oil: IR (film) 2980, 1710, 1445, 1225, 1185, 1100, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0–2.1 (13 H, m), 2.30 (2 H, t, J = 6 Hz), 2.69 (2 H, d, J = 14 Hz), 3.32 (3 H, s); MS m/e 196 (M^+). Anal. ($C_{12}H_{20}O_2$) C, H. Gas Chromatography indicated that this product consisted of two barely resolvable isomers.

***endo*- and *exo*-Tricyclo[5.3.0.0^{1,6}]decan-5-ol (24 and 26).** A stirred solution of **10** (154 mg, 1.02 mmol) in 20 mL of absolute methanol at ice temperature was treated with 135 mg (3.56 mg-atom) of sodium borohydride for 1.5 h. After the solvent was removed in vacuo, the residue was taken up into ether, washed with aqueous ammonium chloride and with saturated brine, and dried ($MgSO_4$). Filtration and solvent removal in vacuo followed by preparative silica gel TLC gave a fraction containing 33 mg (21%) of a mixture of *endo*-**24** and *exo*-**26** (1:1 by NMR), and another fraction containing 78 mg (50%) of pure **24** which was distilled: bp 60–65 °C (1.0 mm); IR (film) 3400, 2960, 2890, 1440, 1345, 1290, 1150, 1090, 1060, 1045, 1028, 1008, 985, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65–0.85 (2 H, m), 0.9–2.0 (12 H, m), 2.41 (1 H, br s), 3.72–4.00 (1 H, m); MS m/e 152 (M^+).

***endo*- and *exo*-Tricyclo[5.4.0.0^{1,6}]undecan-5-ol (25 and 27).** A stirred solution of **11** (154 mg, 0.94 mmol) in 20 mL of absolute methanol at ice temperature was treated with 135 mg (3.56 mg-atom) of sodium borohydride for 1.5 h. After solvent removal in vacuo, the residue was taken up into ether, washed with aqueous ammonium chloride and saturated brine, and dried ($MgSO_4$). Filtration and solvent removal in vacuo, followed by preparative silica gel TLC gave a higher R_f fraction containing 66 mg (42%) of a mixture of *endo*-**25** and *exo*-**27** (7:3 by NMR) and a lower R_f fraction containing 62 mg (40%) of pure **25**: IR (film) 3400, 2980, 2900, 1440, 1330, 1280, 1075, 1050, 1012, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.4–0.8 (2 H, m), 0.8–2.1 (15 H, m), 2.3 (1 H, br s), 3.95 (1 H, t, J = 7 Hz); MS m/e 166 (M^+).

***cis*-1-Methoxybicyclo[5.3.0]dec-5-ene (28).** A solution of **24** (77 mg, 0.48 mmol) and 1 drop (22 mg, 0.15 mmol) of 70% perchloric acid in 5 mL of absolute methanol was stirred at ice temperature for 3 h. The solution was neutralized with concentrated, aqueous sodium bicarbonate, diluted with water, and extracted with 2 × 15 mL of ether. The combined extract was dried ($MgSO_4$) and filtered, and the solvent was removed by distillation at atmospheric pressure. Distillation of the residual oil gave 59 mg (75%) of **28**: bp 35–40 °C (0.05 mm); IR (film) 3000, 1450, 1320, 1270, 1200, 1090, 1060, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.6 (12 H, m), 2.6–2.9 (1 H, m), 3.20 (3 H, s), 5.3–5.8 (2 H, m); MS m/e 166 (M^+). Anal. ($C_{11}H_{18}O$) C, H.

***cis*- and *trans*-1-Methoxybicyclo[5.4.0]undec-5-ene (29 and 31).** A mixture of **25** and **27** (56 mg, 0.30 mmol, in the ratio of 4:1) and 5 drops (110 mg, 0.8 mmol) of 70% perchloric acid in 5 mL of absolute methanol was stirred at ice temperature for 0.5 h. The solution was neutralized with concentrated aqueous sodium bicarbonate, diluted with water, and extracted with 2 × 15 mL of ether. The combined extract was dried ($MgSO_4$) and filtered, and the solvent was removed by distillation at atmospheric pressure. Vacuum distillation gave 46 mg (73%) of a mixture of **29** and **31** (9:1 by NMR): bp 42–45 °C (0.04 mm). These were separated by preparative gas chromatography to give **29**: IR (film) 2970, 1460, 1355, 1190, 1140, 1095, 943, 910, 870, 793, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.2 (14 H, m), 2.47–2.64 (1 H, m), 3.20 (3 H, s), 5.3–5.9 (2 H, m), MS m/e 180 (M^+). Anal. Calcd for ($C_{12}H_{20}O$): H, C, 79.94. Found: 80.45.

Also isolated from the preparative gas chromatogram was **31**: IR (film) 2990, 1450, 1080, 965, 940, 855, 800, 735, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0–1.9 (12 H, m), 1.9–2.1 (2 H, m), 2.87–3.04 (1 H, m), 3.34 (3 H, s), 5.4–5.9 (2 H, m); MS m/e 180 (M^+).

Acknowledgment. We are grateful to the National Science Foundation for support of this work. J.F.R. is pleased to acknowledge the Nicholas L. Tartar Foundation for a summer fellowship.

Spiroannelation via Intramolecular Ketocarbenoid Addition. Stereocontrolled Synthesis of (−)-Acorenone B and (±)-α-Chamigrene

James D. White,*[1a,b] John F. Ruppert,[1b] Mitchell A. Avery,[1b] Sigeru Torii,[1c] and Junzo Nokami[1c]

Contribution from the Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, and the Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama, Japan 700. *Received August 25, 1980*

Abstract: The spirobicyclic structures of (±)-α-chamigrene (**7**) and (−)-acorenone B (**6**) were synthesized by means of a copper-catalyzed, intramolecular cycloaddition of diazo ketones **25** and **47**, respectively. The former was prepared from 4-methyl-4-(*p*-methoxyphenyl)pentanoic acid (**8**) and the latter was obtained in optically active form from (*R*)-(+)-limonene (**35**). Reduction of **26** with lithium in ammonia gave **27**, which was transformed to (±)-α-chamigrene (**7**) via olefin **30** and carbinol **32**. The tricyclic ketone **53**, from **47**, was converted via olefin **55** to spiroketone **56**. Introduction of the conjugated olefin afforded (−)-acorenone B (**6**). Alternatively, **53** was reduced with lithium in ammonia to **54** and this, through a parallel sequence, was taken to (−)-4-epiacorenone B (**67**).

In the preceding paper,[2] the synthesis of spiro[4.5]decanone (**3**, n = 2) and spiro[5.5]undecanone (**3**, n = 3) was described, based upon intramolecular addition of the carbenoid derived from **1**, followed by reductive scission of the tricyclic ketone **2** at the perimeter cyclopropane bond (Scheme I). Furthermore, a variation of this plan was shown to be applicable to the preparation of fused ring systems, e.g., **5**, in a stereocontrolled manner via solvolysis of the cyclopropyl carbinol **4**. Thus, related skeletal types can be obtained in discriminative fashion from a common intermediate **2**.[3]

In order to test the feasibility of this approach in functionally more complex systems, we chose to examine routes to (−)-acorenone B (**6**) and (±)-α-chamigrene (**7**), sesquiterpenes of the spiro[4.5]decane and spiro[5.5]undecane class, respectively, along lines exemplified by the sequence **1** → **2** → **3**. In this paper, we present a detailed account of our results, which have led to the

(1) (a) National Institutes of Health Research Career Development Awardee, 1976–1981. (b) Oregon State University. (c) Okayama University.

(2) J. F. Ruppert and J. D. White, *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) For a preliminary account, see J. F. Ruppert and J. D. White, *J. Chem. Soc., Chem. Commun.*, 976 (1976).

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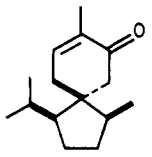

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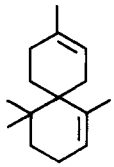

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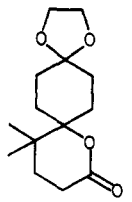
total synthesis of these two sesquiterpenes.[4]

(±)-α-Chamigrene. Although the synthesis of a simple spiro[5.5]undecanone **3** (n = 3) had been demonstrated,[2] the construction of a spiro center flanked by several alkyl substituents using methodology established for the model system was problematic. In view of the broad distribution of sesquiterpenes of the chamigrane class,[5] many possessing substituents densely clustered around the spiro carbon, the synthesis of this skeletal type seemed particularly inviting.[6] α-Chamigrene (**7**), the parent member of this group and a component of *Schizandra chinensis*,[7] was selected as the focus of these studies, in part because it possesses the nucleus from which a number of halogenated derivatives found in marine organisms can be potentially derived.[8]

The initial approach to **7** was predicated on the assumption that it would be possible to introduce the C-1 methyl substituent after construction of the spirocyclic framework. Toward this end, the carboxylic acid **12** was prepared from 4-methyl-4-(*p*-methoxyphenyl)pentanoic acid (**8**), as shown in Scheme II. Thus, **8**, obtained by Friedel–Crafts alkylation of anisole with 4,4-dimethylbutyrolactone,[9] was subjected to Birch reduction with lithium in a mixture of liquid ammonia, tetrahydrofuran, and *tert*-butyl alcohol, and the resultant cyclohexadiene, without isolation, was treated with aqueous tartaric acid to afford keto acid **9**. It proved difficult to convert **9** cleanly to ketal **12**, due to the facile lactonization to **17** under the acidic conditions em-



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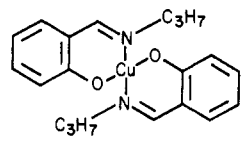

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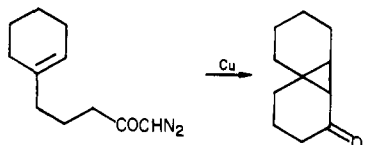


18 19

ployed for ketalization. However, this problem was easily circumvented by protection of **9** as its methyl ester **10** with diazomethane. Ketalization to **11** then proceeded smoothly, and saponification yielded the desired ketal acid **12** as a viscous oil which deteriorated significantly if stored longer than a day.

The acid chloride **13**, prepared from the sodium salt of **12** in benzene by treatment with oxalyl chloride, proved to be an even more labile substance than the parent acid, and, after ascertaining the presence of carbonyl absorption at 1790 cm^{-1}, **13** was transformed promptly to diazo ketone **14** by reaction with diazomethane in ether. This diazo ketone was found to be a relatively stable, yellow oil which could be purified by chromatography on alumina. It showed characteristic bands in its IR spectrum at 1650 and 2110 cm^{-1} and a singlet at δ 5.32 in its NMR spectrum for the proton α to the ketone and diazo functions.

A variety of catalyst systems was explored for the thermal decomposition of **14**, with interesting and potentially significant results. Whereas it had been shown that **18** underwent smooth decomposition to afford cycloadduct **19** in the presence of copper bronze,[2] this catalyst as well as several copper salts (e.g., Cu_2Cl_2, $Cu(OAc)_2$) gave only intractable materials when applied to **14**. A cursory examination of the reaction mixture by NMR spectroscopy in each case suggested that the likely source of difficulty lay in the ketal function of **14**, which appeared to be reactive toward copper(0, I, or II) in the heterogeneous reaction medium employed. It was therefore reasoned that a soluble, chelated form of copper might offer a more sanguine prospect for mediating this cycloaddition and, indeed, it was found that, when **14** was exposed to an anhydrous sample of bis(*N*-*n*-propylsalicylidenaminato)copper(II) (**20**)[10] in refluxing cyclohexane, **15** was produced in 66% yield after chromatographic purification.

The observation that a soluble, complexed form of copper(II) was effective in the conversion of **14** to **15**, while insoluble copper salts were not, is presumably associated with decreased electrophilicity of the catalyst in this form and a consequently diminished reactivity toward the ketal oxygens. In related studies,[11] we have found that copper-catalyzed cycloaddition of diazo ketones generally proceeds in good yield with complexed, soluble copper(II) when the substrate includes polar, nucleophilic functional groups. However, in simple, nonfunctionalized systems such as **18**, the soluble catalyst offers no advantage over finely divided, metallic copper in a heterogeneous medium.

The dissolving-metal reduction of **15** was expected to take place largely by scission of the cyclopropane bond on the perimeter of the carbocyclic skeleton on the basis of stereoelectronic arguments advanced by Norin[12] and by Dauben[13] and by analogy with the model systems studied in our own laboratory.[2] In fact, exposure of **15** to lithium in liquid ammonia containing ether afforded the crystalline, spiro ketone **16** in 90% yield. The change from **15** to **16** was accompanied by the expected shift in ketone carbonyl frequency from 1672 to 1708 cm^{-1}, and, while this does not exclude the possibility of reductive cleavage of the alternate cyclopropane bond to give a fused bicycloundecanone, the NMR spectrum of **16**, which shows a two-proton singlet at δ 2.55 and a two-proton multiplet at δ 2.33, is consistent only with the spiro structure shown. A careful examination of the reaction mixture from the lithium–ammonia reduction of **15** failed to reveal any trace of a second ketone, although a small amount (ca. 5%) of the secondary alcohol from overreduction of **16** was present.

With the spiroundecanone **16** in hand, the next task was introduction of a methyl substituent at the methylene carbon between the ketone and spiro center. Enolate alkylation adjacent to a spiro carbon atom is opposed by a severe steric barrier, and hence it was not surprising to find that treatment of **16** with base, followed by methyl iodide, gave none of the desired ketone but instead afforded a mixture of the O-methylation product **21** and **22**, resulting from substitution at the more exposed methylene carbon. A possible solution to this problem appeared to lie in a direct methylation of the intermediate enolate formed during lithium–ammonia reduction of **15**, since it has been shown that it is possible to trap, in a kinetically controlled process, the enolate produced in reductions of this type.[14] However, when **15** was treated with lithium in ammonia–THF, followed by a large excess of methyl iodide, O-methylation was again the principal product, accompanied by 10–15% of the desired **27**. Thus, even though it is possible to suppress proton transfer in this reduction–alkylation

(4) For preliminary accounts, see: J. D. White, S. Torii, and J. Nokami, *Tetrahedron Lett.*, 2879 (1974); J. F. Ruppert, M. A. Avery, and J. D. White, *J. Chem. Soc., Chem. Commun.*, 978 (1976).

(5) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, "Natural Products Chemistry", Vol. II, Academic Press, New York, 1974, p 153.

(6) For previous syntheses of (±)-α-chamigrene, see: (a) A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 56 (1968); (b) T. Kato, S. Kanno, and Y. Kitahara, *Tetrahedron*, **26**, 4287 (1970).

(7) Y. Ohta and Y. Hirose, *Tetrahedron Lett.*, 2483 (1968).

(8) Inter alia: A. G. Gonzalez, J. Darias, and J. D. Martin, *Tetrahedron Lett.*, 2381 (1973); J. J. Sims, W. Fenical, F. M. Wing, and P. Radlick, *J. Am. Chem. Soc.*, **95**, 972 (1973); B. M. Howard and W. Fenical, *Tetrahedron Lett.*, 1687 (1975).

(9) D. I. Schuster and W. V. Curran, *J. Org. Chem.*, **35**, 4192 (1970).

(10) L. Sacconi and M. Ciampolini, *J. Chem. Soc. C*, 276 (1964).

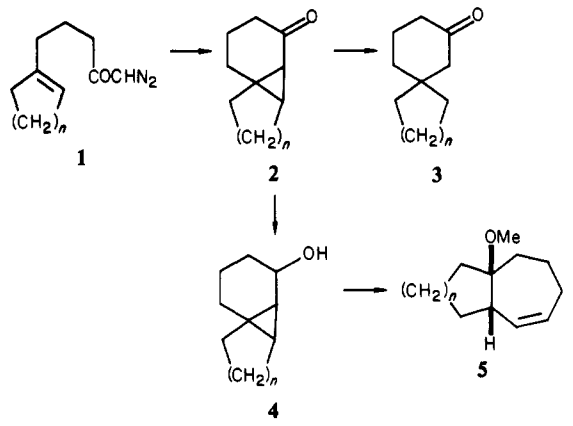
(11) J. F. Ruppert, S. Torii, and J. D. White, unpublished results.

(12) T. Norin, *Acta Chem. Scand.*, **19**, 1289 (1965).

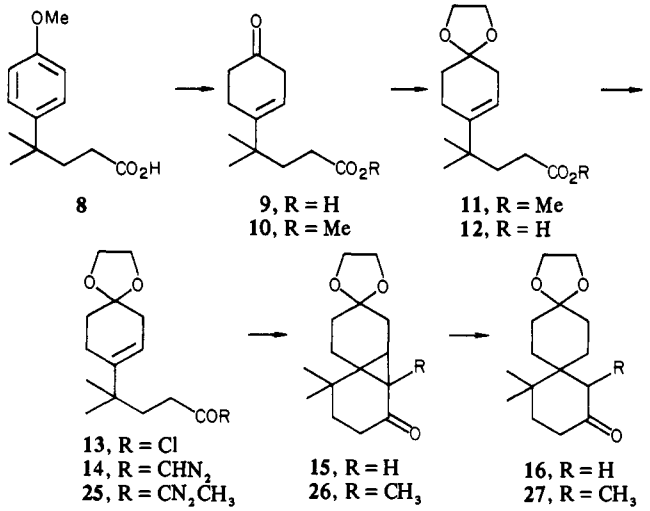
(13) W. G. Dauben and E. J. Devigny, *J. Org. Chem.*, **31**, 3794 (1966).

(14) G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Am. Chem. Soc.*, **93**, 4945 (1971).

Scheme I

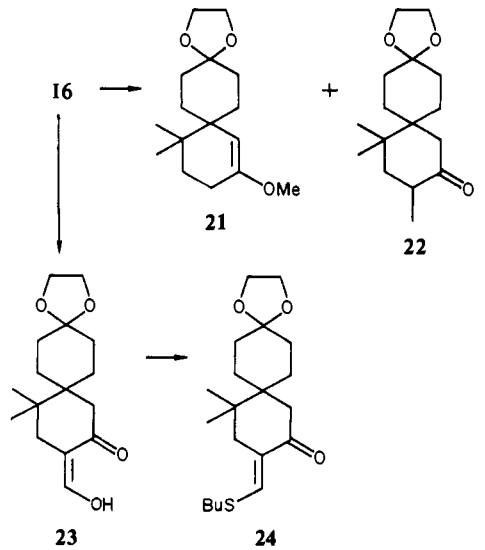


Scheme II



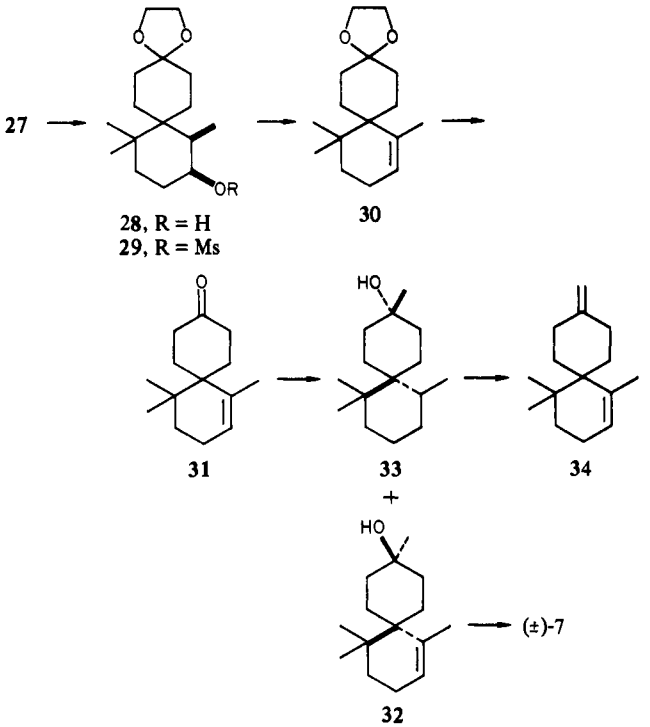
sequence, steric factors overwhelmingly favor attack by the alkylating agent at the oxygen of the kinetically produced enolate in this situation.

Thwarted in our attempts to effect methylation of **16**, we resorted to a scheme in which **16** was blocked at C-3 so that alkylation might be forced at C-5. Justifiably, this brutish approach likewise met with failure for, although **16** was converted cleanly with ethyl formate in the presence of sodium hydride to **23** which in turn could be transformed to the (*n*-butylthio)methylene ketone **24**,[15] the latter resisted methylation altogether.



With access to the chamigrene nucleus from **16** cut off by the steric barrier associated with alkylation adjacent to a spiro center, it became clear that a strategy of the type outlined in Scheme I could only be effective if the requisite methyl substituent was incorporated into the diazo ketone precursor as the homologue **25**. To this end, a straightforward modification of Scheme II, in which **13** was treated with diazoethane,[16] afforded **25** in excellent yield (from **12**). When **25** was exposed to anhydrous bis(*N*-*n*-propylsalicylidenaminato)copper(II)[10] in benzene at 75 °C, the cyclopropyl ketone **26** was produced in 45% yield after chromatographic purification. The diminished efficiency of this cycloaddition, as compared with that of **14**, is attributed to an intramolecular 1,2-hydrogen shift which competes with cycloaddition in the higher homologue and leads to a vinyl ketone.[17] This route nevertheless afforded a satisfactory pathway to the desired chamigrene precursor since, when **25** was reduced with lithium–ammonia, the spiro ketone **27** was obtained in excellent yield.

The remaining steps from **27** to (±)-α-chamigrene involved straightforward manipulation of the two carbonyl functionalities, and the first operation carried out was reduction of **27** with lithium tri-*tert*-butoxyaluminum hydride. This furnished a single alcohol, presumably cis isomer **28**, in quantitative yield. The latter was converted to its mesylate **29** which, without purification, was treated with Me_2SO at 60 °C to give olefin **30** in 80% yield.[17]



The ketal function of **30** was removed by hydrolysis in THF containing aqueous perchloric acid, and the resulting ketone **31** was reacted with methyllithium in ether. A mixture of two, diastereomeric, tertiary alcohols, which could be separated by chromatography, was produced in the ratio 7:3. It can be assumed that the geminal methyl substitution of **31** effectively locks conformational mobility about the spiro carbon in this system, so that the ratio of alcohols formed represents the proportion of equatorial and axial attack at the ketone. On this basis, the major alcohol should possess the axial hydroxyl group, as in **32**, and the minor isomer should be the equatorial alcohol **33**.[18] Although this stereochemical point was not proven rigorously, the two alcohols did behave differently under dehydration in a manner consistent

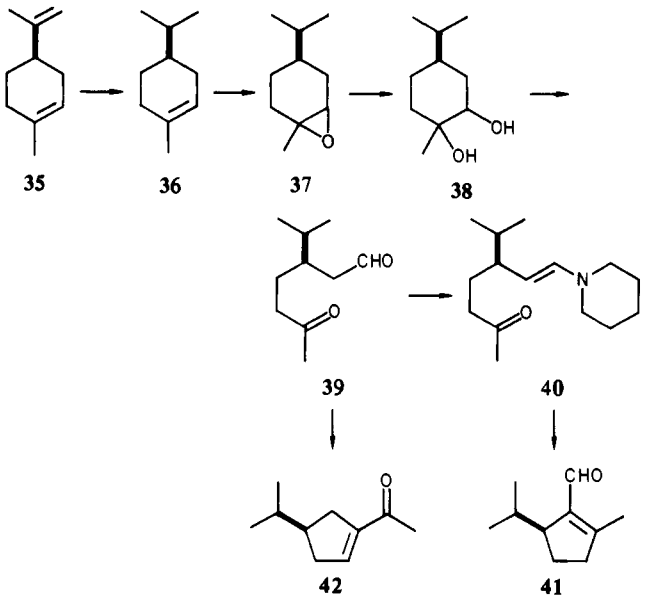
(15) J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35**, 192 (1970).
(16) C. J. V. Scanio and D. L. Lickei, *Tetrahedron Lett.*, 1363 (1972).
(17) F. Weygand and H. J. Bestmann in "Newer Methods of Preparative Organic Chemistry", Vol. III, W. Foerst, Ed., Academic Press, New York, 1964, p 451.
(18) E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975).

with these assignments. Thus, **32**, in the presence of Me_2SO at 50–60 °C, underwent facile elimination to a substance which, after purification by preparative GLC, was shown to be (±)-α-chamigrene (**7**) by comparison with an authentic sample. By contrast, **33** could be dehydrated only with difficulty and afforded mostly exo olefin **34**.

(−)-Acorenone B. In contrast to **7**, which contains only one chiral center, acorenone B (**6**) incorporates an asymmetric spiro carbon, flanked on each side by additional chiral groups. Thus, it was of interest to determine whether this system, with its three contiguous asymmetric centers, was amenable to stereoselective synthesis by using the spiroannelation methodology exemplified above.[19]

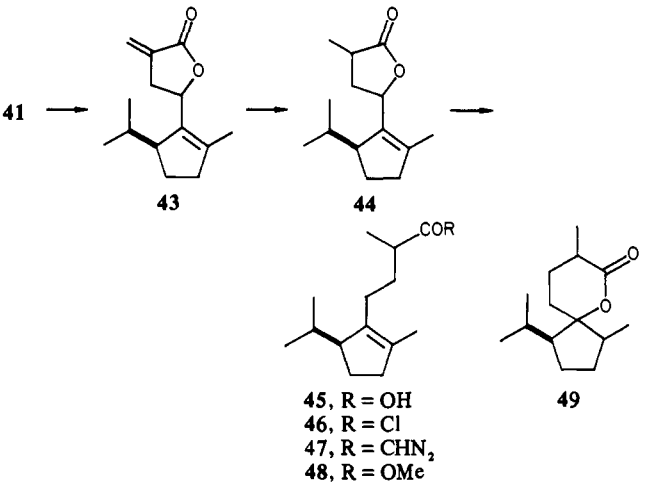
The naturally occurring, levo enantiomer of acorenone B, which occurs as a constituent of the hybrid grass *Bothriochloa intermedia*,[20] has been shown to possess the absolute configuration represented in **6**.[21] Although several syntheses of racemic acorenone B have been reported,[22] no synthesis of the natural enantiomer had been described prior to the completion of our work.[23]

In selecting a strategy for an asymmetric synthesis of **6**, we chose to employ the isopropyl substituent as the controlling element for directing stereochemistry at the two other asymmetric centers. We therefore sought a starting material in which the center bearing the isopropyl group in the correct absolute configuration was readily accessible in optically pure form. A particularly convenient source of chirality for our purpose proved to be (*R*)-8,9-dihydrolimonene (**36**), available by partial hydrogenation over



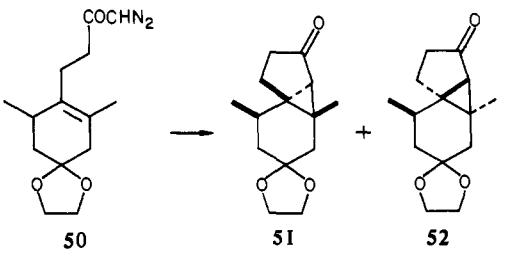
Adams' catalyst of naturally derived (*R*)-(+)-limonene (**35**). Following a sequence developed originally by van Tamelen,[24] **36** was converted with peracetic acid to epoxide **37** (as a mixture of epimers) and the epoxide was hydrolyzed in aqueous perchloric acid to a crystalline mixture of diols **38**. Oxidative cleavage of **38** with sodium metaperiodate afforded keto aldehyde **39**. Attempts to convert **39** directly to aldehyde **41** by an internal aldol condensation led to low yields of **41**, which proved difficult to separate from ketone **42**, resulting from the alternate condensation mode. However, a two-step procedure, in which **39** was first converted to enamine **40** (isolated and purified) with piperidine, gave **41** cleanly after condensation and hydrolysis in acetic acid. The overall yield of **41** from (*R*)-(+)-limonene by this route was 45%.

Elaboration of the aldehyde function of **41** to the isovaleroyl



chain of **45** was accomplished by a variation of the Reformatsky reaction[25] which had been exploited in the preparation of the model systems discussed previously.[2] Thus, passage of a mixture of **41** and ethyl 2-bromomethylacrylate through a column of granular zinc furnished the unstable lactone **43**,[26] which was promptly hydrogenated over Adams' catalyst to give the dihydro derivative **44** as an oily mixture of epimers. Hydrogenolysis of **44** over palladium on calcium carbonate furnished the carboxylic acid **45** in an overall yield of 50% from **41**. As with the analogous acid **12**, **45** showed a propensity for lactonization to spiro structure **49** which required that this material be characterized (and stored) as its methyl ester **48**. For the conversion of **45** to diazo ketone **47**, the crude acid was first treated with oxalyl chloride to give the acyl chloride **46** (1790 cm^{-1}), which was then reacted with diazomethane in ether. The diazo ketone **47** was obtained as a yellow-orange oil which showed the expected infrared bands at 2110 and 1640 cm^{-1} and a one-proton singlet at δ 5.3 in its NMR spectrum. However, this material proved to be unstable to chromatography on either silica or alumina, so that it was impossible to ascertain whether epimers of **47** were present at this stage.

With **47** in hand, it was now feasible to test a crucial element in our spiroannelation strategy, namely, the question of whether the carbenoid derived from **47** would select only one of the faces of the π bond in the cyclopentene for addition. There are solid grounds for anticipating stereoselectivity in this reaction, particularly in light of the observation by Deslongchamps[27] that **50**



(19) For a review of spiro[4.5]decane sesquiterpenes, see J. A. Marshall, S. F. Brady, and N. H. Andersen, *Prog. Org. Chem. Nat. Prod.*, **31**, 283 (1974).
(20) R. J. McClure, *Diss. Abstr. Int. B*, **30**, 1046 (1969).
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(22) H. Wolf and M. Kolleck, *Tetrahedron Lett.*, 451 (1975); H. Wolf, M. Kolleck, and W. Rascher, *Chem. Ber.*, **109**, 2805 (1976); W. Oppolzer and K. K. Mahalanabis, *Tetrahedron Lett.*, 3411 (1975); W. Oppolzer, K. K. Mahalanabis, and K. Battig, *Helv. Chim. Acta*, **60**, 2388 (1977); B. M. Trost, K. Hiroi, and N. Holy, *J. Am. Chem. Soc.*, **97**, 5873 (1975).
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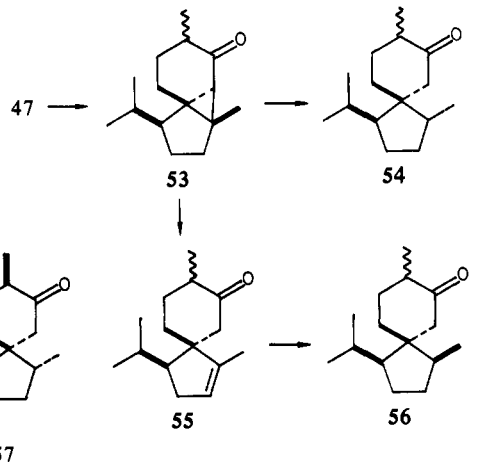
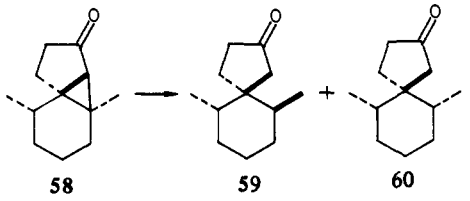
affords a 9:1 ratio of the stereoisomeric cycloaddition products **51** and **52**, respectively. This result implies that a carbene (as its copper complex) possesses a substantial steric requirement and suggests that **47**, containing an isopropyl substituent on a relatively

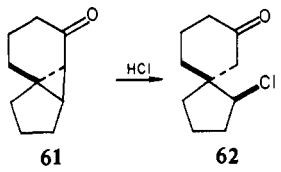


flat cyclopentene ring, should exhibit an even higher preference for addition of the carbenoid to the face of the π system opposite the blocking group. In practice, when **47** in refluxing cyclohexane was exposed to copper powder, two substances were produced which were shown through subsequent transformations to be epimeric only with respect to the methyl group α to the ketone. Hence, it was apparent that cycloaddition of **47** had occurred with virtually complete stereoselectivity to yield a tricyclic structure **53**, in which the relative (and absolute) configurations of the isopropyl substituent and adjacent spiro center were defined as shown. Stereoisomers with respect to the methyl group α to the carbonyl in **53** are, of course, of no consequence since this center becomes trigonal in acorenone B. Therefore, no attempt was made to separate epimers at this point.

By analogy with cyclopropyl ketones **15** and **26**, reduction of **53** with lithium–ammonia was expected to result in scission of the perimeter cyclopropane bond, since this is again the linkage most closely aligned with the carbonyl π system. A primary concern, however, was the stereochemical outcome of this reduction. A priori, it seemed reasonable that protonation (quasi electrophilic substitution) of the carbanionic intermediate might occur with retention, yielding the cisoid relationship of isopropyl and methyl substituents required for **6**. Alternatively, inversion would lead to a trans orientation of these groups characteristic of other members of the acorane class of sesquiterpenes such as acorone (**57**).[28] Piers and Worster demonstrated that the lithium–ammonia reduction of **58** affords **59** and **60** in a ratio of ca.

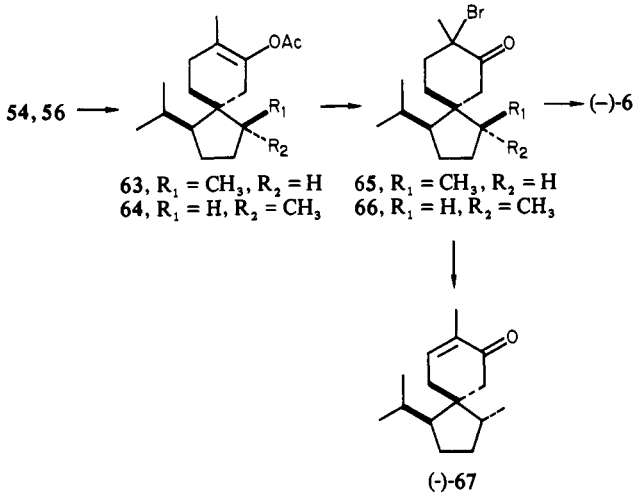


9:1,[29] and subsequent investigations by Caine have confirmed that inversion is the dominant mode in reductive cleavage of cyclopropyl ketones of this type.[30] In keeping with these results, it was found that reduction of **53** with lithium in ammonia afforded largely spiro ketone **54** and only traces of the desired **56**. Numerous attempts were made to influence the proportion of **54** to **56** in this reduction with little success. The presence or absence of cosolvents or of alcohols as proton donors had no effect on this ratio, although the overall yield was slightly higher with added *tert*-butyl alcohol and THF; generally, **54** predominated by at least 4:1. Whatever the mechanistic reason for this outcome,[31] the lithium–ammonia reduction of **53** is thus of no value for the synthesis of acorenone B. Fortunately, an alternative plan, suggested by the derivation of chloro ketone **62** from treatment of **61** with anhydrous HCl,[2]



was available which would obviate this difficulty. In the case of **53**, exposure to HCl in chloroform did not give the tertiary halide but rather the cyclopentene **55**. This result afforded us the opportunity of installing the required configuration at C-4 through hydrogenation of **55** from the side opposite the C-1 isopropyl substituent, and, in fact, **56** was prepared in 60% yield from **53** by using rhodium on carbon as the hydrogenation catalyst.

Conversion of **56** to (−)-acorenone B required only introduction



of a double bond in conjugation with the ketone and, for this purpose, a straightforward, α-bromination was adopted. Thus, **56** was transformed to enol acetate **63** with acetic anhydride containing a trace of perchloric acid and this substance was brominated in a buffered mixture of acetic acid and carbon tetrachloride to give, after hydrolysis, α-bromoketone **65**.[32] The latter, upon treatment with lithium chloride and lithium carbonate in DMF, furnished acorenone B (**6**) in 34% yield (from **56**) after purification by preparative gas chromatography. Although the optical rotation (−19°) of our synthetic material was slightly higher than that reported for natural acorenone B,[20] the infrared, ultraviolet, nuclear magnetic resonance, and mass spectra of (−)-**6** exactly matched those of the racemic modification synthesized independently.[22] A parallel sequence departing from **54** and proceeding through **64** and the bromo ketone **66** afforded (−)-4-epiacorenone B (**67**). This substance was readily distinguishable from **6** on gas chromatography and had spectral properties in excellent agreement with those recorded for (±)-**67**.[33]

Experimental Section

Melting points were determined on a Kofler hot stage microscope and are corrected; boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 or 727B infrared spectrophotometer. Ultraviolet (UV) spectra were obtained by using a Cary Model

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(31) Existing evidence (J. F. Ruppert, Ph.D. thesis, Oregon State University, 1977; see also ref 30) is in agreement with equilibration of the carbanion prior to protonation, so that configuration in the reduction of cyclopropyl ketones is determined primarily by steric and/or conformation effects.
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15 ultraviolet spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined on a Varian Associates Model EM-360 or HA-100 spectrometer with tetramethylsilane (Me_4S) as an internal standard. Chemical shifts are reported in δ units. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra (MS) and exact mass determinations were obtained by using a CEC-110C spectrometer at an ionizing potential of 70 eV and were provided by Drs. Rottschafer and Wielesek at the Department of Chemistry, University of Oregon, Eugene, Ore. Elemental analyses were performed by Micro-Tech laboratories, Inc., Skokie, Ill. Preparative GLC separations and analysis were carried out by using a Varian-Aerograph autoprep 700 instrument with (1) a 10 ft × 0.375 in. column of 30% Carbowax 20M on Chromosorb W or (2) a 5 ft × 0.25 in. column of 20% SE-30 on Chromosorb.

4-Methyl-4-(4-oxocyclohexenyl)pentanoic Acid (9). To a stirred solution of 2.22 g (0.01 mol) of 4-methyl-4-(*p*-methoxyphenyl)pentanoic acid[9] and 15 mL of *tert*-butyl alcohol in a mixture of 17 mL of tetrahydrofuran and 50 mL of liquid ammonia was added 0.39 g (0.056 mol) of lithium metal in several pieces. After the solution was stirred for 3 h, 2.90 g (0.056 mol) of ammonium chloride was added and the mixture was stirred at room temperature until most of liquid ammonia had evaporated. To the residue was added 50 mL of water, and the aqueous solution was acidified with 10% HCl. The neutral material was extracted with ether, and the extracts were washed with water. This aqueous extract was combined with the acidic portion, which was extracted with aqueous sodium bicarbonate. The alkaline extracts were washed with ether and acidified with 10% HCl. When the acidic aqueous solution was heated to 30–35 °C with stirring, a light yellow oil separated. This oil was taken up into ether, and the ether layer was washed with aqueous sodium chloride, dried ($MgSO_4$), and concentrated to yield 2.10 g (94%) of **9** as a pale yellow oil: IR (neat) 3500–2400, 1708, 1410, 1390, 1360, 1300–1280, 1210–1180, 1010, 910, 803 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (6 H, s), 1.50–1.87 (2 H, m), 2.00–2.25 (2 H, m), 2.35 (4 H, s), 2.77 (2 H, d, J = 4 Hz), 5.53 (1 H, t, J = 4 Hz), 10.10 (1 H, broad s).

Methyl 4-Methyl-4-(4-oxocyclohexenyl)pentanoate (10). To a solution of 1.05 g (5 mmol) of **9** in 2 mL of ether was added an excess of an ethereal solution of diazomethane. The yellow mixture was allowed to stand for 1 h and was filtered. Removal of the solvent in vacuo gave 1.06 g (99%) of virtually pure **10** as a colorless oil: IR (neat) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (6 H, s), 1.25–2.20 (4 H, m), 2.42 (4 H, s), 2.90 (2 H, d, J = 4 Hz), 3.72 (3 H, s), 5.62 (1 H, t, J = 5 Hz).

Methyl 4-Methyl-4-(4,4-ethylenedioxycyclohexenyl)pentanoate (11). A mixture of 1.12 g (5 mmol) of **10**, 0.47 g (7.5 mmol) of ethylene glycol, and 50 mg of *p*-toluenesulfonic acid in 30 mL of dry benzene was refluxed overnight by using a Dean–Stark apparatus. The solvent was evaporated in vacuo, and the residue was taken up into ether. The ether solution was washed with ice-water and dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The residue was purified by chromatography on alumina; elution with methylene chloride gave 0.95 g (72%) of **11** as an oil: IR (neat) 2950, 1735, 1440, 1375, 1290, 1120, 1060, 1040, 865 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (6 H, s), 1.25–2.35 (10 H, m), 3.55 (3 H, s), 3.85 (4 H, s), 5.25 (1 H, m); MS m/e 268 (M^+). Anal. ($C_{15}H_{24}O_4$) C, H.

4-Methyl-4-(4,4-ethylenedioxycyclohexenyl)pentanoic Acid (12). A mixture of 0.81 g (3.0 mmol) of **11** and 0.67 g (12 mmol) of potassium hydroxide in 17 mL of 50% aqueous ethanol was stirred at room temperature overnight and then acidified with 10% HCl. The solvent was removed on a rotary evaporator, and the residue was dissolved in ether. After the mixture was washed with water, the ethereal layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.71 g (93%) of **12** as a viscous oil: IR (neat) 3500–2400, 1705, 1417, 1374, 1293, 1247, 1216, 1115, 1059, 1036, 990, 944, 862 cm^{-1}; ^1H NMR (CCl_4) δ 1.03 (6 H, s), 1.50–1.80 (4 H, m), 1.90–2.30 (6 H, m), 3.83 (4 H, s), 5.76 (1 H, m). Anal. ($C_{14}H_{22}O_4$) C, H.

1-Diazo-5-methyl-5-(4,4-ethylenedioxycyclohexenyl)hexan-2-one (14). To a stirred suspension of 180 mg (7.5 mmol) of sodium hydride (50% mineral oil suspension, washed with anhydrous hexane and petroleum ether) in 20 mL of dry benzene was added dropwise a solution of 1.02 g (4.0 mmol) of **12** in 7 mL of dry benzene. The suspension was stirred at room temperature for 1 h and then cooled to 5 °C as 2.8 mL of oxalyl chloride was added. The mixture was stirred at 5 °C for 10 min and at room temperature for 1 h. Filtration by suction under nitrogen and evaporation of the filtrate at reduced pressure gave a pale yellow oil which showed strong absorption at 1790 cm^{-1}. This oil was taken up into 3 mL of benzene and was added slowly to a solution of 0.02 mol of diazomethane (prepared from 2.4 g of *N*-nitrosomethylurea) in 80 mL of ether at 0 °C. The mixture was stirred overnight at 0–10 °C, filtered, and concentrated in vacuo at 20 °C to give an oil. This was purified by chromatography on 20 g of alumina, eluting with $CHCl_3$, to yield 0.90 (82%) of **14** as a pale yellow oil: IR (neat) 3080, 2070, 1645, 1370, 1336, 1117, 1060, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (6 H, s), 1.50–1.82 (4 H, m), 2.05–2.55 (6 H, m), 4.05 (4 H, s), 5.29 (1 H, s), 5.44 (1 H, m).

2-Diazo-6-methyl-6-(4,4-ethylenedioxycyclohexenyl)heptan-3-one (25). To a stirred suspension of 50 mg of sodium hydride (50% mineral oil suspension washed with anhydrous hexane) in 10 mL of dry benzene was added 127 mg (1 mmol) of **12** in 3 mL of dry benzene. The mixture was stirred for 1 h at room temperature and was then cooled to 5 °C while 0.8 mL of oxalyl chloride was added. Stirring was continued for an additional 1 h at room temperature. The mixture was filtered by suction under a nitrogen atmosphere, and the filtrate was concentrated and dissolved in 2 mL of dry benzene. This solution was added slowly to an ethereal solution of distilled diazoethane[34] at 0 °C, and the mixture was stirred overnight at 0–10 °C. Removal of the solvent under reduced pressure at 10 °C gave 130 mg of **25** as a yellow oil: IR (neat) 2940, 2050, 1640, 1375, 1295, 1255, 1120, 1060, 1040, 945, 865 cm^{-1}; ^1H NMR (CCl_4) δ 1.03 (6 H, s), 1.18–2.32 (10 H, m), 1.80 (3 H, s), 3.84 (4 H, s), 5.25 (1 H, t).

2,2-Dimethyl-9,9-ethylenedioxytricyclo[5.4.0.0^{1,6}]undecan-5-one (15). To a solution of 250 mg of bis(*N*-*n*-propylsalicylidenaminato)copper(II) (**20**) in 15 mL of benzene and 180 mL of cyclohexane at 80 °C was added dropwise a solution of 835 mg (0.03 mol) of **14** in 6 mL of benzene. The mixture was stirred at 80–85 °C for 8 h, after which the solvent was removed under reduced pressure to leave a dark green residue. This was taken up into a mixture of 50 mL of ethanol and 20 mL of acetone, and hydrogen sulfide was passed through the suspension. After being left standing for 1 h, the mixture was filtered and the filtrate was concentrated to a brown oil. This was purified by preparative layer chromatography on silica gel, eluting with $CHCl_3$, to give 492 mg (66%) of **15**: IR (neat) 2940, 2860, 1678, 1475, 1367, 1115, 1065, 1037, 990, 942, 860 cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (3 H, s), 1.09 (3 H, s), 1.18–2.33 (11 H), 3.81 (4 H, s); MS m/e 250 (M^+).

2,2,6-Trimethyl-9,9-ethylenedioxytricyclo[5.4.0.0^{1,6}]undecan-5-one (26). To a mixture of 40 mL of cyclohexane and 50 mg of bis(*N*-*n*-propylsalicylidenaminato)copper(II) (**20**) (dried in an oven at 80–100 °C for 10 min before use) dissolved in 5 mL of dry benzene was added 250 mg of **25** in 2 mL of dry benzene with vigorous stirring at 75–80 °C for 12 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in a mixture of 20 mL of ethanol and 10 mL of acetone. An excess of hydrogen sulfide was passed through this suspension, and the mixture was allowed to stand for 1 h. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was chromatographed on alumina, using hexane–THF (3:1) as eluant, to give 102 mg (45%) of **26**: IR (neat) 2940, 2860, 1672, 1475, 1363, 1110, 1063, 1035, 945, 930, 873, 862 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (3 H, s), 1.13 (6 H, s), 1.18–2.33 (11 H, m), 3.83 (4 H, s); MS m/e 264 (M^+). Anal. ($C_{16}H_{24}O_3$) C, H.

2,2-Dimethyl-9,9-ethylenedioxyspiro[5.5]undecan-5-one (16). To a solution of 750 mg (0.03 mol) of **15** in 5 mL of anhydrous ether and 40 mL of liquid ammonia was added 138 mg (0.2 g-atom) of lithium in small pieces. The mixture was stirred for 1 h, and 300 mg of ammonium chloride was added cautiously. The ammonia was allowed to evaporate, and the residue was taken up into 30 mL of ether. To this solution was added 20 mL of a saturated aqueous solution of tartaric acid, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extract was washed with saturated sodium chloride solution and dried ($MgSO_4$). Removal of the solvent in vacuo gave 720 mg (90%) of **16** as an oil which crystallized upon standing: IR (neat) 3000–2800, 1710, 1470–1450, 1425, 1374, 1238, 1110, 1093, 1037, 943, 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (6 H, s), 1.20–1.90 (10 H, m), 2.33 (2 H, m), 2.50 (2 H, s), 3.90 (4 H, s); MS m/e 252 (M^+). Anal. ($C_{15}H_{24}O_3$) C, H.

2,2,6-Trimethyl-9,9-ethylenedioxyspiro[5.5]undecan-5-one (27). To a stirred solution of 30 mg (0.11 mmol) of **26** in 3 mL of ether and 20 mL of liquid ammonia was added 5 mg of lithium metal. An additional 10 mg of lithium metal was added after several minutes, and stirring was continued for 1 h. A deep blue color remained at the end of this period. To this mixture was added 20 mL of ether followed by 30 mg of ammonium chloride. The liquid ammonia was allowed to evaporate, 5 mL of water was added to the residue, and the mixture was neutralized with an aqueous solution of tartaric acid. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with an aqueous solution of sodium chloride and water and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was purified by preparative layer chromatography on silica gel plates (Merck PF_{254}) developed with hexane–THF (3:1). The fraction with R_f = 0.7 afforded 27 mg (90%) of **27**: IR (neat) 2950,

(34) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).
(35) J. Dickstein, M. Bodnar, and R. M. Hoegerle, U.S. Patent 3094554 [*Chem. Abstr.*, **59**, 12647 (1963)].

2860, 1708, 1450, 1375, 1238, 1188, 1100, 1032, 930 cm^{-1}; ^1H NMR (CCl_4) δ 1.02 (3 H, s), 1.17 (3 H, s), 1.20 (3 H, d), 1.40–2.40 (11 H, m), 3.82 (4 H, s); MS *m/e* 266 (M^+). Anal. ($C_{16}H_{26}O_3$) C, H.

Reductive Methylation of 15. To a solution of 70 mg of lithium in 15 mL of distilled liquid ammonia was added 500 mg (2 mmol) of **15** in 3 mL of dry THF. After the mixture was stirred for 1 h, the ammonia was allowed to evaporate at 15 °C and 2.81 g (20 mmol) of methyl iodide was added dropwise. A vigorous reaction took place, and a white suspension was produced. The mixture was refluxed overnight, cooled, and treated with a solution of aqueous tartaric acid. This mixture was extracted with ether, and the ethereal extract was washed with water and dried (Na_2SO_4). Removal of solvent and purification of the residue by preparative layer chromatography (elution with chloroform) gave 365 mg (70%) of 2,2-dimethyl-9,9-ethylenedioxy-5-methoxyspiro[5.5]undec-5-ene (**21**): IR (neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (6 H, s), 1.02 (2 H, t, *J* = 6 Hz), 1.20–2.25 (12 H), 2.56 (3 H, s), 4.00 (4 H, s), 4.91 (1 H, s); MS *m/e* 266 (M^+). In addition, 60 mg of impure **27** was obtained from a band at higher R_f (0.75).

2,2-Dimethyl-9,9-ethylenedioxy-4-((*n*-butylthio)methylene)spiro[5.5]undecan-5-one (24). A mixture of 160 mg of sodium hydride (50% mineral oil suspension, washed with anhydrous hexane), 400 mg (1.6 mmol) of **16**, and 420 μL (ca. 4 mmol) of ethyl formate in 10 mL of dry dimethoxyethane was stirred under nitrogen at room temperature for 24 h. The solvent was removed on a rotary evaporator, the residue was cooled to 5 °C, and 5 mL of an aqueous solution of tartaric acid was added. The mixture was extracted with ether, and the extract was washed with a saturated aqueous solution of sodium chloride and dried ($MgSO_4$). Removal of the solvent in vacuo left 340 mg of virtually pure **23**. This was taken up into 20 mL of benzene, 115 mg of *n*-butyl mercaptan, and 10 mg of *p*-toluenesulfonic acid were added, and the mixture was refluxed overnight in a Dean–Stark separator. The solvent was removed by evaporation, and 30 mL of an aqueous solution of sodium bicarbonate was added. This mixture was extracted with ether, and the ethereal layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent left a residue which was purified by preparative layer chromatography on silica gel to give 100 mg (18%) of **24**: ^1H NMR ($CDCl_3$) δ 0.92 (6 H, s), 0.96 (3 H, t, *J* = 7 Hz), 1.22–1.88 (14 H), 2.22 (2 H, s), 2.50–2.87 (4 H, m), 3.99 (4 H, s), 6.20 (1 H, s); MS *m/e* 352 (M^+). In addition, 122 mg of a diketone, resulting from the hydrolysis of the ketal function of **24**, was isolated.

***cis*-2,2,6-Trimethyl-9,9-ethylenedioxyspiro[5.5]undecan-5-ol (28).** To a stirred solution of 153 mg of lithium tri-*tert*-butoxyaluminum hydride in 8 mL of THF at 0 °C was added 53 mg (0.20 mmol) of **27**. After 2 h the solvent was removed on a rotary evaporator and 10 mL of ether followed by 3 mL of water was added cautiously to the residue. The ether solution was washed twice with a saturated aqueous solution of sodium chloride and dried (Na_2SO_4). After removal of the solvent, the residue was purified by preparative layer chromatography on silica gel. Elution with hexane–THF (3:1) gave 50 mg (33%) of **28**: IR (neat) 3400, 1456, 1374, 1338, 1280, 1105, 938, 883, 849 cm^{-1}; ^1H NMR (CCl_4) δ 0.80–1.10 (9 H), 1.35–1.80 (13 H, m), 2.29 (1 H, broad s), 3.82 (4 H, s). Anal. ($C_{16}H_{28}O_3$) C, H.

2,2,6-Trimethyl-9,9-ethylenedioxyspiro[5.5]undec-5-ene (30). To a stirred solution of 54 mg (0.20 mmol) of **28** in 5 mL of pyridine (dried over barium oxide) was added 0.02 mL (0.20 mmol) of methanesulfonyl chloride. The mixture was stirred for 2 h at 0 °C. This solution was diluted with 10 mL of ether and neutralized with 10% hydrochloric acid. The ether layer was separated, washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo at room temperature. The residue was purified by chromatography on alumina eluting with methylene chloride to give the mesylate **29**: IR (neat) 3000–2850, 1475–1460, 1370–1330, 1172, 1100, 1030, 965, 923, 900, 865, 840, 755 cm^{-1}; ^1H NMR (CCl_4) δ 0.80–1.05 (9 H), 1.10–2.60 (13 H, m), 2.93 (3 H, s), 3.82 (4 H, s).

A mixture of **29** and 2 mL of dimethyl sulfoxide was stirred for 7 h at 60 °C. The reaction mixture was cooled to room temperature and extracted with chloroform, and the extract was washed with water. The chloroform layer was dried ($MgSO_4$) and concentrated to give 40 mg (80%) of **30**: IR (neat) 3050, 1475–1440, 1375, 1259, 1110, 1093, 945, 892 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (6 H, s), 1.10–1.80 (10 H, m), 1.90 (3 H, s), 3.81 (4 H, s), 5.35 (1 H, m). Anal. ($C_{16}H_{26}O_2$) C, H.

2,2,6-Trimethylspiro[5.5]undec-5-en-9-one (31). To a stirred solution of 19 mg (0.076 mmol) of **30** in 3 mL of THF at 0 °C was added 1 mL of 1.5 M perchloric acid. After being stirred at 0 °C for 1 h, the mixture was neutralized with saturated sodium carbonate. The solution was extracted three times with ether, washed with water, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a solid residue which was purified by preparative layer chromatography on silica gel, eluting with hexane–THF (5:1). The band at R_f = 0.47 gave 15 mg (96%) of **31**: IR (neat) 3030, 2950, 1717, 1475, 1415, 1390, 1330, 1171, 995, 950, 820 cm^{-1}; ^1H NMR (CCl_4) δ 0.93 (6 H, s), 1.10–1.65 (6 H, m), 1.81 (3 H, s), 2.00–2.40 (4 H, m), 5.35 (1 H, m); MS *m/e* 206 (M^+). Anal. ($C_{14}H_{22}O$) C, H.

2,2,6,9-Tetramethylspiro[5.5]undec-5-en-9-ol (32). To a stirred solution of 17 mg (0.08 mmol) of **31** in 5 mL of ether at 0 °C was added an excess of methyllithium in ether. The mixture was stirred for 1 h, after which it was quenched with 1 mL of aqueous ammonium chloride and the organic layer was extracted with ether. The extract was washed with saturated, aqueous sodium chloride, dried ($MgSO_4$), and concentrated to give 15.0 mg (80%) of **32** and **33** as a colorless solid. Thin-layer chromatography showed the presence of two diastereomers (R_f = 0.31 (70%) and R_f = 0.27 (30%)); separation of these isomers was carried out by preparative layer chromatography on silica gel, eluting with hexane–THF (5:1), to give **32**: IR (Nujol) 3300, 3000–2800, 1470–1435, 1372, 1126, 977, 900, 712 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (6 H, s), 1.20 (3 H, s), 1.12–2.20 (13 H), 5.20–5.50 (1 H, m). Anal. ($C_{15}H_{26}O$) C, H.

(±)-α-Chamigrene (7). To a stirred solution of 10.0 mg (0.045 mmol) of **32** in 1 mL of pyridine in an ice-water bath was added 0.1 mL of methanesulfonyl chloride. The mixture was stirred vigorously for 1 h, 1 mL of water was added, and the solution was acidified with aqueous tartaric acid to pH 4–5. This mixture was extracted with ether (10 mL), and the extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in 1 mL of dimethyl sulfoxide, and the solution was heated to 50–60 °C with stirring for 1 h. After being cooled, the mixture was diluted with 5 mL of water and extracted with petroleum ether. The extract was washed with water, dried, and concentrated, and the residue was purified by preparative GLPC to give 5.0 mg (55%) of (±)-**7** whose IR and NMR spectra were superimposable in every detail on those of an authentic specimen.

(4*R*)-Isopropyl-1-methylcyclohexene (36). A mixture of 63.5 g (0.46 mol) of (*R*)-(+)-limonene (**35**) and 160 mg of platinum oxide in 200 mL of 95% ethanol was stirred at room temperature under 1 atm of hydrogen. After 11.2 L (0.46 mol) of hydrogen had been absorbed, the solution was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo, and the residue was distilled to give 55.2 g (87%) of **36**: bp 55–60 °C (20 mm); IR (film) 1450, 1380, 1360, 1090, 1055, 798 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (6 H, d, *J* = 6 Hz), 1.0–2.3 (8 H, m), 1.60 (3 H, s), 5.18–5.47 (1 H, m).

(4*R*)-Isopropyl-1-methylcyclohexene Oxide (37). To a mixture of 55.2 g (0.40 mol) of **36** and 73 g of sodium carbonate in 500 mL of dichloromethane stirred at ice temperature was added dropwise 120 g (0.63 mol) of 40% peracetic acid over a 1.5-h period. After a further 2.5 h, the mixture was washed with water, aqueous sodium bicarbonate, and concentrated brine and dried ($MgSO_4$). Filtration, followed by removal of solvent in vacuo and distillation of the residue, gave 54.9 g (89%) of **37**: bp 33–35 °C (0.07 mm); IR (film) 1465, 1430, 1208, 1120, 1040, 1020, 870, 843, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (6 H, d, *J* = 6 Hz), 0.9–2.2 (8 H, m), 1.30 (3 H, s), 2.84–3.04 (1 H, m).

(4*R*)-Isopropyl-1-methylcyclohexane-1,2-diol (38). A solution of 54.4 g (0.352 mol) of **37** and 20 mL of 3% aqueous perchloric acid in 300 mL of tetrahydrofuran was stirred at ice temperature. After 5 h the solution was diluted with 300 mL of water and extracted with 3 × 200 mL of dichloromethane. The extract was dried ($CaCl_2$) and filtered, and the solvent was removed in vacuo. The residue was taken up in 150 mL of dichloromethane and purified on a short column of Activity IV silica gel (500 g). Removal of the solvent and distillation of the residue gave 47.45 g (76%) of **38** which crystallized on standing: mp 77–80 °C; bp 90–95 °C (0.07 mm); IR (Nujol) 3500, 1460, 1370, 1170–1030, 960, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (6 H, d, *J* = 6 Hz), 1.22 (3 H, s), 1.0–1.9 (8 H, m), 2.30 (2 H, broad s, exchanges with D_2O), 3.60 (1 H, t, *J* = 4 Hz); MS *m/e* 172 (M^+).

(3*R*)-Isopropyl-6-oxoheptanal (39). A solution of 45.65 g (0.266 mol) of **38** in 700 mL of 95% ethanol was added to a solution of 69 g (0.32 g-atom) of sodium metaperiodate in 700 mL of water. A white solid was precipitated as the reaction temperature rose to 37 °C. After 1.3 h, 1 L of water was added, and the mixture was extracted with 3 × 300 mL of ether. The organic extract was washed with saturated, aqueous sodium bicarbonate and saturated brine and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo and the residue was distilled to give 41.43 g (91%) of **39**: bp 83–86 °C (0.05 mm); IR (film) 2760, 1730, 1460, 1410, 1385, 1360, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (3 H, d, *J* = 6 Hz), 0.82 (3 H, d, *J* = 6 Hz), 1.0–2.0 (4 H, m), 2.13 (3 H, s), 2.2–2.7 (4 H, m), 9.75 (1 H, t, *J* = 2 Hz); MS *m/e* 170 (M^+).

(3*S*)-Isopropyl-6-oxo-1-piperidinohept-1-ene (40). To a solution of 35.6 g (0.209 mol) of **39** in 150 mL of anhydrous ether stirred at ice temperature was added dropwise 19.6 g (0.23 mol) of freshly distilled piperidine over a 0.5-h period. After a further 3 h at ice temperature, the solution was washed with saturated brine and dried ($MgSO_4$). Filtration, followed by solvent removal in vacuo, gave 47.90 g (96%) of oily **40**: IR (film) 1720, 1650, 1445, 1380, 1194, 1117, 943, 860 cm^{-1}; ^1H

NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6 Hz), 0.85 (3 H, d, J = 6 Hz), 1.1–2.0 (10 H, m), 2.15 (3 H, s), 2.2–2.6 (2 H, m), 2.6–3.0 (4 H, m), 4.05 (1 H, d of d, J = 8, 14 Hz), 5.72 (1 H, d, J = 14 Hz); MS m/e 237 (M^+).

(5*S*)-Isopropyl-2-methylcyclopent-1-enecarboxaldehyde (41). To a solution of 46.04 g (0.194 mol) of **40** in 600 mL of anhydrous ether at reflux was added dropwise 28 g (0.468 mol) of glacial acetic acid over a 0.5-h period. After 6 h at reflux the solution was cooled and neutralized with saturated, aqueous sodium bicarbonate. The mixture was washed with saturated brine, dried ($MgSO_4$), and filtered. Solvent removal in vacuo, followed by two consecutive vacuum distillations, gave 25.66 g (87%) of **41**: bp 50–55 °C (0.07 mm); UV (95% ethanol) λ_{max} 254 nm (ϵ 9,750) (lit.[24] λ_{max} 254–255 nm (ϵ 10,800)); IR (film) 2750, 1660, 1630, 1460, 1375, 1340, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65 (3 H, d, J = 6.8 Hz), 0.90 (3 H, d, J = 6.8 Hz), 1.0–2.7 (3 H, m), 1.75 (1 H, q, J = 6.8 Hz), 2.17 (3 H, s), 2.7–3.3 (2 H, m), 10.02 (1 H, s). The 2,4-dinitrophenylhydrazone of **41** had a melting point of 173.5–174.5 °C.

2-Methylene-4-((5*S*)-isopropyl-2-methylcyclopentenyl)butyrolactone (43). A solution of 3.0 g (19.7 mmol) of **41** and 4.6 g (23.8 mmol) of ethyl 2-bromomethylacrylate in 50 mL of anhydrous tetrahydrofuran was passed dropwise through a column of activated zinc granules (No. 10 mesh) saturated with tetrahydrofuran and preheated to mild reflux. After 1.5 h, when passage was complete, the column was flushed with 50 mL of tetrahydrofuran. The dark solution was diluted with 100 mL of ether and treated with ice-cold, 1% sulfuric acid. The organic layer was separated and washed with saturated brine, dried ($MgSO_4$), and filtered. Removal of the solvent in vacuo gave 5.0 g of **43** which was used without purification: IR (film) 1775, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.0–5.55 (1 H, m), 5.55–5.7 (1 H, m), 6.2–6.34 (1 H, m).

2-Methyl-4-((5*S*)-isopropyl-2-methylcyclopentenyl)butyrolactone (44). A mixture of 5.0 g of crude **43** and 100 mg of platinum oxide in 20 mL of 95% ethanol was stirred at room temperature under hydrogen at atmospheric pressure. After 4 h, when 475 mL (19.7 mmol) of hydrogen had been absorbed, the mixture was diluted with 100 mL of ether, washed with water, saturated brine, and dried ($MgSO_4$). Filtration, followed by removal of the solvent in vacuo and purification by chromatography on neutral alumina (Activity II), gave 2.20 g (50% based on **41**) of **44** after distillation: bp 100–105 °C (0.05 mm); IR (film) 1775, 1460, 1375, 1330, 1195, 1106, 1107, 927, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (3 H, d of d, J = 1, 7 Hz), 0.85 (3 H, d of d, J = 1, 7 Hz), 1.22 (3 H, d, J = 7 Hz), 1.72 (3 H, s), 1.4–3.0 (9 H, m), 4.85–5.4 (1 H, m).

2-Methyl-4-((5*S*)-isopropyl-2-methylcyclopentenyl)butanoic Acid (45). A mixture of **44** (1.50 g, 6.80 mmol) and 0.5 g of 10% palladium-on-calcium carbonate in 20 mL of 95% ethanol was rapidly stirred at room temperature under hydrogen at atmospheric pressure. After 3 h, when 224 mL (9.3 mmol) of hydrogen was absorbed, the mixture was diluted with ether, washed with aqueous ammonium chloride and saturated brine, and dried ($MgSO_4$). Filtration, followed by removal of the solvent in vacuo, gave 1.51 g (100%) of pure **45**: IR (film) 1710, 1460, 1405, 1375, 1285, 1240, 943 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (3 H, d, J = 6.5 Hz), 0.90 (3 H, d, J = 6.5 Hz), 1.20 (3 H, d, J = 6.5 Hz), 1.6 (3 H, s), 11.8 (1 H, broad s, variable). The methyl ester of **45** was prepared with diazomethane and was purified by preparative GLC (Carbowax column): MS m/e 283.193 (M^+), calcd for $C_{15}H_{26}O_2$ 283.193.

2-Methyl-4-((5*S*)-isopropyl-2-methylcyclopentenyl)butanoyl Chloride (46). A solution of 1.51 g (5.34 mmol) of **45** in 5.0 g (39 mmol) of freshly distilled oxalyl chloride was stirred at room temperature for 5 min. A colorless gas was evolved. Removal of excess oxalyl chloride in vacuo, followed by addition of 1 mL of hexane and evaporation in vacuo, gave 1.64 g of crude **46**: IR (film) 1790, 1450, 1370, 943 cm^{-1}.

1-Diazo-3-methyl-5-((5*S*)-isopropyl-2-methylcyclopentenyl)pentan-2-one (47). A solution of 1.64 g of crude **46** in 5 mL of hexane was slowly added to an ice-cold, stirred solution of diazomethane (prepared from 10 g (56 mmol) of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide and distilled twice from potassium hydroxide pellets) in 110 mL of ether. After 1 h, the solvent was removed in vacuo, and the residue was taken up into ether, filtered, and dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave 1.65 g of **47** as an unstable, orange oil: IR (film) 2110, 1640, 1460, 1360, 1312, 1140, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (3 H, d, J = 7 Hz), 0.90 (3 H, d, J = 7 Hz), 1.13 (3 H, d, J = 7 Hz), 1.63 (3 H, s), 5.30 (1 H, s).

4,(7*S*)-Dimethyl-(10*S*)-isopropyltricyclo[5.3.0.0^{1,6}]decan-5-one (53). A mixture of 1.65 g of **47** and 3 g of copper powder in 350 mL of cyclohexane was heated at reflux for 10 min with rapid stirring. A colorless gas was evolved. Filtration, followed by removal of the solvent in vacuo and purification by preparative GLC (Carbowax column), gave 514 mg (34% from **45**) of oily **53**: IR (film) 1680, 1460, 1385, 1310, 1207, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.5–2.5 (m); MS m/e 220.186 (M^+), calcd for $C_{15}H_{24}O$ 220.183.

(4*R*),8-Dimethyl-(1*S*)-isopropyl-(5*R*)-spiro[4.5]decan-7-one (54). To a solution of 90 mg (0.41 mmol) of **53** and 150 mg (2.05 mmol) of *tert*-butyl alcohol in 10 mL of distilled ammonia and 0.5 mL of anhydrous ether stirred at −40 °C was added 60 mg (8.5 mg-atom) of lithium in small pieces over a 5-min period. After 0.5 h, when the solution had turned blue, ammonium chloride was slowly added until the color was discharged, and the ammonia was allowed to evaporate. The residue was taken up into ether, and the ethereal solution was washed with water and saturated brine, dried ($MgSO_4$), and filtered. Solvent removal in vacuo, followed by chromatography of the residual oil on neutral alumina (Activity II), gave 70 mg (77%) of **54**: IR (film) 2980, 2810, 1710, 1445, 1370, 1310, 1223, 1205, 1155, 1067 cm^{-1}.

1,8-Dimethyl-(4*S*)-isopropyl-(5*S*)-spiro[4.5]dec-1-en-7-one (55). A solution of 514 mg (2.34 mmol) of **53** in 30 mL of chloroform was stirred at ice temperature while a stream of dry hydrogen chloride was passed through the solution. After 6.5 h the solution was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and filtered. Removal of the solvent in vacuo gave 537 mg of **55**: IR (film) 1710, 1460, 1370, 1208, 1160, 1065, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.23–5.4 (1 H, m).

(4*S*),8-Dimethyl-(1*S*)-isopropyl-(5*R*)-spiro[4.5]decan-7-one (56). A mixture of 537 mg of **55** and 100 mg of 5% rhodium-on-carbon in 40 mL of absolute ethanol was stirred at room temperature under hydrogen at atmospheric pressure. After 22 h, when 54.5 mL (2.26 mmol) of hydrogen had been taken up, the mixture was filtered and the solvent was removed in vacuo. The residue was purified by preparative GLC (Carbowax column) to give 307 mg (60% from **53**) of oily **56**: IR (film) 1710, 1450, 1370, 1045 cm^{-1}; MS m/e 222.197 (M^+), calcd for $C_{15}H_{26}O$ 222.198.

7-Acetoxy-(4*S*),8-dimethyl-(1*S*)-isopropyl-(5*R*)-spiro[4.5]dec-7-ene (63). A mixture of 307 mg (1.38 mmol) of **56** and 30 mL of a reagent, prepared by dissolving 4.8 mL of acetic anhydride and 0.05 mL of 70% perchloric acid in 45 mL of ethyl acetate, was stirred at room temperature for 10 min. The solution was neutralized with saturated aqueous sodium bicarbonate, and the organic layer was separated, dried ($MgSO_4$), and filtered. Solvent removal in vacuo gave 349 mg of **63**: IR (film) 1760, 1465, 1365, 1215, 1113 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (3 H, s); MS m/e 264 (M^+).

7-Acetoxy-(4*R*),8-dimethyl-(1*S*)-isopropyl-(5*R*)-spiro[4.5]dec-7-ene (64). A mixture of 63 mg (0.284 mmol) of **54** in 6 mL of a reagent, prepared by dissolving 4.8 mL of acetic anhydride and 0.05 mL of 70% perchloric acid in 45 mL of ethyl acetate, was stirred at room temperature for 10 min. The mixture was neutralized with saturated sodium bicarbonate solution, and the organic layer was separated, dried ($MgSO_4$), and filtered. Solvent removal in vacuo gave 75 mg of **64**: IR (film) 3000, 2920, 1760, 1460, 1360, 1212, 1112 cm^{-1}.

8-Bromo-(4*S*),8-dimethyl-(1*S*)-isopropyl-(5*R*)-spiro[4.5]decan-7-one (65). To a stirred solution of 349 mg of **63** in 30 mL of a buffer, prepared by dissolving 2.0 g of sodium acetate in 160 mL of glacial acetic acid and 40 mL of carbon tetrachloride, at ice temperature was added dropwise a solution of 110 mg (1.38 mmol) of bromine in 1 mL of the same buffer. After 10 min, when addition was complete, the solution was diluted with chloroform. The organic layer was separated, washed with water and saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). Filtration, followed by removal of the solvent in vacuo, gave 474 mg of **65**: IR (film) 1715, 1460, 1370, 1285, 1120 cm^{-1}.

8-Bromo-(4*R*),8-dimethyl-(1*S*)-isopropyl-(5*R*)-spiro[4.5]decan-7-one (66). To a stirred solution of 75 mg of **64** in 5 mL of a buffer, prepared by dissolving 2.0 g of sodium acetate in 160 mL of glacial acetic acid and 40 mL of carbon tetrachloride, at ice temperature was added dropwise a solution of 45 mg (0.29 mmol) of bromine in 5 mL of the same buffer. After 10 min, when the addition was complete, the solution was diluted with chloroform and the organic layer was separated, washed with water and saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). Filtration, followed by removal of the solvent in vacuo, gave 88 mg of **66**: IR (film) 3000, 2920, 1720, 1440, 1370, 1268, 1195 cm^{-1}.

(−)-Acorenone B (6). A mixture of 474 mg of **65**, 1.0 g of lithium carbonate, and 0.5 g of lithium chloride in 30 mL of dimethylformamide was stirred at 140 °C for 15 min. After being cooled, the mixture was diluted with ether, washed twice with water and once with saturated brine, and dried ($MgSO_4$). Filtration, followed by removal of the solvent in vacuo, gave an oil which was purified by glc (Carbowax column) affording 103 mg (34% from **56**) of **6**: $[\alpha]_D^{20}$ (chloroform) −19°; UV (methanol) λ_{max} 240 nm (log ϵ 3.81); IR (film) 1670, 1460, 1425, 1375, 1360, 1160, 1115, 1085, 1072, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (3 H, d, J = 6 Hz), 0.86 (3 H, d, J = 6.5 Hz), 0.95 (3 H, d, J = 6.5 Hz), 1.05–2.0 (7 H, m), 1.76 (3 H, d, J = 1.8 Hz), 2.05–2.3 (2 H, m), 2.24 (1 H, d, J = 8.2 Hz), 2.72 (1 H, d, J = 8.2 Hz), 6.58–6.73 (1 H, m); MS m/e 220 (M^+); the spectral data and GLC retention time of **6** and those of an authentic sample of (±)-acorenone B were identical.

(-)-4-Epiacorenone B (67). A mixture of 88 mg of 66, 0.3 g of lithium carbonate, and 0.15 g of lithium chloride in 5 mL of dimethylformamide was stirred at 140 °C for 15 min. The mixture was diluted with ether, washed twice with water and once with saturated brine, and dried ($MgSO_4$). Filtration, followed by removal of the solvent in vacuo, yielded an oil which was purified by preparative GLC (Carbowax column) to give 17 mg (30% from 54) of 67: $[\alpha]_D^{20}$ (ether) -50°; IR (film) 1670, 1445, 1425, 1360, 1235, 1140, 1115, 1080, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, J = 6.5 Hz), 0.88 (6 H, d, J = 3 Hz), 0.95-2.17 (7 H, m), 1.76 (3 H, d, J = 2 Hz), 2.17-2.57 (2 H, m), 2.36 (2 H, d, J = 2 Hz), 6.63-6.78 (1 H, m); MS m/e 220.180, calcd for $C_{15}H_{24}O$ 220.183.

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Cation-Complexing Properties of Synthetic Macrocyclic Polyether-Diester Ligands Containing the Furan, Benzene, Tetrahydrofuran, and Thiophene Subcyclic Units[1]

Jerald S. Bradshaw,*[2] Steven L. Baxter, John D. Lamb, Reed M. Izatt,* and James J. Christensen

Contribution from the Departments of Chemistry and Chemical Engineering and Contribution No. 224 from the Thermochemical Institute, Brigham Young University, Provo, Utah 84602.
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Abstract: Thirteen new macrocyclic polyether-diester ligands containing the furan, 3,4-dimethoxyfuran, tetrahydrofuran, and thiophene subcyclic units have been prepared by reacting a diacid dichloride with the appropriate glycol. The tetrahydrofurano ligands were also prepared by reducing the furan ring of the furano ligands. Certain of these ligands and corresponding macrocyclic polyether-diester ligands containing a benzene subcyclic unit have been shown to form complexes with alkylammonium and metal cations. Complexation with alkylammonium cations was accompanied by significant chemical-shift changes in the ^1H NMR spectra. Free energies of activation (ΔG^*) for the dissociation of the alkylammonium complexes were determined from their temperature-dependent ^1H NMR spectra. The relative kinetic stability (as measured by the ΔG^* values) for complexes between benzylammonium perchlorate and ligands containing an aromatic subcyclic unit increased with increasing ring size in the order 18- < 21- < 24-membered ring. Formation constants as well as ΔH and $T\Delta S$ values were determined in methanol by a calorimetric titration technique for the reaction of Na^+, K^+, Cs^+, and Sr^{2+} with the tetrahydrofurano ligands. The complexes formed between the 18-membered ring containing a tetrahydrofuran subcyclic unit and the alkali-metal cations were about as stable as those formed from 2,6-diketo-18-crown-6 (**2**) but were less stable than those formed from the corresponding pyridine analogue (**1**). The 21- and 24-membered ring compounds containing a furan subcyclic unit were found to be effective carriers of Cs^+ across a $CHCl_3$ liquid membrane separating aqueous phases.

We have reported the synthesis of macrocyclic polyether-diester compounds and compared their cation complexation properties to those of the crown ethers.[3-11] Generally, they do not complex metal cations as strongly as do the crown ethers.[4,5,9,11] However, the diester ligands containing a pyridine subcyclic unit are an exception to this general rule. For example, the pyridino diester compound containing 18 ring members (**1**, Figure 1) forms complexes with metal cations and ammonium salts which are comparable in stability to those formed by any of the crown compounds.[8,9] It is significant that in addition to forming stable complexes with the various cations, compound **1** is relatively easy and inexpensive to prepare compared to most of the crown ether compounds.[8,12]

Macrocyclic polyether compounds containing the 2,5-furan and tetrahydrofuran and the 3,4-thiophene and the 1,3-benzene subcyclic units have been studied in some detail by Cram and his co-workers[13] and by Gray and Reinhoudt and their coworkers.[14] Gray, Reinhoudt, and their co-workers have also studied macrocyclic polyether compounds containing 3,4-furan and thiophene and 1,2-benzene subcyclic units.[15]

We now report the synthesis of macrocyclic polyether-diester compounds containing the furan, tetrahydrofuran, and thiophene subcyclic units (compounds **3-15**, Figure 1). Free energies of activation (ΔG^*_c) for the interaction of alkylammonium salts with these and some closely related ligands containing the benzene subcyclic unit (compounds **16-22**) as well as those of the diester ligand 2,6-diketo-18-crown-6 (**2**) are reported. In addition, log K, ΔH, and $T\Delta S$ values are given for the reaction of several metal cations with some of these compounds (**1-5, 10, 11**, and **16**). The use of several of these compounds to carry metals across a liquid

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