS OF THE ABC RING SYSTEM OF THE TIGLIANES AND DAPHNANES BY A ZIRCONIUM-MEDIATED INTRAMOLECULAR ENYNE CARBOCYCLIZATION

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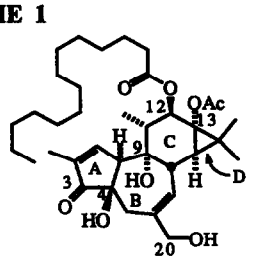
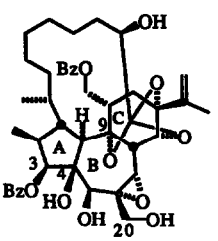
Abstract: A novel synthetic route to the ABC ring system of the daphnanes and tiglianes based on intramolecular enyne carbocyclization is described that provides access to a new family of diterpene tumor promoter analogs.

Phorbol 12-myristate 13-acetate has long been of interest in cancer research as one of the most potent tumor promoters in multistage carcinogenesis.[2] More recently, phorbol esters and structurally analogous daphnanes and ingenanes (Scheme 1) have also been found to exhibit a wide array of other biological activities, providing new leads for chemotherapeutic design. The regulatory enzyme protein kinase C (PKC) has been identified as the primary receptor for many of these compounds.[3]

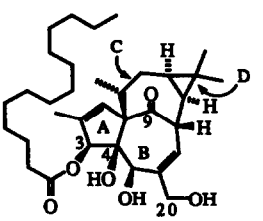
SCHEME 1



phorbol 12-myristate 13-acetate (tigliane)



gnidimacrin (daphnane)



ingenol 3-tetradecanoate (ingenane)

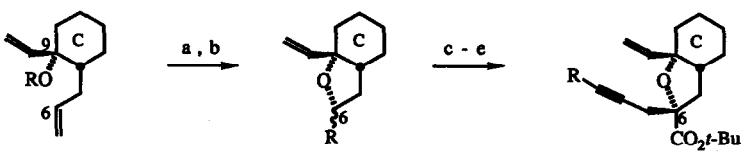
Computer modelling studies conducted in our laboratory have led to the identification of functionality arrays common to these diterpene families as well as structurally unrelated PKC activators, providing the basis for understanding their similar enzymic recognition. Our best correlation of atomic coordinates and orbital interactions is obtained for the respective C3 and/or C4, C9, and C20 oxygens of the diterpenes. A hypothesis for the spatial orientation of the lipophilic group between the A and C rings has also been formulated through these correlations.[4]

In an effort to advance our understanding of the functionality requirements for diterpene recognition by the PKC receptor and to establish simplified synthetic routes to these important diterpene families, we considered bicyclization approaches which would directly produce the AB ring system of the tigliane and daphnane families. The intramolecular enyne carbocyclization[5] of systems such as **9** (Scheme 2) appeared to be particularly promising. We expected that the enyne substrate could be readily derived from simple cyclohexane derivatives, and that the cyclopentenone product would allow access to various functionality arrays in the A ring. At a more fundamental level, this approach provided an opportunity to test whether the intramolecular enyne carbocyclization could be extended to the synthesis of hydroazulenes. The entropic problems that generally

disfavor direct closures to seven-membered rings in such reactions were expected to be minimized by incorporation of an ether bridge in the enyne substrate.

The examination of this strategy began with the known dienol **4**, derived in two steps from cyclohexanone (Scheme 2).[6] Regioselective epoxidation of the trimethylsilyl ether **5** followed by aqueous acid treatment afforded the alcohols **6** in 68% yield (two steps), as a 2:1 epimeric mixture. Jones oxidation and esterification of the crude acid **7** gave the *t*-butyl esters **8** in 72% yield (two steps). The alkyne was introduced by alkylation of the lithium enolate of **8** with 1-bromo-3-trimethylsilyl-2-propyne[7] in the presence of four equivalents of HMPA to provide an inseparable 3.9:1 mixture of enyne **9** and its C6 epimer in 61% yield.

SCHEME 2



4 R = H
5 R = TMS

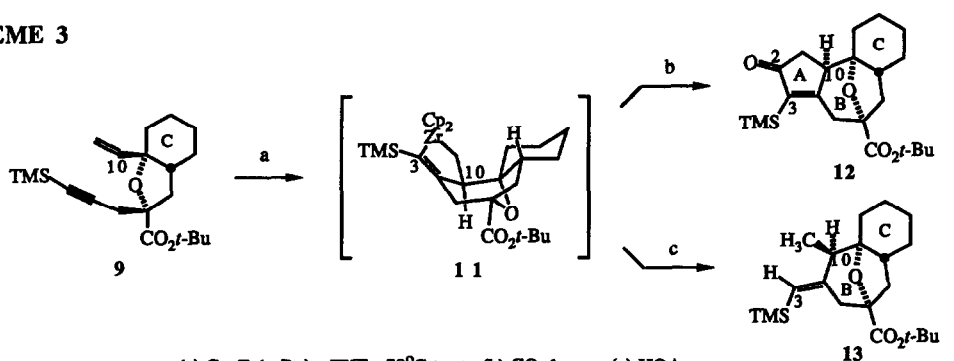
6 R = CH_2OH
7 R = CO_2H
8 R = CO_2t-Bu

9 R = TMS
10 R = H

(a) TMS-Imidazole (neat), 70°C. (b) *m*-CPBA, CH_2Cl_2, 0°C; then aq. *p*-TsOH. (c) H_2CrO_4 / aq. H_2SO_4, acetone, 0°C. (d) $(CH_3)_2C{=}CH_2$, cat. H_2SO_4, rt. (e) LDA, THF, HMPA, -78°C; then 3-TMS-2-propynyl-1-bromide, -78°C to rt. (f) K_2CO_3, MeOH.

Pauson-Khand carbocyclizations ($Co_2(CO)_8$, CO, heat)[5a] of silylated substrate **9** as well as the terminal alkyne **10** were unsuccessful. The predominant side reaction appeared to be fragmentation of the propargylic moiety of the enyne. However, the zirconocene-based procedure developed by Negishi[5b] proved satisfactory for this transformation (Scheme 3). Treatment of enyne **9** with $Cp_2Zr(n\text{-}Bu)_2$ followed by carbonylation provided enone **12** in 29% yield as a single stereoisomer. Acetic acid protonation of the intermediate zirconacycle **11** afforded **13**, in 25% yield.

SCHEME 3



9

11

12

13

(a) $Cp_2Zr(n\text{-}Bu)_2$, THF, -78°C to rt. (b) CO, 1 atm. (c) HOAc.

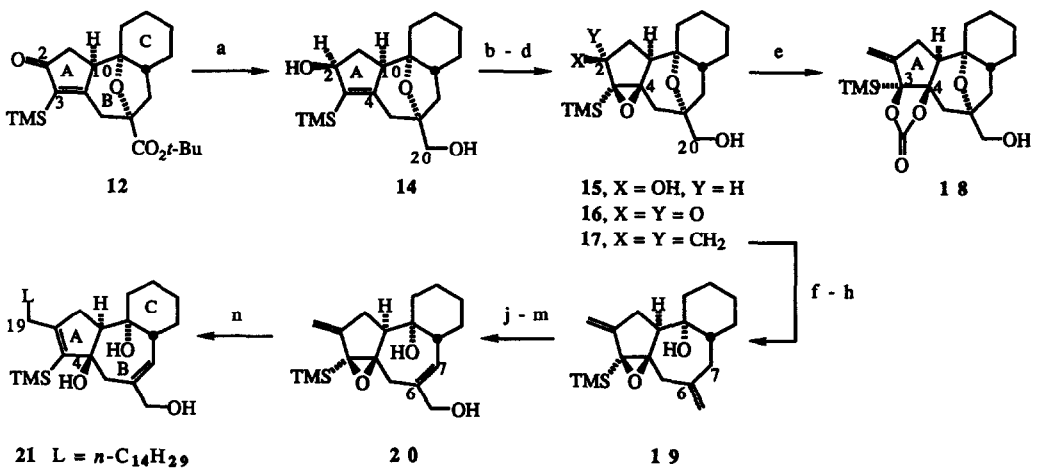
The stereochemistry at C10 was assigned from the observed allylic coupling (1.8 Hz) between the hydrogens at C3 and C10 in the protonolysis product **13**, indicative of an axial C10 hydrogen.[8] This result is

also in accord with computer modelling studies (Macromodel 2.0), which indicate that enone **12** is nearly 5 kcal/mol lower in energy than its C10 epimer. This energy difference, which is also expected in the zirconacycle intermediates, is attributed to the observation that zirconacycle **11** has a chair pyran ring, while the pyran ring in the C10-epimeric zirconacycle would be boat-like.

As illustrated in Scheme 4, cycloadduct **12** provides ready access to tigliane and daphnane analogs. Reduction of **12** with diisobutylaluminum hydride (DIBAL) gave the diol **14** as a single isomer in 70% yield, consistent with hydride addition from the convex face of the AB ring system. The resultant C2 β-OH allows for directed introduction of the C3 and C4 oxygens. Thus vanadium-catalyzed directed epoxidation[9] gave a single epoxide **15** (60% yield), as well as small amounts of a cyclopentenone byproduct from oxidation at C2. The yield of epoxide relative to enone was optimized by the addition of 3Å sieves to the epoxidation reaction mixture. Regioselective oxidation of the secondary alcohol of **15** with one equivalent of pyridinium chlorochromate (PCC)[10] afforded the ketone **16** in 70% yield (less than 5% of the keto-aldehyde overoxidation product was found). Wittig methylenation[11] provided a 71% yield of the vinyloxirane **17**.

At this stage, the vinyloxirane **17** was reacted with carbon dioxide under palladium (O) catalysis[12] to give a 50% yield of the cyclic carbonate **18**. This reaction sequence provides for the stereocontrolled introduction of the *cis*-diol functionality of the daphnanes as well as the related ingenanes and may be applied to functionalization of A-ring cyclopentenones afforded by the intramolecular aldol condensation approaches to ingenanes reported by Rigby and Mehta.[13] Alternatively, the C6-C7 alkene was introduced starting with **17** by use of a protocol previously reported by our group.[1b,14] The durability of the A-ring vinyloxirane moiety to a variety of basic and nucleophilic conditions in this sequence is noteworthy (Scheme 4).

SCHEME 4



(a) DIBAL, toluene, -78°C to rt. (b) cat. $VO(acac)_2$, *t*-BuOOH, 3Å sieves, toluene. (c) PCC, CH_2Cl_2. (d) $Ph_3P{=}CH_2$, THF. (e) cat. $Pd(OAc)_2$/BuLi, $P(O\text{-}iPr)_3$, THF, CO_2 (50 psi), 40°C. (f) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0°C. (g) $(n\text{-}Bu)_4NBr$, THF, reflux. (h) *n*-BuLi, THF, -78°C. (j) SeO_2, *t*-BuOOH, CH_2Cl_2, 0°C. (k) $SOCl_2$, propylene oxide, Et_2O, 0°C. (l) AgOAc, KOAc/TMEDA, MeCN. (m) K_2CO_3, aq. MeOH. (n) $(n\text{-}C_{14}H_{29})_2CuLi$, Et_2O, -40°C.

We have proposed that the lipophilic group of the biologically active diterpenes is situated between the A and C rings (see Scheme 1).[4b] The functionality in **20** was designed to allow a similar disposition of a hydrocarbon chain such that S_N2' addition to the terminus of the vinyloxirane[15] would attach such a group to C2. We found that treatment of **20** with an excess of di(*n*-tetradecyl)copper lithium gave the corresponding analog **21** in approximately 50% yield. Similar results were obtained with the cuprates derived from *n*-butyllithium and *n*-decyllithium.

In summary, we have established methodology for the synthesis of a family of simple tigliane-daphnane analogs **21** based on a zirconium-mediated enyne carbocyclization. This work demonstrates both the extension of the carbocyclization methodology to cycloheptanoid synthesis and the control of stereochemistry[16] from a preexisting ring system with the zirconocene-mediated carbocyclization reaction.

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