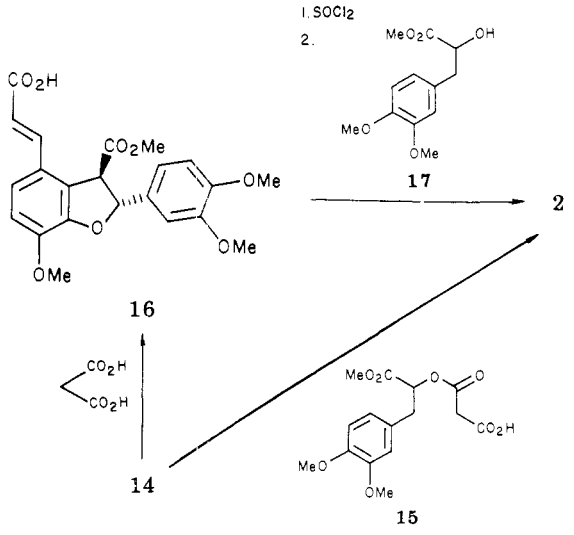
Scheme III



280 (M^+). Jones' oxidation of **6** yielded the acid **7** (82%): mp 105 °C dec; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.32 (s, 3 H), 3.72 (s, 2 H), 3.87 (s, 3 H), 5.15 (s, 2 H), 6.93 (d, J = 9 Hz, 1 H), 7.32 (d, J = 9 Hz, 1 H), 9.12 (br s, 1 H); IR 1755, 1730, 1710 cm^{-1}; MS m/e 296.093 (M^+). Removal of the acetates on **7** to obtain the diol acid **8** was accomplished in quantitative yield by treatment with methanolic sodium methoxide at 0 °C. Reaction of **8** with sodium acetate in refluxing acetic anhydride afforded a 78% yield of the desired benzopyranone **9**: mp 134–136 °C; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.54 (s, 2 H), 3.79 (s, 3 H), 5.23 (s, 2 H), 6.84 (d, J = 9 Hz, 1 H), 7.04 (d, J = 9 Hz, 1 H); IR 1745, 1735 cm^{-1}; MS m/e 236.069 (M^+). None of the isomeric benzofuranone, which would have resulted from lactonization of the acid with the phenolic oxygen, could be detected in the reaction mixture.

With a satisfactory synthesis of **9** in hand, we turned to the elaboration of **9** into the required dihydrobenzofuran ring system **14**. Piperidinium benzoate catalyzed condensation[7] of **9** with veratral afforded the aldol product **10** as a mixture of double bond isomers. Opening of the lactone ring in **10** was effected by heating with an excess of methanolic sodium methoxide, yielding the alcohol ester **11** (62%) as the E isomer exclusively: ^1H NMR ($CDCl_3$) δ 1.99 (br s, 1 H), 3.36 (s, 3 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.24 (d, J = 12 Hz, 1 H), 4.38 (d, J = 12 Hz, 1 H), 5.75 (br s, 1 H), 6.44 (d, J = 2 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 6.79 (dd, J = 2 and 8.5 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 1 H), 6.99 (d, J = 8.5 Hz, 1 H), 7.86 (s, 1 H); IR 1703 cm^{-1}. Oxidation of the alcohol ester **11** with PCC[8] resulted in low yields of the desired E aldehyde **12**; however, oxidation using Me_2SO/oxallyl chloride[9] afforded a 78% yield of **12** accompanied by 14% of the methyl thiomethyl ether (**13**). The structure of **12** was supported by its ^1H NMR [($CDCl_3$) δ 3.39 (s, 3 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 3.90 (s, 3 H), 5.95 (s, 1 H), 6.40 (d, J = 2 Hz, 1 H), 6.64 (d, J = 9 Hz, 1 H), 6.74 (dd, J = 2 and 9 Hz, 1 H), 6.94 (d, J = 8.5 Hz, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 7.97 (s, 1 H), 9.79 (s, 1 H)], IR (1705, 1690 cm^{-1}), and MS[m/e 372.122 (M^+)]. Cyclization of **12** with HBr in benzene/chloroform afforded a 67% yield of the *trans*-dihydrobenzofuran aldehyde **14**: ^1H NMR ($CDCl_3$) δ 3.74 (s, 3 H), 3.83 (s, 6 H), 3.94 (s, 3 H), 4.66 (d, J = 7 Hz, 1 H), 5.81 (d, J = 7 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 6.87 (d, J = 2 Hz, 1 H), 6.91 (dd, J = 2 and 8 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), 7.38 (d, J = 8.5 Hz, 1 H), 9.75 (s, 1 H); IR 1730, 1680 cm^{-1}; MS m/e 372 (M^+). The trans stereochemistry was suggested by a lack of shielding of the 3-carbomethoxyl group by the 2-aryl substituent, which would be expected for *cis*-**14**.[10] Confirmation of the trans stereochemistry rests on the conversion of **14** to **2**.

Elaboration of **14** into heptamethyl lithospermate can be realized via two related methods (Scheme III). Knoevenagel condensation of **14** with the malonic acid monoester **15** (obtained in 70% yield from methyl 3,4-dimethoxyphenyllactate (**17**)[11] and Meldrum's acid[12]) afforded heptamethyl lithospermate (**2**) in modest yield. A more efficient procedure involves condensation of **14** with malonic acid resulting in the cinnamic acid **16** (75%). Acid chloride formation using thionyl chloride in benzene, followed by treatment with **17**, afforded **2** and its diastereomer in 50% yield: ^1H NMR ($CDCl_3$) δ 3.04–3.14 (m, 2 H), 3.69 (br s, 6 H), 3.79 (s, 3 H), 3.83 (br s, 9 H), 3.89 (s, 3 H), 4.41 (d, J = 5 Hz, 1 H), 5.25 (m, 1 H), 5.97 (d, J = 5 Hz, 1 H), 6.25 (dd, diastereomers, J = 2 and 16 Hz, 1 H), 6.66–6.89 (m, 7 H), 7.15 (dd, diastereomers, J = 3.5 and 8.5 Hz, 1 H), 7.68 (dd, diastereomers, J = 3 and 16 Hz, 1 H); IR (CCl_4) 1748, 1725, 1615, 1265, 1160, 1030, 980 cm^{-1}; MS m/e 636.219 (M^+, 12), 414 (43), 337 (65), 223 (23), 222 (100), 191 (17), 181 (57), 163 (13), 151 (90). The spectral data agree with those obtained by Wagner[5] on optically active heptamethyl lithospermate obtained by methylation of extracts of *Lithospermum officinale*.

Thus, an efficient route to the lithospermic acid system from readily available starting materials has been realized. Application of this general route toward the synthesis of lithospermic acid (**1**) is in progress, and will be reported in due course.[13]

Acknowledgment. This work was supported by Public Health Service Grant 1-R01-GM24856-01 and Biomedical Research Support Grant PHS S05 RR 7031. R.A.R. gratefully acknowledges fellowship support by the Lubrizol Corporation.

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Stereospecific Total Synthesis of (±)-Isocomene (Berkheyaradulene)

Summary: The unusual triquinane sesquiterpene **2** has been synthesized in eight steps from bicyclic enone **3** through utilization of three separate organometallic addition reactions suitably interspersed between hydrolytic and oxidative steps.

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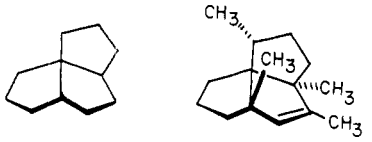
Sir: No substance possessing a tricyclo[6.3.0.0^{4,8}]undecane ring system (1) had been isolated from natural sources and characterized prior to 1972. In that year, retigeranic acid, a pentacyclic sesterterpene produced by *L. retigers*, was shown to contain this bridged spirane arrangement of three cyclopentane rings in a segment of its carbon skeleton.[1] In 1977, two groups independently reported on their completed efforts to delineate the structure of the novel sesquiterpene **2**. Zalkow and co-workers coined the name



1 2

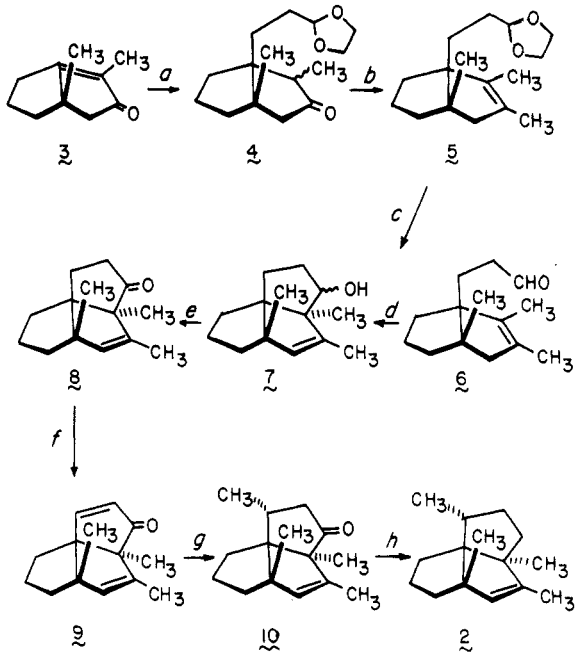
isocomene for the colorless oily hydrocarbon, in recognition of its acquisition from the dried stems and leaves of *Isocoma wrightii*, rayless goldenrod toxic to cattle and sheep.[2] On the other hand, Bohlmann's group determined **2** to be a constituent of the roots of *Berkheya radula*, a plant native to southern Africa, and have referred to this interesting triquinane as *berkheyaradulene*.[3] We favor the shorter and more euphonic name.

As a consequence of our general interest in polyquinane systems,[4,5] efforts were directed to the development of a short, stereoselective total synthesis of **2**. Our successful strategy forms the subject of this report.

Treatment of bicyclic enone **3**, readily available from 2-methylcyclopentanone by the method of Yoshikoshi,[6] with the Grignard reagent of β-bromopropionaldehyde ethylene ketal[7] in the presence of the cuprous bromide–dimethyl sulfide complex[8] resulted in smooth conjugate addition to give **4** (68%) (Scheme I). No significance was attached to the absence of stereochemical homogeneity at the substituted α-carbonyl site, since the asymmetry of this center was to be lost in the subsequent step. Thus, repeated exposure of **4** to ethereal methyllithium afforded the tertiary alcohols which, without purification, were dehydrated with thionyl chloride in pyridine at room temperature. That the elements of water had been lost to give exclusively the more highly substituted double bond isomer **5** was clearly apparent from the ^{1}H NMR spectrum [($CDCl_3$) δ 4.98–4.65 (m, 1 H), 4.05–3.72 (m, 4 H), 2.1 (br s, 2 H), 1.95–1.1 (m, 10 H), 1.48 (br s, 6 H), and 1.02 (s, 3 H)].

With the acquisition of **5**, means for effecting cyclization to a tricyclic framework were explored. Although direct stannic chloride promoted closure[9] of **5** to the desired $ROCH_2CH_2OH$ derivative of **7** (**7** = ROH) could be readily accomplished (72%), the subsequent conversion of **7** proved inefficient, seemingly because of facile Wagner–Meerwein shifts. However, mild hydrolysis of **5** in aqueous acetic acid at room temperature furnished a mixture of aldehyde **6** (62%) and tricyclic alcohol **7** (19%) which was

Scheme I



[a] $BrMgCH_2CH_2CHOCH_2CH_2O$, 0.25 equiv of $CuBr(Me_2S)$, THF, Me_2S, −78 °C, 68%. [b] CH_3Li, ether then $SOCl_2$, py, 25 °C, 79%. [c] HOAc-H_2O (1:1), 25 °C, 20 h, 62% of **6** and 19% of **7**. [d] $SnCl_4$, C_6H_6, 5–10 °C, 2 h, 95%. [e] Jones' oxidation, 76%. [f] $LiN(i\text{-}Pr)_2$, THF, −78 °C, 1 h; C_6H_5SeCl, 3 h; MCPBA, CH_2Cl_2, −78 °C, 2 h; hexane, reflux, 2 h, 88%. [g] $(CH_3)_2CuLi$, ether, −20 °C, 1 h then 0 °C, 2 h, product not purified. [h] $H_2NNH_2 \cdot H_2O$, K_2CO_3, triethylene glycol, reflux, 1.5 h, remove H_2O, heat at 200 °C, 3 h (80%).

easily separated by chromatography. The independent closure of **6** to **7** in the presence of stannic chloride was particularly efficient (95%). Subsequent Jones' oxidation delivered ketone **8**, examination of whose IR [ν_{max} (neat) 1735 cm^{-1}], ^{1}H NMR [($CDCl_3$) δ 5.10 (m, 1 H), 2.6–1.0 (series of m, 10 H), 1.60 (d, J = 0.6 Hz, 3 H), 1.27 (s, 3 H), and 1.05 (s, 3 H)], and ^{13}C NMR spectra[10] showed that formation of the third five-membered ring in this manner had proceeded with exceptionally good regiochemical control to produce uniquely the internal double bond isomer.[11]

Selenation of **8** by reaction of its enolate with phenylselenyl chloride followed by selenoxide elimination[12] proved highly suitable as a route to dienone **9** (88% yield). The widely different chemical shifts of the α (δ 5.94, d, J = 11 Hz) and β protons (δ 7.31, d, J = 11 Hz) associated with the unsaturated ketone moiety conforms to the anticipated high rigidity of the carbon framework and consequent approximate planarity of the cyclopentenone ring.

Condensation of **9** with lithium dimethylcuprate gave a single C_{15} ketone (**10**) which was directly subjected in crude form to Wolff–Kishner reduction. The hydrocarbon resulting from heating **10** with hydrazine hydrate and potassium carbonate in triethylene glycol[13] at 200 °C was isolated by preparative vapor-phase chromatography (2 ft

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× 0.25 in. column packed with 5% SE-30 on Chromosorb W, 100 °C) in 80% overall yield for the two steps. The IR and ^{1}H NMR spectra of this hydrocarbon were identical with those of both isocomene and berkheyaradulene.[14] Since the endo surface of the π bond in **9** is far more hindered than the exo, the stereochemistry of cuprate addition is predictable, delivery of a methyl group from the exo surface providing independent proof of both structure and stereochemistry of the natural product.

The structural features of **2** are such that three vicinal quaternary carbons form the central core of the molecule. Nonetheless, the present approach[15,16] makes the sesquiterpene conveniently available and sets a promising foundation for the projected synthesis of retigeranic acid which we would hope to report on at a later date.[17]

(14) The two samples had not previously been compared spectroscopically. The authors are indebted to Professors F. Bohlmann and L. Zalkow for making copies of the spectra of authentic **2** available to them. Compounds **5**, **8**, and **9** were analyzed by standard combustion methods.

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(16) **Note Added in Proof.** Since submission of our manuscript, two additional syntheses of (±)-isocomene have been claimed. In the first (Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493), suitable comparison with the natural product was made in convincing fashion. However, the second approach [Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979**, 620] relies at a key stage on a catalytic hydrogenation of a methyl-substituted double bond which must, for steric reasons discussed herein, ultimately deliver an epimer of isocomene. This particular claim must therefore be regarded as specious; our inquiries concerning spectral acquisition for comparison purposes have not been acknowledged.

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Recent Reviews. 4

Reviews are listed in order of appearance in the sources indicated. In multidisciplinary review journals, only those reviews which fall within the scope of this Journal are included. Sources are listed alphabetically in three categories: regularly issued review journals and series volumes, contributed volumes, and monographs. Titles are numbered serially, and these numbers are used for references in the index.

Major English-language sources of critical reviews are covered. Encyclopedic treatises, annual surveys such as *Specialist Periodical Reports*, and compilations of symposia proceedings are omitted.

This installment of Recent Reviews covers the first half of the 1979 literature. Previous installment: *J. Org. Chem.* **1979**, *44*, 1752. For regularly issued journals and series volumes, the coverage in this installment continues from the last items included in Recent Reviews 3.

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