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(7) LCIA, lithium cyclohexylisopropylamide.
(8) This compound has been fully characterized by spectral properties and elemental composition.
(9) Bissulfenylation of an imino ether anion has been observed. See B. M. Trost and R. A. Kunz, *J. Org. Chem.* **39**, 2475 (1974).
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(13) Camille and Henry Dreyfus Teacher Scholar Grant Recipient.

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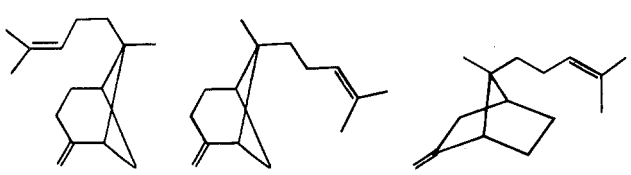
Synthesis of the *Valeriana Waalichi* Hydrocarbon Sesquifenchene. A Route to Specifically Functionalized 7,7-Disubstituted Bicyclo[2.2.1]heptane Derivatives

Summary: A highly stereoselective route to C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives from norbornadiene is reported which has been employed in a total synthesis of sesquifenchene.

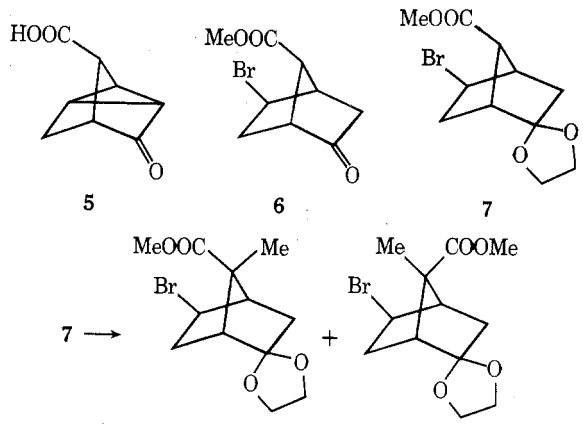
Sir: Bhattacharyya[1] reported some time ago the isolation of a new bicyclic sesquiterpene hydrocarbon from Indian Valerian root oil and proposed the β-*cis*-bergamotene structure **1** on the basis of chemical and spectroscopic studies.[1] Erman[2] demonstrated structure **1** to be untenable by synthesis and revised the structure to the trans isomer **2**. A recent report[3] on an unambiguous synthesis of **2** clearly ruled out structure **2** for Bhattacharyya's sesquiterpene which appeared not even to be a member of the bergamotene class.

Based on the close resemblance of the ir and nmr spectra of Bhattacharyya's compound and those of β- and epi-β-santalene, it has been suggested[3,4] that this compound [sesquifenchene (**3**)][4] is a substitution product of α-fenchene with a γ,γ-dimethyllallyl grouping present. Two recent syntheses have confirmed the structure **3**.[5] We wish to report the details of our synthesis of sesquifenchene which contains a highly stereoselective route to C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives.



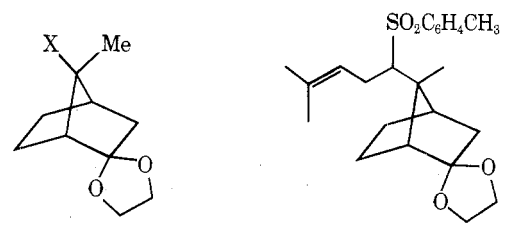
1 **2** **3**

The starting point of our synthesis was the cyclopropyl keto acid **5**, mp 143–144°, obtained in 55–60% overall yield from norbornadiene (**4**).[6] Reaction of acid **5** with refluxing 48% HBr–acetic acid (1:1) for 1.5 hr produced cleanly a bromo acid,[6b] mp 92° (90%).[7] Ketalization (2-methyl-2-ethyl-1,3-dioxalane–benzene–TsOH, 18 hr) of **6** resulted in a 90% yield of pure crystalline bromo ketal **7**, mp 74–75°. Alkylation of the ester enolate derived from **7** (lithium diisopropylamide–THF, −78°) with methyl iodide (−78° → 0°, 1.5 hr) resulted in a 75% isolated yield after chromatography on silica gel of the bicyclo[2.2.1]heptane derivative **8**.



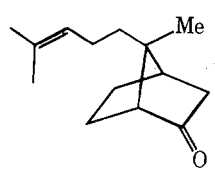
5 **6** **7**

8 **9**



10, X = COOMe
11, X = CH_2I
12, X = $CH_2SO_2C_6H_4CH_3$
14, X = $CH_2CH_2C{=}C(CH_3)_2$

13



15

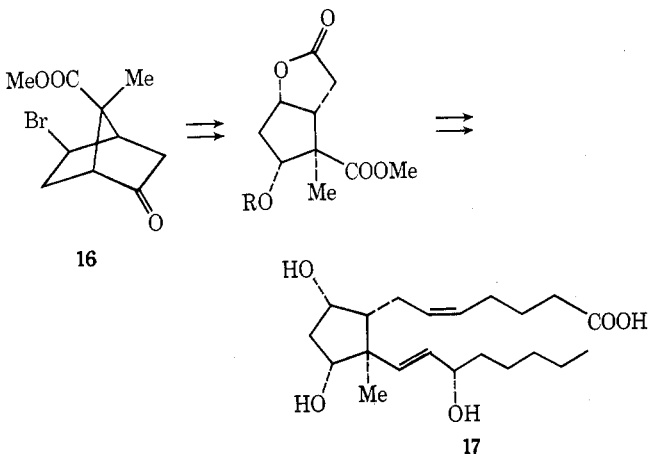
The nmr spectrum of **8** (mp 77–78°) included methyl resonances at δ 1.28 (s, 3 H) and 3.62 (s, 3 H). The corresponding isomer **9** (nmr indicated methyl resonances at δ 1.58 and 3.58) could be isolated in ~5% yield. Initial evidence for structure **8** was obtained in the following manner. Deketalization of **8** afforded a bromo ketone (**16**) whose methyl resonance moved upfield to δ 1.30 owing to shielding by the carbonyl. The bromo ketone derived from **9** exhibited no difference in the chemical shift of the methyl group. The conversion of **8** to sesquifenchene corroborates the stereochemical assignment.

The conversion of **8** to sesquifenchene requires (a) reductive cleavage of the carbon–bromine bond, (b) side-chain elaboration of the γ,γ-dimethylallyl grouping, and (c) methylenation of the protected keto function. Treatment of **8** with tributyltin hydride (1.5 equiv) in benzene containing azobisisobutyronitrile at 50–55° for 1.5 hr resulted in a 94% isolated pure yield of ester **10**. Reduction ($LiAlH_4$–ether, 4.5 hr) of ester **10** followed by tosylation [*p*-toluenesulfonyl chloride (1 equiv)/pyridine, 0°] and exchange with iodide [sodium iodide (3 equiv)–acetone, reflux] produced a 78% overall yield of iodide **11** from **10**. Sulfone formation was carried out in 77% yield (pure) with 2 equiv of sodium *p*-toluenesulfinate in anhydrous DMF at 135–140° (15 hr). The nmr spectrum of **12**, mp 117–118°, exhibited peaks at δ 1.46 (s, 3 H, CCH_3), 2.45 (s, 3 H, $ArCH_3$), 3.02 (s, 2 H, CH_2S), 3.82 (m, 4 H, OCH_2CH_2O), and an AB quartet (aromatic protons, J = 8 Hz) centered at 7.45. Metalation of sulfone **12** at −20° with *n*-butyllithium (1.3 equiv) in THF followed by cooling to −78°, addition of 1-bromo-3-methyl-2-butene (1.6 equiv), and gradual warming to 0° over 1.5 hr resulted in formation of sulfone **13** in near-

quantitative yield.[8] Nmr analysis of the coupled sulfone revealed lack of aliphatic methyl resonance, a consequence of coupling at the γ position and no terminal vinyl resonance. The new sulfone was reduced (Li–$EtNH_2$, −78°, 30 min) and the product chromatographed (hexane–ether, 10:1) on silica gel to yield pure ketal **14** in 82% overall yield from sulfone **12.** Nmr analysis of **14** revealed an olefinic proton at δ 5.00 (t, J = 6.5 Hz), ketal absorption at 3.78 (m, 4 H), two olefinic methyl resonances (1.58 and 1.65), and a saturated methyl resonance at 1.18 (5, 3 H). Deketalization [acetic acid–water (3:7), 85°, 1.5 hr] produced a 97% yield of ketone **15** which was methylenated with methylene triphenylphosphorane in DMSO[9] affording sesquifenchene identical by nmr, ir, glc, and tlc with a sample kindly provided by Professor Bessière-Chrétien and Dr. C. Grison. The nmr spectrum of synthetic **3** displayed a sharp singlet due to the C-8 methyl at δ 0.96, two broadened peaks due to $C{=}C(CH_3)_2$ at 1.60 and 1.67, two methylene protons ($=CH_2$) at 4.58 and 4.77, and one olefinic proton at 5.05 (broadened triplet), in addition to a complex series of peaks in the region 1–2.5 due to remaining protons.

A particularly interesting feature of this synthesis of *dl*-sesquifenchene is the efficiency and high stereoselectivity of the alkylation of ester **7** to provide C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives. In this connection, mention should be made of the possible utilization of **8** and derivatives thereof for construction of 12α-methylprostaglandins (*e.g.*, **17**) *via* a Corey-like intermediate (see Scheme I).

Scheme I



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(7) Satisfactory ir, tlc, glc, and analytical data were obtained. Nmr spectra were obtained (in CCl_4 at 60 MHz unless otherwise indicated) for each intermediate and were in every instance in complete accord with the assigned structure. Chemical shifts are expressed in parts per million downfield from tetramethylsilane and coupling constants in hertz.
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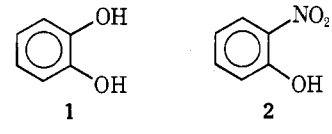
Benzocrown Amino Ethers[1]

Summary: Sixteen new multiheteromacrocycles are reported whose major rings contain O, NH, NTs, CH_2CH_2, and *o*-C_6H_4 units.

Sir: In the design of host molecules for particular complexing tasks, the placement of specific heteroatoms and rigid hydrocarbon groups in desired places in multiheteromacrocycles of different ring sizes provides an interesting synthetic challenge. Good synthetic methods for preparing benzocrown ethers,[2] crown ethers,[3] and crown amino ethers[4] without high dilution have been reported. Certain crown amino ethers have been synthesized with high dilution[5a] or flow cell techniques,[5b] and several benzo-15-crown-5 and benzo-12-crown-4 amino ethers have been prepared from *o*-hydroxyaniline or *o*-phenylenediamine and appropriate dichloro polyethers.[6] We report here simple syntheses of the listed benzocrown amino ethers and their derivatives.[7]

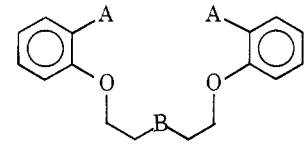
Preparation of **5, 6,** and **9** from **1–4** involved potassium carbonate in dimethylformamide (DMF) at reflux for 5–16 hr.[8] Reductions of **6** and **9** with hydrazine–palladium–carbon in ethanol gave **7** and **10,** respectively. Tosyl or mesyl



1 **2**

$O(CH_2CH_2OTs)_2$ $TsN(CH_2CH_2OTs)_2$

3 **4**



	A	B	Mp, °C	Yield, %	From
5	OH	O	84–86	40	1+3
6	NO_2	O	68–69	77	2+3
7	NH_2	O	63–65	91	6
8	NHMs	O	131–132	71	7
9	NO_2	NTs	123–124	86	2+4
10	NH_2	NTs	147–148	92	9
11	NHTs	NTs	172–173	96	10