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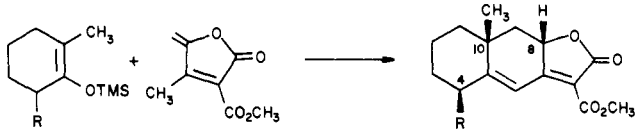
Synthesis of *dl*-7,8-Epialantolactone. A Tandem S_N2' Dehydrobromination-Organocuprate Addition Exemplified

Sir:

The development of methods for total synthesis of the α-methylene-γ-butyrolactones continues to be a vigorous and productive area of research. Recently, we reported an annelation approach to certain eudesmane and elemane sesquiterpenes, in which the 1,6-annelation reagent **2** is used in construction of the linear tricyclic lactone **3a**.[1]

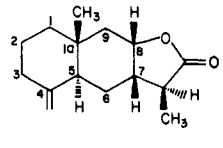


1a, R = H
b, R = CH_3

2

3a, R = H
b, R = CH_3
c, R = Br

The relative stereochemistry at C(8) and C(10) in **3** is identical with that present in dihydrocallitrisin (**4**), a new sesquiterpene lactone isolated from the heartwood of *Callitris columellaris*.[2] This configuration is rare and differs from that found in the more common eudesmane sesquiterpenes such as alantolactone (**5**).[3] Herein, we establish the flexibility of our approach to these sesquiterpenes by reporting the synthesis of *dl*-7,8-epialantolactone (**9**). In a future report, we will present the first total synthesis of *dl*-dihydrocallitrisin (**4**).



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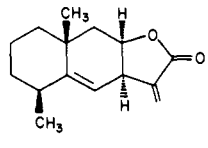


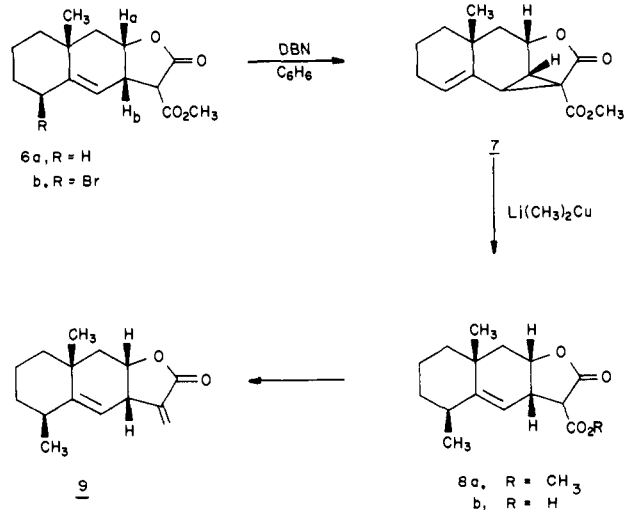
5

An obvious albeit stereochemically perilous approach to **9** would involve the diene lactone **3b**. To this end, **2** was reacted[1] with silyl enol ether **1b** to give the keto lactone resulting from 1,6 addition to **2**; however, this keto lactone resisted all attempts at cyclization to **3b**. A conceptually superior route to **9** was at hand when we discovered that **3a** undergoes selective bromination at C(4) with *N*-bromosuccimide[4] in refluxing carbon tetrachloride to give bromo diene **3c** (99% yield; mp 118-119 °C dec).[5]

Conjugate reduction of alkylidenemalonic esters has been performed with a variety of metal hydrides.[6] The instability of bromo diene **3c** to base suggested the use of sodium cyanobrohydride in acidic medium and we were delighted to find that bromo diene **3c** reacts with sodium cyanoborohydride in THF-ethanolic hydrogen chloride (3:1) to give allylic bromide **6b** in 97% yield (mp 121-122 °C dec; IR 5.62, 5.75 μ). Diene lactone **3a** also undergoes conjugate reduction to give **6a** (mp 92-94 °C) suggesting that this technique will be generally useful in preparation of cis-fused γ-butyrolactones from fused ring α-carboalkoxy-α,β-butenolides.

That the stereochemistry at the lactone fusion in **6a** and **6b** is as shown rests on ^1H NMR spectral data and inferential crystallographic analysis of **9** (vide infra). Thus, the vicinal coupling constant $J_{a,b}$ for **6a** and **6b** is 7.5 Hz, which strongly suggests the presence of a cis-lactone fusion in these intermediates.[7] Stereochemistry at C(4) follows from comparison of chemical shift data for the C(10) methyl group in **6a** (δ 1.12) and **6b** (1.46); the dramatic downfield shift of the angular methyl resonance in **6b** relative to that in **6a** must be a result of deshielding by the axial bromine atom.

Treatment of **6b** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene solution at room temperature (1 h) results in an internal S_N2'-like displacement of bromide ion from the enolate of **6b** to give vinylcyclopropane **7**[8] in 95% isolated yield (mp 113-114 °C; IR 5.65, 5.79 μ; electron impact mass spectrum, *m/e* 262).



6a, R = H
b, R = Br

7

8a, R = CH_3
b, R = H

9

Activated vinylcyclopropanes undergo homoconjugate and vinylogous homoconjugate addition depending on the nature of the reagent used; with lithium dialkylcuprates, exclusive 1,7 addition has been observed.[9] Addition of lithium dimethylcuprate to vinylcyclopropane **7** (ether solution, −20 to −5 °C, 40 min) gives the desired 1,7-addition product **8a** in 75% yield. Conversion of **8a** to *dl*-7,8-epialantolactone (**9**) is accomplished by hydrolysis to the lactone acid **8b** (aqueous-methanolic sodium hydroxide followed by acidification) and α-methylenation[10] of **8b**: (1) formalin-diethylamine, (2) sodium acetate-acetic acid. The structure of **9** thus obtained (70% yield; mp 109-110 °C; IR 5.69 μ) was firmly established by crystallographic study.

Suitable crystals of **9** were grown from an EtOAc-hexane solution and belonged to the monoclinic crystal class. Accurate cell constants, determined by a least-squares fitting of 15 moderate 2θ values, were a = 10.592 (2), b = 12.650 (2), c =

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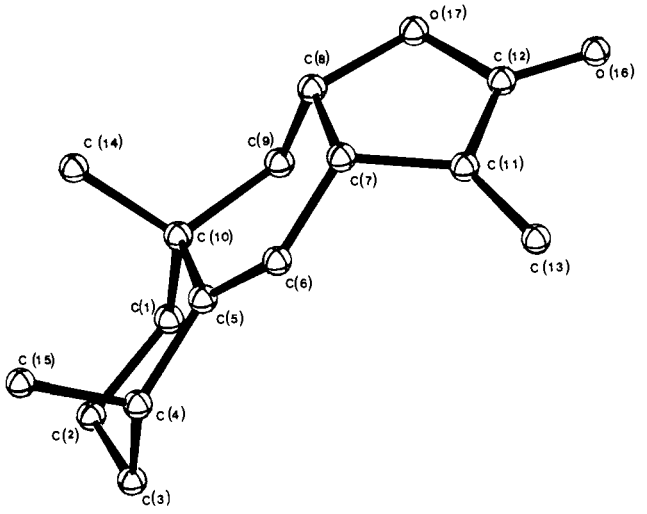

Figure 1. A computer-generated perspective drawing of 7,8-epialantolactone (**9**). Hydrogens are omitted for clarity.

11.365 (2) Å; β = 122.77 (5)°. The systematic extinctions conformed to the common monoclinic space group $P2_1/c$ and a density measurement indicated one molecule of composition $C_{15}H_{20}O_2$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a fully automated four-circle diffractometer using graphite monochromated Cu K_α (1.54178 Å) X-rays and a variable speed ω-scan technique. A total of 1861 diffraction maxima were surveyed and, after correction for Lorentz, polarization and background effects, 1738 (9390) were judged observed ($F_o \geq 3\epsilon(F_o)$).[11] The structure was solved using a multisolution weighted sign determining procedure. All of the nonhydrogen atoms were visible on the subsequent E synthesis and hydrogens were located on a difference synthesis. The structure was refined by the full-matrix least-squares technique using anisotropic nonhydrogens and fixed isotropic hydrogens to the current residual of 0.095.

Figure 1 is a computer generated perspective drawing of the final X-ray model less hydrogens. All bond distances and angles generally agree well with generally accepted values.

There is abundant experimental evidence suggesting that the preferred mode of addition of organocuprates to α,β-unsaturated ketones is that favoring antiparallel approach of the reagent to the π system of the enone.[12] In cyclohexenone ring systems, the stereochemical result is generally axial substitution.[13] To our knowledge, stereochemistry of organocuprate addition to activated vinylcyclopropanes has not been tested. We note that the addition of lithium dimethylcuprate to **7** results in axial substitution at C(4). Thus, the advantageous tandem S_N2' dehydrobromination–organocuprate addition (**6b** → **7** → **8a**) serves to substitute an alkyl group for a halogen atom with complete stereochemical control.[14] The overall yield of *dl*-epialantolactone **9** from diene lactone **3a** is ~48%.

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Supplementary Material Available: Tables of fractional coordinates, bond distances, and bond angles for **9** (2 pages). Ordering information is given on any current masthead page.

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Kinetic Isotope Effects in the Mechanisms of Thermal Allylic Rearrangements

Sir:

The reversible, thermal interconversion of allylic sulfoxides and sulfenates has been shown to occur via a pericylic process.[1] The corresponding 1,3 migration of a phenylsulfinyl group across an allylic framework (referred to in subsequent discussion here as the sulfoxyallylic rearrangement) appears to be a much slower and, presently, a mechanistically unresolved accompanyment which initially escaped detection in the course of discovery of the more mobile 2,3-sigmatropic change. Recently, however, both the analogous thiaallylic[2-7] and the sulfoxyallylic rearrangements[8] have been widely applied in synthetic schemes and have earned the designations of synthons.[7,8] In the thermal thiaallylic rearrangement the 1,3 migration of sulfur has been shown[3-6] to involve a hypervalent sulfur intermediate, probably possessing a trigonal-bipyramid-like structure and capable of permutational isomerism. The evidence for this reaction course rests on solvent and substituent rate effects,[5,6] sulfur (heavy atom) isotope effects,[3] and secondary (side chain) deuterium isotope effects,[4] all of which are consonant only with an associative transition state (TS). Because of the apparent structural similarities it was assumed[4,8] that the sulfoxyallylic rearrangement takes place

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