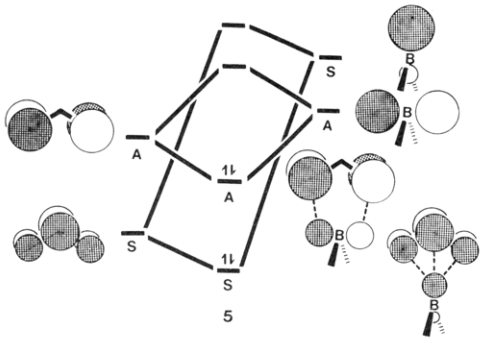

Figure 2. A qualitative PMO orbital correlation diagram for the allylborane automerization transition-state **5** derived by interaction of the allyl and BH_2 fragments. Both the symmetric (S) and antisymmetric (A) MO's describing the bonding to boron are stabilized. The S combination necessarily incorporates cross-ring bonding.

at C_3. Nonetheless, we take the large barrier as a qualitative reflection of the difficulty to concerted rearrangement apparently experienced by allylamines.[5]

To obtain some insight into the possibility for pseudopericyclic behavior in the amine system, we constructed an optimized PRDDO–ST pathway in C_s symmetry from the cyclic intermediate **4** to separated NH_2 and allyl radicals via SCF–CI and GVB–CI calculations.[10] Although the energy varies little, the nitrogen lone pair utilization is rapidly dissipated. At r(N–C) = 1.69 and 1.92 Å, for example, the APS valencies at N and the N–C bond orders have fallen to 3.5/0.68 and 3.1/0.50, characteristic of pseudopericyclic and pericyclic transition states, respectively. The molecular orbitals of the latter point are just those expected for a genuine pericyclic shift. This result suggests the existence of a very restricted range of transition-state geometries for which the postulated pseudopericyclic character can be expected to be manifested when nitrogen is the migrating atom. The situation is reminiscent of the geometrical determination of transition-state character found for the rearrangements of bicyclies **6**,[4] where only pericyclic-shift intermediate structures are geometrically accessible.

The single step, concerted rearrangement of allylborane **3** via transition-state **5**, exhibits a change in the valency of boron from 3.1 (at **3**) to 3.8 (at **5**) accompanied by a B–C bond order variation from 1.01/0.03 to 0.73/0.73. In this case, C_3 (**5**) develops only a slight positive charge (–0.01 → 0.13) in accord with a transannular B–C_3 bond order of 0.37 and a charge at boron of –0.23. The optimized C_s transition state (Figure 1), in contrast to the nitrogen analogue, is strongly puckered such that the B–C_3 distance is only 1.725 Å (vs. r(B–C_2) = 1.553 Å for PRDDO-optimized allylborane). Pentacoordination at boron, a well-known tendency for this element,[11] is clearly signified. The excellent agreement between the calculated energy barrier for **3** (11 kcal/mol) and the observed $\Delta H^{\ddagger}$ values for dialkylallylboranes (10–15 kcal/mol[6]) is undoubtedly fortuitous. Nevertheless, the much reduced energy requirement for cyclization of **3** relative to **2** can be attributed to the additional cross-ring bonding in the former. Previous workers have clearly recognized the concerted nature of the 1,3-boron migration, though they have consistently depicted the transition state as a monocyclic entity (e.g., **7**).[6]

In contrast to the NH_2 analogue, the transition-state **5** is cyclically delocalized (cf. the APS bond orders in Figure 1). Moreover, a clear pseudopericyclic interchange of orbital roles is indicated in the localized MO framework. Specifically, the bonding to boron in **5** is described by a symmetrically related pair of B,C_2,C_3 and B,C_4,C_3 three-center LMO's. When **5** is converted to **3** (or **3'**) the first (or second) such LMO transforms into the B–C_2 (or B–C_4) bond orbital, while the second (or first) gives rise to the C=C π bond and simultaneously liberates the formally vacant p orbital on boron.

The BH_2 automerization would thus seem to conform to the pseudopericyclic model. A difficulty arises, however, because Lemal and co-workers have defined the concept in terms of a "(mono)cyclically delocalized transition state",[3a] whereas **5** is bicyclically delocalized. Nevertheless, the borane rearrangement in our view can be regarded as pseudopericyclic. This assessment is based on a consideration of the shape of the "orbital interchange" LMO's. On the NH_2 pathway, pure two-center N–C_2 and N–C_4 orbitals are found in **4**. As a result, two full N–C bonds are reflected, C_3 carries a localized electron lone pair, and cyclic delocalization is absent; the rearrangement is not pseudopericyclic. Two center B–C_2 and B–C_4 LMO's might also arise in the transition state for the BH_2 reaction, but C_3 would then carry a formally vacant orbital and a formal positive charge. In fact, the B–C_2, B–C_4 LMO's diffuse onto C_3, producing cyclic delocalization *together with and inseparable from* a strong cross-ring B–C_3 interaction. Figure 2 illustrates an equivalent description in the alternative canonical (delocalized) MO framework in terms of the interaction of the S and A group orbitals of allyl and BH_2 in **5**. Hence, *a pseudopericyclic interchange of orbital roles via a cyclically delocalized transition state necessitates a strong transannular interaction when the nonbonding orbital in question is empty.*

Our investigations of this concept continue. In particular, the differences among and between first and second row shift species and the question of d orbitals are being taken up.

Acknowledgment. We are grateful to the Danish Natural Science Research Council for generous provision of computer facilities (J.nr.11-0923).

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A New Protocol for Stereocontrolled Lactone Annulation

Summary: Through regiocontrolled alkylation of cyclopentanone enolates with methyl 4-bromo-3-methoxycrotonate, base-promoted cyclization, and ketalization, α,β-unsaturated esters having a diquinane molecular framework are produced. Controlled reduction of the

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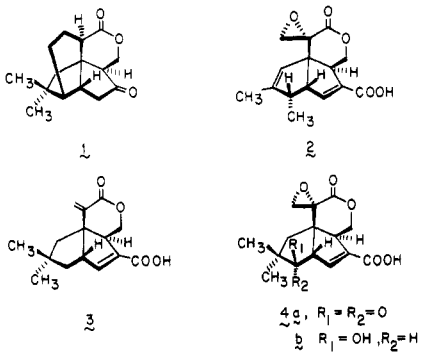
carbalkoxy group, application of the Claisen rearrangement, and implementation of an intramolecular Michael addition–oxidation sequence completes a scheme which leads efficiently to tricyclic lactones having structural features common to a number of sesquiterpenoid natural products.

Sir: In recent years, various strains of *Aspergillus* and *Streptomyces* have come to be recognized as producers of structurally novel tri- and tetracyclic lactones which in common share a diquinane[1] backbone. Included in this group are the antitumor agent quadrone (**1**),[2,3] the lipophilic antibiotic pentalenolactone (**2**),[4,5] and various shunt metabolites arising during biosynthesis of the latter such as pentalenolactones E (**3**),[6] G (**4a**),[7] and H (**4b**).[8] In the

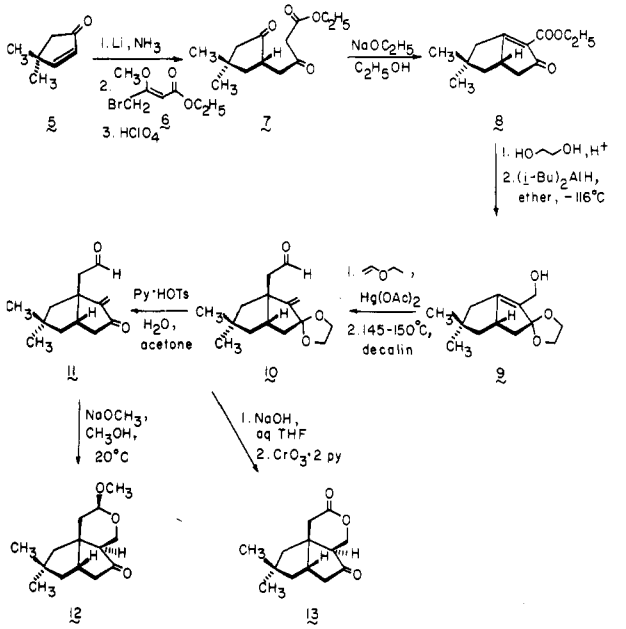


1 **2** **3** **4** a, $R_1 = R_2 = O$; b, $R_1 = OH, R_2 = H$

context of a synthetic program targeted at various polyquinane natural products,[9] we have developed a relatively simple and perhaps general solution to the problem of incorporating a six-ring lactone into such a matrix. The pivotal operation in our scheme involves *kinetically controlled nucleophilic addition to an aldehyde carbonyl group and ensuing intramolecular capture of the resulting alkoxide function by a proximally positioned α,β-unsaturated ketone Michael acceptor.*

Reduction of 4,4-dimethylcyclopentenone (**5**)[10] with lithium in liquid ammonia[11] gave an enolate which was treated directly with **6**,[12] a γ-electrophilic equivalent of acetoacetate. The diketo ester **7**,[13] which was obtained following hydrolysis with 30% perchloric acid[12b] (85% from **5**), experienced rapid cyclization to **8** (84%) in the presence of ethanolic sodium ethoxide. The protected allylic alcohol **9** was reached by ketalization with ethylene glycol and controlled reduction of the ester functionality [$(i\text{-Bu})_2$AlH, ether, −116 °C].[14] Introduction of a cis-locked acetaldehyde substituent as in **10** was achieved by conventional vinyl ether formation ($CH_2{=}CHOCH_2CH_3$, $Hg(OAc)_2$, 24 h, 82%) and thermal isomerization (decalin, 145–150 °C, 2 h, 69%). After deketalization with pyridinium tosylate[15] in aqueous acetone (20 °C, 2 h, 100%), the highly functionalized bicyclic **11** was isolated [^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.64 (t, J = 2 Hz, 1 H), 6.10 (s, 1 H), 5.33 (s, 1 H), 2.80 (d, J = 2 Hz, 2 H), 2.7–2.0 (m, 3 H), 1.96 (s, 2 H), 1.90–1.71 (m, 1 H), 1.30–1.15 (m, 1 H), 1.09 (s, 3 H), and 1.01 (s, 3 H)].

Molecular models revealed that intramolecular Michael addition within **11** would be especially facilitated upon conversion of the aldehyde carbonyl carbon to a tetrahedral center. For this reason, chemospecific nucleophilic attack at the aldehydo group emerged as an important goal. Were circumstances of this type to be realized, geometric factors within the intermediate serve to position the alkoxide oxygen directly above the π orbital of the enone β carbon. At the experimental level, this plan was simply realized. Thus, addition of methanolic sodium methoxide to a solution of **11** in methanol at room temperature provided **12** (91%) as a single compound believed to be the β-methoxy stereoisomer.[16] Analogously, cyclization of **11** in tetrahydrofuran containing aqueous sodium hydroxide delivered a lactol, Collins oxidation of which gave the desired **13**. The lactone ring protons of **13** were noted to compare



5 **6** **7** **8** **9** **10** **11** **12** **13**

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(16) The stereochemistry of **12** is not known with certainity. The configuration shown in the formula is based upon the less hindered approach of methoxide ion to the aldehyde carbonyl and eventual equatorial orientation of this substituent. The ^{13}C NMR spectrum ($CDCl_3$) consists of 14 lines: 216.75, 100.47, 59.75, 55.69, 54.05, 53.44, 49.19, 47.68, 44.34, 41.24, 40.51 (2C), 31.11, and 30.44 ppm.

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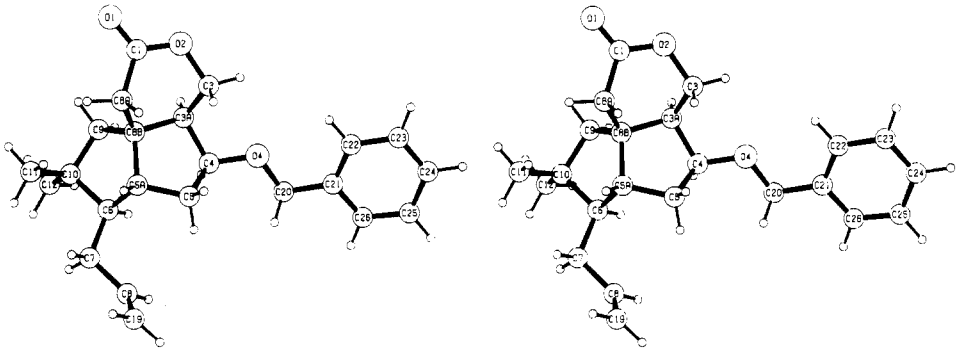
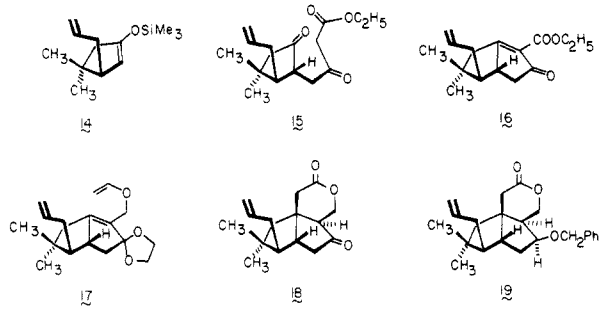


Figure 1. Computer-generated stereodrawing of **19** as determined by X-ray analysis.

closely to those of **3**,[6] thereby suggesting that the new chiral center had been properly introduced with the indicated exo stereochemistry. This configurational assignment, which results as a consequence of endo protonation, is established below.

Incorporation of additional side chains, which can be readily accomplished, offers no drawbacks to this protocol. For example, CuBr·Me_2S-promoted[17] conjugate addition of allylmagnesium bromide[18] to **5**, followed by enolate capture with chlorotrimethylsilane and triethylamine,[19] leads to **14**. Without purification, **14** was treated with lithium amide in ammonia–tetrahydrofuran[19] and processed as before to give **15** (62% from **5**). Noteworthy is



the fact that the allyl group constitutes a stereochemical control element which directs introduction of the sidechain at C_2 exclusively trans. Particularly revealing in this regard is the ^{13}C NMR spectrum of **16** (75%), which gives clear indication of isomeric purity.[20] Upon arrival at **17** [$HOCH_2CH_2OH$, TsOH, C_6H_6, 98%; $(i\text{-}Bu)_2AlH$, ether, −100 °C, 68%; $CH_2{=}CHOCH_2CH_3$, $Hg(OAc)_2$, 90%], the stage was set to evaluate whether the allyl group would seriously impede the Claisen rearrangement. This was not observed, **18** being obtained with an efficiency (68%) comparable to that noted earlier for **10**. Following deketalization (91%), the susceptibility to cyclization was probed. Treatment with sodium hydroxide in aqueous tetrahydrofuran and subsequent Jones oxidation afforded **18** in 52% overall yield. Again, certain features of the ^1H NMR spectrum of this product were strikingly similar to those of pentalenolactone E methyl ester.

Confirmation of the stereochemical features of tricyclic lactones **13** and **18** was achieved by making recourse to X-ray crystal structure analysis. Due to the oily nature of the predescribed substances, attention was turned to the preparation of a suitably crystalline derivative. Success was realized by chemoselective reduction of **18** with *tert*-butylamineborane[21] (THF, 0 °C, 4 h, 70%) and alkylation of the resulting secondary alcohols with benzyl triflate (CH_2Cl_2, −35 °C).[22] The stereochemically homogeneous[23] lactone ether **19** (39%), mp 68.8–69.5 °C, afforded triclinic crystals of space group $P\bar{1}$ with a = 9.172 (3), b = 9.340 (3), c = 13.322 (3) Å, α = 94.14 (2), β = 97.49 (2), γ = 113.94 (2)°, and d_{calcd} = 1.149 g cm^{-3} for Z = 2 ($C_{23}H_{30}O_3$, M = 354.49). A total of 2749 reflections were measured for $\theta < 57°$, of which 2160 were considered observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[24] and was refined by full-matrix least squares. The final discrepancy indices are w = 0.121 and R_w = 0.183 for the 2160 observed reflections. The computer-generated stereodrawing of **19** is presented in Figure 1. Immediately recognized is the all-cis arrangement of the allyl side chain and lactone ring.

The tandem Claisen rearrangement/nucleophile-induced cyclization demonstrated herein holds promise as an important technique for the synthesis of certain sesquiterpenoid lectones. Currently under study, for example, is the feasibility of elaborating pentalenolactone E methyl ester and quadrone from **13** and **18**, respectively.

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Supplementary Material Available: Tables of the final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for **19** (4 pages). Ordering information is given on any current masthead page.

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