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AN APPROACH TO THE TIGLIANES, DAPHNANES, AND INGENANES VIA THE DIVINYLCYCLOPROPANE REARRANGEMENT

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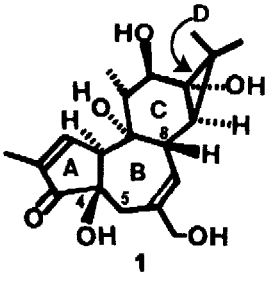
The divinylcyclopropane rearrangement has been shown to be of considerable potential in the construction of the backbone of the tigliane, daphnane, and ingenane families of natural products.

The cis-divinylcyclopropane rearrangement has found increasing use as a method of generating natural products containing a seven-membered carbocycle. First applied to the synthesis of the monocyclic (±)-dictyopterene A,[2] more highly developed methodology[3] for generation of functionalized divinylcyclopropanes has recently extended it to syntheses of (±)-β-himachalene[3c] and the pseudoguaianes (±)-damsinic acid and (±)-confertin.[3e,4]

This rearrangement clearly offers manifold advantages including an efficient and facile method for ring construction as exemplified by the previously noted syntheses and, as a consequence of its endo transition state,[5] a mechanism for controlling ring stereochemistry. The confluence of these elements as suggested in Scheme I and elaborated herein is expected to figure significantly in our synthesis studies on the tri- and tetracyclic diterpenes of the pharmacologically fascinating tigliane, daphnane, and ingenane families.[6] In particular, it is

Scheme I



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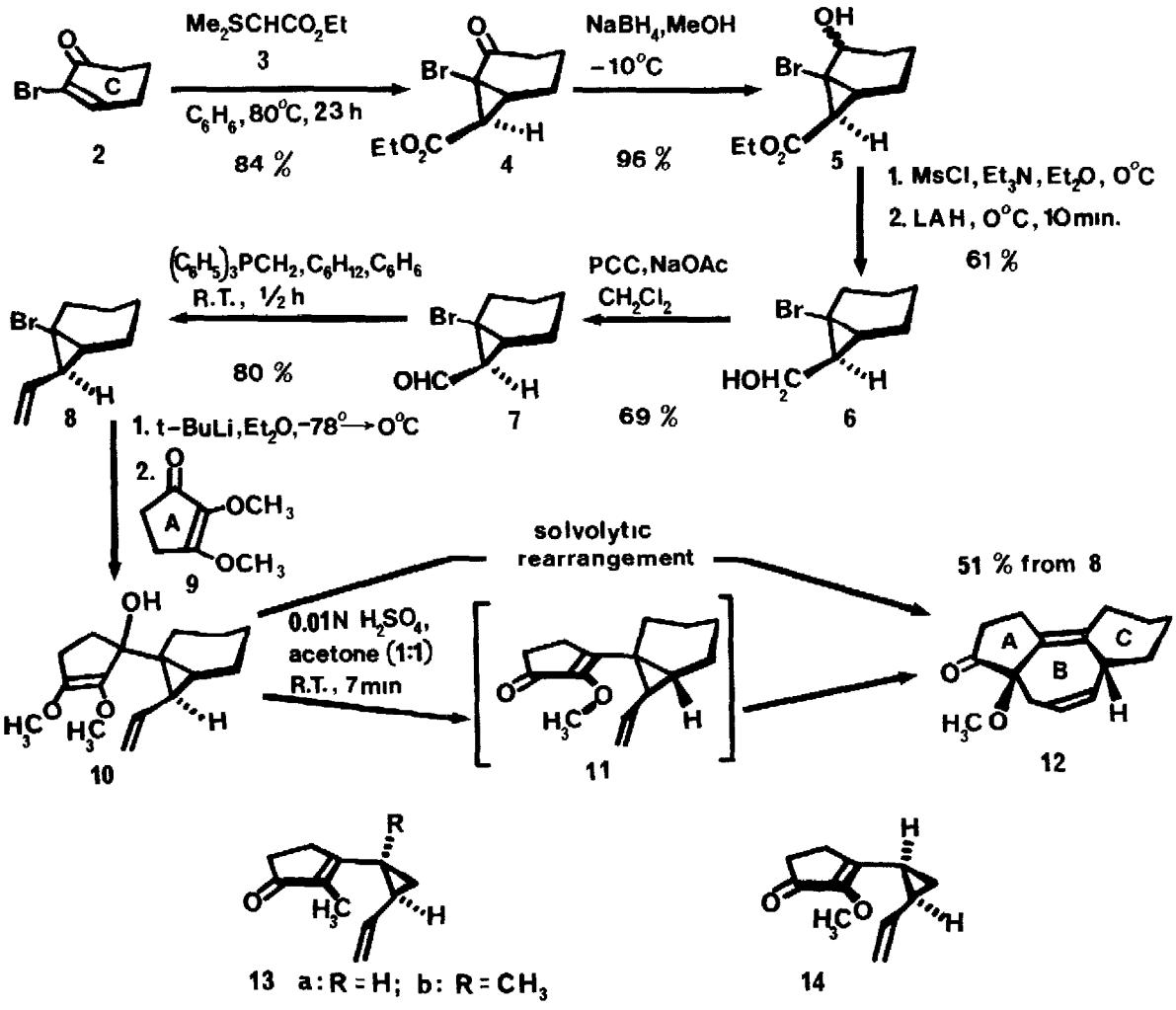
expected that the C ring stereochemistry generated under the steric influence of the D ring appendages could be used to uniquely control the stereochemistry developed at C-4 (and by extension C-5). This stereochemistry may be otherwise difficult to generate, in the case of the tigliane phorbol (1), the C-4 α-OH stereochemistry appears to be thermodynamically preferred.[7] As a consequence of this stereoinduction, the synthetic problem would be reduced to the less formidable objective of preparing a suitably functionalized C ring precursor, i.e., cyclohexane synthesis.

No divinylcyclopropanes similar to those required for the tigliane, daphnane, and ingenane precursors have been reported. Furthermore, while the obvious approach to these families would require an oxygen-based substituent (or its equivalent) at C-4 of the divinylcyclopropane (Scheme I), the steric and electronic influence of such a unit on the rearrangement was unknown. n-Alkyl groups at this position are known to greatly retard but not preclude the rearrangement.[8] For the purposes of this preliminary study, the 1-bromo-2-vinylcyclopropane 8 needed for the preparation of a suitable model system (i e., 11) was constructed via the following six-step sequence.[3d,9]



Condensation of the α-bromoenone 2[10] with the sulfur ylid 3[11] in dry benzene resulted in a 84% yield of the adduct 4,[12] with no endo isomer detected. This remarkably high stereoselectivity is somewhat surprising in view of the 2 : 1 ratio reported for addition to cyclohexenone.[11] The efficiency of the reaction of this ylid (3) with 2 is also noteworthy in that its reaction with ethyl α-bromoacrylate and α-bromoacrylonitrile has been reported[13] to occur in progressively much poorer yields due to a prototropic shift after conjugate addition of the ylid, resulting in bromide rather than dimethylsulfide displacement. Analogously, the major isolable byproduct from our reaction is a methyl thioether presumably formed by prototropic shift, bromide displacement, and then bromide nucleophilic attack on a sulfonium methyl. Its formation was found to be minimized by performing the reaction at the highest temperature compatible with the stability of the ylid, ca. 80°C. Thus, the success in our example can perhaps be ascribed to the lower basicity of ketone versus nitrile and ester enolates.[14]

The ketoester 4 was reduced by sodium borohydride to a mixture of epimeric alcohols 5.[15]

Mesylation[16] of 5 followed in the same flask by addition of excess lithium aluminum hydride gave the alcohol 6[17] in 59% yield from the ketoester. Oxidation of 6 with sodium acetate-buffered pyridinium chlorochromate[18] provided the aldehyde 7,[19] which upon reaction with the methylene Wittig reagent generated[20] from methyltriphenylphosphonium bromide in benzene and potassium t-amylate in cyclohexane[21] furnished the required 1-bromo-2-vinylcyclopropane 8,[22] a somewhat light-sensitive, unstable liquid.

The other precursor, 2,3-dimethoxy-2-cyclopentenone 9,[23] was obtained in 74% yield by treatment of finely ground 2,3-dihydroxy-2-cyclopentenone with excess diazomethane in tetrahydrofuran at 4°C for 14 hours and then quenching with excess methanol.[24] Metal-halogen exchange between bromovinylcyclopropane 8 and t-butyllithium followed by addition of the ketone 9 gave the 1,2-adduct 10. Room temperature acidic hydrolysis immediately after isolation of the crude product gave a 51% yield of the crystalline, air-sensitive,[25] tricyclic methoxyketone 12,[26] without any indication of its divinylcyclopropane precursor 11.

In regard to the facility of this rearrangement and its more general synthetic consequences, it is of interest to note that divinylcyclopropane 13a has been previously found to have a half-life of 316 hours at room temperature (23-25°C) and 33 minutes at 80°C. Replacing the hydrogen on the cyclopropane geminal to the enone with a methyl group 13b results in a reduction of room temperature halflife to 54 hours and at 56.5°C, 96 minutes.[27] For comparison purposes the α-methoxyenone 14 was prepared in connection with this study and found to rearrange with a half-life of only 9.3 hours at room temperature and 17 minutes at 57.0°C. These cursory kinetics studies are not complete or accurate enough to determine the change in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as a function of substituents, nevertheless they do suggest that the replacement of the cis-methyl group with oxygen-based functionality and the increased alkyl substitution of the cyclopropane ring may both contribute to the reduction of the halflife of 11. Alternatively, 12 may be formed via a solvolytic Cope rearrangement mechanism.[28]

This preliminary study has verified that the divinylcyclopropane rearrangement provides a promising route to the tiglianes, daphnanes, and ingenanes. Research on the mechanistic and synthetic ramifications of this study is in progress.

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References and Notes

1. (a) Fellow of the Alfred P. Sloan Foundation, 1979-1981, (b) National Science Foundation Predoctoral Fellow, 1975-1978, (c) Harvard University Undergraduate Research Participant, 1979.

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8 See references 2, 3b-e, and 5b.

9. Products were purified by "flash" column chromatography (W.C Still, M. Kahn & A. Mitra, J. Org. Chem., 43, 2923 (1978)). All new compounds reported were homogenous by TLC and gave satisfactory IR and NMR spectra and exact mass or combustion analyses.

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12. 4 IR(CCl_4) 1740(s), 1720(s) cm^{-1}, NMR($CDCl_3$) δ4 21(q,J=7.2 Hz,2H), 1 29 (t.J=7.2 Hz,3H).

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15. Epimers 5a & b were formed in a 1·2 ratio. 5a,b: IR(CCl_4) 1740(vs) cm^{-1}, NMR($CDCl_3$) 5a· δ4.21(q,J=7.1 Hz, 2H) superimposed on m(1H), 1 29(t,J=7.1 Hz,3H), 5b· 4.2-4 5(m,1H), 4 20 (q,J=7.2 Hz,2H), 1 29(t,J=7.2 Hz,3H).

16 D.K. Crossland & K.L. Servis, J. Org. Chem., 35, 3195 (1970) (Et_2O instead of CH_2Cl_2).

17. 6: NMR($CDCl_3$) δ3.96(dd,J=11.8,5.3 Hz,1H), 3.59(dd, J=11 8,8.4 Hz,1H), 1.84(s,1H).

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25. A sample of pure product left exposed to ambient conditions over several days substantially decomposed to low R_f material The rearrangement products of 13a & b are also found to be prone to air oxidation (M.P. Filosa, private communication) Phorbol itself is rather air sensitive and its oxidation has at least been partly elucidated (R. Schmidt & E. Hecker, Cancer Res., 35, 1375 (1975)).

26. 12: IR(CCl_4) 1745(vs), 1705(w) cm^{-1}, NMR($CDCl_3$) δ5.4-5.7(m,2H), 3.13(s,3H), UV(CH_3CN) 238 nm (ε_{max}3000); mp(uncorr.) 52-53°.

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