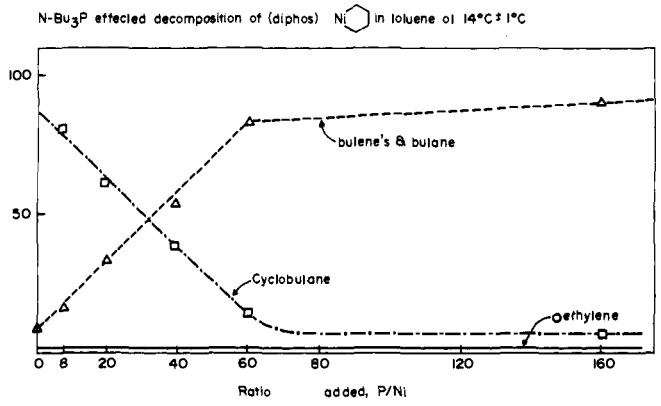
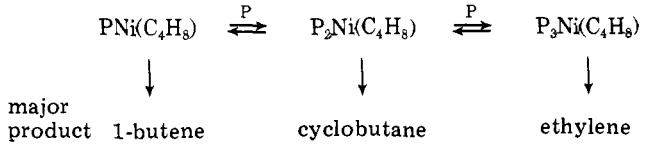


Figure 3.

4. At this point and at higher P/Ni ratios the decomposition ratios are very similar to those resulting from the triphenylphosphine complex at P/Ni = 0 and larger values and only for IIIc at P/Ni = 0. A sample of the pure trisphosphine complex, IVa, was decomposed under similar conditions. The major product (>90%) was ethylene. The yields of the gaseous products were close to quantitative and the ratios of the products were independent of the concentration of the starting complex. All of the low molecular weight hydrocarbons were transferred and collected at reduced pressure and analyzed by GLC.[11] These results combined with the NMR data are most consistent with the following scheme:



Since the chelating phosphine does not form a five-coordinate species on mixing with excess phosphine, the phosphine effect, Figure 3, was very different than that observed for the nonchelating phosphines which form five-coordinate complexes.[12]

It is surprising that the high coordination number complex produced ethylene as the major decomposition product. An isomeration of a metallocycle to a bisolefin-metal complex reduces the oxidation state and retains the same coordination number of the metal. Since the trisphosphine metal complexes are coordinately saturated, the conversion to a lower oxidation state would require the loss of a ligand. The unexpected phosphine exchange of IVa with free phosphene independent of IIIa may provide the key to understanding this apparent inconsistency. Since the β-hydride elimination reaction requires an increase in coordination number, it is reasonable that this is the favored mode of decomposition for the low coordination number complexes.[3]

The only possible comparison of electronic effects which can be made are between the two trisphosphine complexes, IVa and b. It appears as though the better σ donor, poorer π acceptor favors an increase in the production of ethylene over cyclobutane. However, this effect may be associated with the III to IV equilibrium.

Experiments designed to sort out the pieces of this intriguing puzzle are presently in progress.

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References and Notes

(1) R. Noyori, Y. Kumagai, and H. Takaya, *J. Am. Chem. Soc.*, **96**, 634 (1974); T. Kata and S. Cerefice, *ibid.*, **91**, 6520 (1969); R. Grubbs, D. Carr, and P. Burk, *Organotrans.-Met. Chem.*, 135 (1974); P. Binger, *Angew. Chem., Int. Ed. Engl.*, **11**, 309 (1972); H. Hall, C. Smith, and D. Plorde, *J. Org. Chem.*, **38**, 2084 (1973).
(2) A. R. Fraser et al., *J. Am. Chem. Soc.*,-**95**, 597 (1973); L. Cassar, P. E. Eaton, and J. Halpern, *ibid.*, **95**, 3515 (1970).
(3) G. Whitesides, J. White, and J. McDermott, *J. Am. Chem. Soc.*, **95**, 4451 (1973); **98**, 6521 (1976); R. Grubbs, H. Eick, and C. Biefield, *Inorg. Chem.*, **12**, 2166 (1973); G. Whitesides and J. McDermott, *J. Am. Chem. Soc.*, **96**, 947 (1974); J. McDermott, M. Wilson, and G. Whitesides, *ibid.*, **98**, 6529 (1976).
(4) P. S. Bruterman and R. J. Cross, *Chem. Soc. Rev.*, **2**, 271 (1973).
(5) R. Grubbs and T. Brunck, *J. Am. Chem. Soc.*, **94**, 2538 (1972); R. West and E. G. Rochow, *J. Org. Chem.*, **18**, 1739 (1953).
(6) All manipulations must be carried out under deoxygenated argon and the temperature must be maintained below −10 °C.
(7) D. G. Morrell and J. K. Kochi, *J. Am. Chem. Soc.*, **97**, 7262 (1975).
(8) The molecular weights were determined by freezing point depression of benzene. The complexes were decomposed with acid and peroxide. The gases were determined by GLC, the phosphine as the phosphine oxide and the nickel as the dimethylglyoxal complex.
(9) A. D. English, P. Meakin, and J. P. Jesson, *J. Am. Chem. Soc.*, **98**, 422 (1976); P. Meakin, A. D. English, and J. P. Jesson, *ibid.*, **98**, 414 (1976).
(10) P. Meier, A. Merbach, M. Dartiguenave, and Y. Dartiguenave, *J. Am. Chem. Soc.*, **98**, 6402 (1976).
(11) The complexes were decomposed at 9 ± 1 °C as 3 × 10^{-3} M solutions in toluene in reaction vessels attached to a gas manifold. As the reactions progressed those reactions which produced 1-butene as a major product also showed 2-butene as a secondary product.
(12) The diphos complex IIIc in the presence of an excess of (n-Bu)$_3$P showed no signals in the region between the signal for IIIc −44.8 ppm and the signal for the free phosphine (+33.1). The phosphine apparently acts as a base to induce the β-hydride elimination.
(13) Sloan Foundation Fellow and a Camille and Henry Dreyfus Foundation Grantee.

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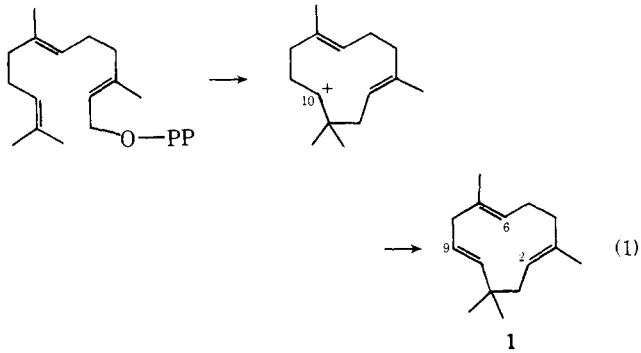
Total Synthesis of Humulene. A Stereoselective Approach

Sir:

The salient structural features of humulene (**1**), a fundamental monocyclic sesquiterpene, include the three olefinic linkages 2*E*, 6*E*, 9*E*, all of which are situated on the cycloundecane ring. Ever since the distinguished but *nonstereoselective* synthesis of humulene accomplished by Corey and Hamanaka in 1967,[1] virtually no synthesis has been reported for this interesting structure. A *highly stereoselective* synthesis of this unique compound is the subject of the present communication.

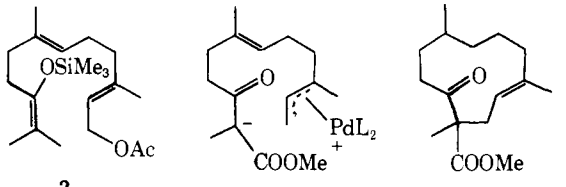
While humulene and the related sesquiterpenes are derived biologically from farnesol by anti-Markovnikov cyclization (eq 1),[2] the laboratory synthesis of these terpenes by such a cyclization has not yet been realized and represents a distinct challenge to the organic chemists. The simplicity of this scheme as a synthetic pathway led to the development of the present efficient synthesis.[3]



(1)

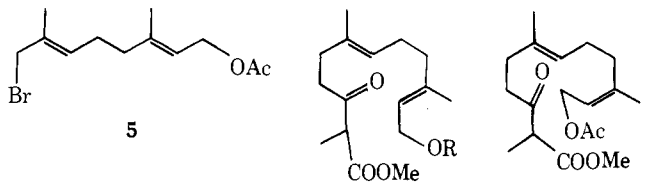
1

A number of experiments on the acid-catalyzed cyclization of the acetate **2**,[4,5] under varying conditions, led to only trace amounts of material corresponding to cycloundecadiene by gas chromatographic analysis. Therefore, a study was made on the generation and behavior of the more stable allylic cation or its functional equivalents. The π-allylpalladium complex **3** is the species of choice and could reasonably be expected to undergo a facile, electrostatically driven,[6] cyclization to **4**.[7]



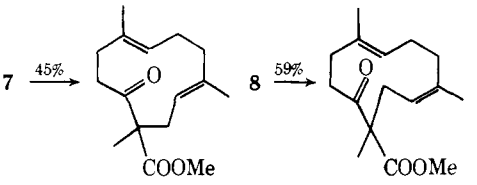
2 3 4

The acyclic sesquiterpene skeleton corresponding to **3** was constructed starting with geranyl acetate via the *E,E*-bromide **5** which was obtained stereoselectively in 40–50% overall yield by the method previously reported:[8] selenium dioxide oxidation followed by treatment with phosphorus tribromide. Reaction of **5** with the dianion (5 equiv) derived from methyl α-methylacetoacetate[9] in tetrahydrofuran at 0 °C for 30 min gave the keto ester **6** (94% yield after chromatographic purification using 1:1 ether–hexane and silica gel), which was then reacetylated with acetic anhydride–pyridine at 25 °C for 10 h to furnish the key intermediate for the cyclization, the acetoxy ketone **7**, as a colorless liquid (quantitative yield) (Anal. Found: C, 66.9; H, 8.9); bp 205 °C (bath temp, 1 mm); homogeneous by TLC; NMR peaks as expected at 1.33 (d, J = 7 Hz, 3 H), 1.60 (s, 3 H), 1.70 (s, 3 H), 2.04 (s, 3 H), 3.56 (q, J = 7 Hz, 1 H), and 3.73 (s, 3 H) ($CDCl_3$); and β-keto ester absorption at 1716–1730 cm^{-1} (liquid film). Starting with neryl acetate and using the same reaction sequences as described above, the *E,Z*-acetoxy ketone **8** was obtained efficiently as a colorless liquid (Anal. Found: C, 66.7; H, 8.9): bp 210 °C (bath temp, 1 mm); homogeneous by TLC; NMR ($CDCl_3$) 1.34 (d, J = 7 Hz, 3 H), 1.62 (s, 3 H), 1.77 (s, 3 H), 2.06 (s, 3 H), 3.56 (q, J = 7 Hz, 1 H), and 3.73 (s, 3 H); IR (liquid film) 1716–1730 cm^{-1}.



5 6, R = H 7, R = Ac 8

The acetate **7** was converted to the corresponding sodium salt by treatment with sodium hydride (1.2 equiv) in dry tetrahydrofuran. The sodio derivative so generated was subjected to cyclization by slow addition to a mixture of tetrakis(triphenylphosphine)palladium (20 mole %),[10] 1,3-bis(diphenylphosphino)propane (20 mole %),[11] hexamethylphosphoric triamide, and tetrahydrofuran at reflux. The addition was conveniently performed using a mechanically driven syringe.[12] After completion of the reaction the product was isolated by column chromatography on silica gel to afford the keto ester **4** as a colorless oil in 45% yield. Neither the position isomer (nine-membered ring)[13] nor the stereoisomer with respect to the olefinic linkage[14] could be detected chromatographically or by NMR analysis. 2-Carbomethoxy-2,5,9-trimethyl-(*E,E*)-4,8-cycloundecadienone (**4**) (Anal. Found: C, 72.9; H, 9.4): bp 140 °C (bath temp, 1 mm); NMR ($CDCl_3$) 1.43 (s, 6 H), 1.59 (s, 3 H), 2.01–3.03 (m, 10 H), 3.74 (s, 3 H), 4.83 (t, J = 7 Hz, 2 H); IR (liquid film) 1744, 1709 cm^{-1}; mass *m/e* 264 (M^+); homogeneous by GLC and TLC (silica gel and silver nitrate–silica gel). Cyclization of **8** under identical conditions gave the *Z,E*-isomer **9** in 59% yield. Again, as was the case with the substrate **7**, the cyclization proceeded in complete stereo- and regiospecific manner. The compound **9** (Anal. Found: C, 72.8; H, 9.4): mp 67–68 °C, NMR ($CDCl_3$) 1.44 (s, 3 H), 1.60 (s, 3 H), 1.65 (s, 3 H), 2.02–3.02 (m, 10 H), 3.73 (s, 3 H), 4.83 (t, J = 7 Hz, 1 H), 5.03 (t, J 7 Hz, 1 H); IR (liquid film) 1741, 1709 cm^{-1}; mass *m/e* 264 (M^+); homogeneous by GLC and TLC (silica gel and silver nitrate–silica gel).



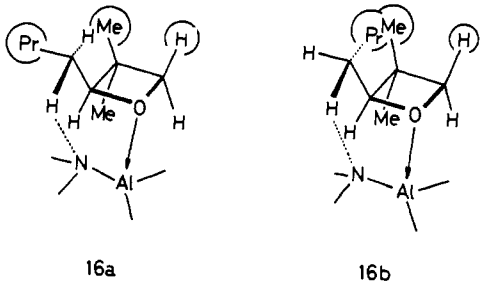
4 9

It is noteworthy that the efficiency of cyclization of the substrate **7** and **8** is strongly dependent upon a crucial selection of catalyst and solvent used. Solvents such as THF or THF–HMPA are much superior to, e.g., benzene, DME, DMF, Me_2SO, or *tert*-butyl alcohol.[15] In the absence of 1,3-bis(diphenylphosphino)propane,[16] a substantial amount (10–25%) of the 22-membered ring compound[17] was produced as a major by-product, which has never been observed in the above reaction conditions.

The crucial intermediate **4**, thus obtained, possesses the two trisubstituted ethylenes needed to prepare humulene (**1**). At this point in the synthesis, the successful accomplishment of the remaining structural modifications, generation of the third double bond stereoselectively, depended upon a careful selection of reagents and reaction conditions, since the cation at C-10 (eq 1) may be expected to suffer a rather complicated rearrangement.[18]

Reduction of the keto ester **4** by excess lithium aluminum hydride in ether at 0 °C for 2 h afforded the diol **10** as a colorless crystalline solid (mp 128 °C, 96% yield)[19] which was converted to the primary tosylate **11** by treatment with *p*-toluenesulfonyl chloride (1.3 equiv) in pyridine at −20 °C for 12 h (95% yield). The key intermediate for the synthesis of humulene, the oxetane **12**,[20] was prepared from **11** in 76% yield by exposure to potassium *tert*-butoxide (2 equiv) in tetrahydrofuran at 0 °C for 1 h.[21] The transformation of **12** to the homoallylic alcohol **13** was carried out stereoselectively in 88% isolated yield by a new method which involved stirring of **12** with diethylaluminum *N*-methylanilide (10 equiv)[22] in benzene at reflux for 40 h. The stereochemistry of **13**, a crucial element in the synthesis and expected from other examples mentioned below, was confirmed by the appearance of characteristic strong infrared absorption at 970 cm^{-1} and also by NMR analysis ($J_{C(9)H-C(10)H}$ = 16 Hz). The conversion of the intermediate **13** to humulene (**1**) was accomplished by a sequence of straightforward steps. Thus, oxidation of **13** by the Corey–Kim method[23] gave the aldehyde **14** which was converted to the tosylhydrazone **15**, mp 116–116.5 °C, using tosylhydrazine (1.1 equiv) in ethanol at reflux for 1 h (88% yield from **13**). Lithium aluminum hydride reduction of **15** in dioxane (reflux for 40 h)[24] followed by short-path column chromatography on silica gel (hexane) to remove the polar by-products furnished humulene (**1**) (42% yield) uncontaminated by stereoisomeric and other impurities. Comparison of NMR, infrared, and mass spectra and TLC, silver nitrate–silica gel TLC, and GLC behavior of the synthetic product with natural humulene confirmed the assigned structure **1**.[25]

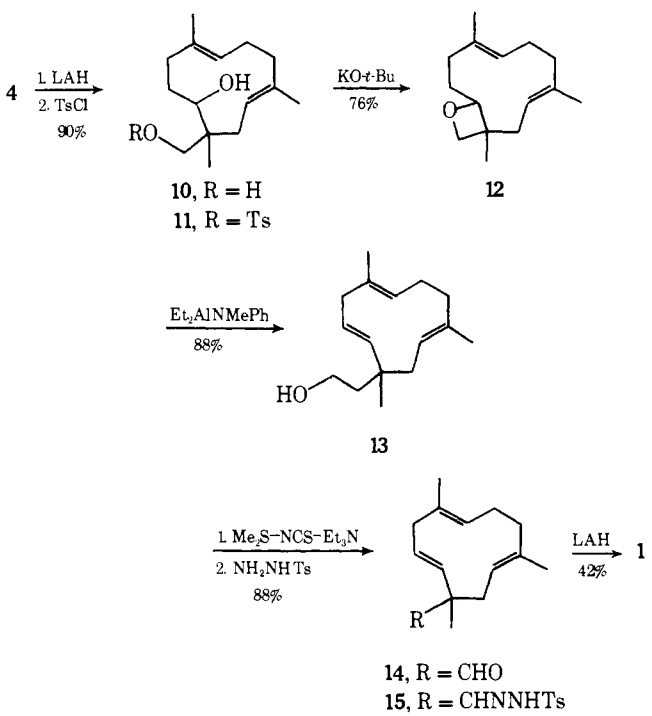
The presently described synthesis depends heavily on the novel oxetane ring opening by organoaluminum reagent. To



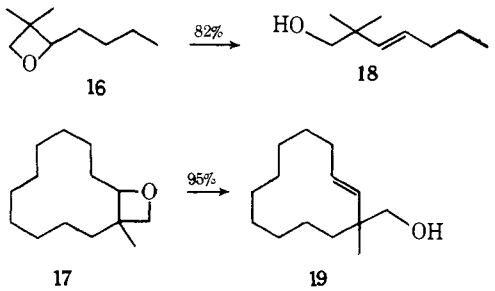
16a 16b

Figure 1. Possible transition states for the ring cleavage of oxetane, **16**.

Scheme I



illustrate the potential of this method in other systems, the rearrangements of **16**[26] and **17**[27] have been investigated. Indeed, the oxetane **16** or **17** on treatment with excess diethylaluminum *N*-methylanilide[22,28] in benzene at reflux for 40 h afforded **18**[29] and **19**[30] in 82 and 95% yields, respectively, thus emphatically demonstrating the applicability of this methodology to more general systems of synthetic interest.



Of crucial importance to this rearrangement was our previous observation that the reaction of aluminum amide with the oxirane ring produced the corresponding allylic alcohol regio- and stereospecifically.[31] The unusual specificity of these reactions was explained by a cyclic syn-elimination mechanism where the ring opening has substantial stereochemical requirements. The high stereoselectivities (~99%) of the present olefin forming process can likewise be rationalized in a following manner. Thus, the relative conformational energies of **16a** and **16b** would determine the product ratio from **16** (Figure 1). The conformer **16a** appears to be favorable in all respects and should give rise to the *E*-olefinic alcohol **18**. In the alternate structure **16b**, severe nonbonding interactions develop between the *n*-propyl chain and methyl substituent of the oxetane ring which preclude the formation of the *Z*-isomer.

Acknowledgments. We thank Dr. N. Hashimoto (Kirin Brewery Co. Ltd.), for a generous sample of humulene, and to Professor H. Shirahama for spectroscopic data of humulene. We give special thanks to Dr. K. Ohno (Toray Industries Inc.) for helpful discussions.

References and Notes

(1) E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **89**, 2758 (1967).
(2) General review for terpene biosynthesis: see for an example, H. C. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins", W. A. Benjamin, New York, N.Y., 1964.
(3) Recently, Professor S. Ito and co-workers reported a nonstereoselective synthesis of germaclane-type sesquiterpene from farnesol; M. Kodama, Y. Matsuki, and S. Ito, *Tetrahedron Lett.*, 1121 (1976). The method depends upon an anion-induced intramolecular cyclization. See also, M. Kodama, Y. Matsuki, and S. Ito, *ibid.*, 3065 (1975), and T. Kato, T. Kobayashi, and Y. Kitahara, *ibid.*, 3299 (1975).
(4) S. Hashimoto, A. Itoh, Y. Kitagawa, H. Yamamoto, and H. Nozaki, in press.
(5) The acetate **2** was prepared from farnesol by the following sequences of reactions: (1) acetylation, (2) terminal epoxidation, (3) hydrobromic acid ring opening of the oxirane ring, (4) Corey–Kim oxidation to yield the bromoketone, (5) reductive debromination by Zn–Me_3SiCl in tetrahydrofuran.
(6) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
(7) The utility of allylic alkylation via π-allylpalladium complexes: (a) for a recent development, B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, **95**, 292 (1973); B. M. Trost and T. R. Verhoeven, *ibid.*, **98**, 630 (1976); B. M. Trost and J. P. Genet, *ibid.*, **98**, 8516 (1976); (b) for initial work and general reviews, J. Tsuji, *Acc. Chem. Res.*, **2**, 144 (1969); "Organic Synthesis by Means of Transition Metal Complex", Springer Verlag, New York, N.Y., 1975.
(8) P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 486 (1972).
(9) S. N. Huckin and K. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).
(10) Prepared by the method of D. R. Coulson, *Inorg. Synth.*, **13**, 121 (1972).
(11) T. Yoshida, M. Iwamoto, and S. Yuguchi, Japan Patent, 11934 (1967); *Chem. Abstr.*, **68**, 105358 (1968); W. Hevertson and H. R. Watson, *J. Chem. Soc.*, 1490 (1962).
(12) Perfusor IV of B. Braun Melsungen AG was used for this experiment.
(13) Professor B. M. Trost reported the alkylation of allylic acetate with the sodium salt of dimethyl malonate catalyzed by palladium proceeded with retention of configuration at the carbon undergoing displacement, whereas a substantial amount (63–10%) of regioisomer was also produced in this reaction: B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, **41**, 3215 (1976).
(14) The complete stereospecificity was determined by chromatographic ($AgNO_3$–silica gel TLC and GLC) and spectroscopic (NMR) analyses.
(15) In these solvent systems, the major product was found to be acyclic trienes produced by elimination of acetic acid.
(16) Other diphosine ligands including 1,2-bis(diphenylphosphino)ethane and 1,4-bis(diphenylphosphino)butane were slightly less efficient for the cyclization of **7** (42 and 45% yields, respectively).
(17) NMR ($CDCl_3$) 1.30 (s, 6 H], 1.56 (s, 12 H), 3.70 (s, 6 H); IR (liquid film) 1710, 1735 cm^{-1}; mass *m/e* 528 (M^+, calcd for $C_{32}H_{48}O_6$:528); homogeneous by TLC (R_f 0.34, silica gel, hexane–ether, 2:1; using the same solvent systems R_f of **4**: 0.46).
(18) The cation at C-10 of humulene structure (eq 1) is known to be one of the most important synthetic intermediates in sesquiterpene biosynthesis, for a general review, see G. A. Cordell, *Chem. Rev.*, **76**, 425 (1976).
(19) NMR ($CDCl_3$) 2.84 (bs, 2 H, OH) and 3.27–3.88 (m, 3 H, CH_2OH and CHOH); IR (Nujol) 3250 cm^{-1} (vs).
(20) Bp 110 °C (bath temp, 1 mm); NMR ($CDCl_3$) 1.37 (s, 3 H), 3.93–4.41 (m, 3 H); IR (liquid film) 975 cm^{-1}; mass *m/e* 220 (M^+).
(21) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1967); see also R. Zurtlüsh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Am. Chem. Soc.*, **90**, 6224 (1968).
(22) For a general review of aluminum amide, see T. Mole and E. A. Jeffery, "Organoaluminum Compounds", Elsevier, New York, N.Y., 1972, p 229. For the present reaction, diethylaluminum *N*-methylanilide was prepared from lithium *N*-methylanilide and diethylaluminum chloride (molar ratio, 1:1) in benzene at 0 °C for 30 min.
(23) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972); *J. Org. Chem.*, **38**, 1233 (1973).
(24) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963); L. Caglioti, *ibid.*, **22**, 487 (1966).
(25) S. Dev, *Tetrahedron*, **9**, 1 (1960); N. P. Damodaran and S. Dev, *ibid.*, **24**, 4113 (1968); J. A. Hartsuck and I. C. Paul, *Chem. Ind. (London)*, 977 (1964); A. T. McPhail, R. T. Reed, and G. A. Sim, *ibid.*, 976 (1964); *J. Chem. Soc. B*, 112 (1966).
(26) The oxetane **16** was prepared by the sequential treatment of 2,2-dimethyl-3-hydroxypropanal first with *n*-butyllithium then with tosyl chloride in 40% yield: Bp 56 °C (11 mm); NMR ($CDCl_3$) 1.17 (s, 3 H), 1.20 (s, 3 H); IR (liquid film) 970 cm^{-1}.
(27) Prepared from 2-carbomethoxy-2-methylcyclododecanone by the following

sequence of reactions: (1) lithium aluminum hydride reduction (95%), (2) selective tosylation (86%), and (3) treatment of the primary tosylate with potassium *tert*-butoxide in tetrahydrofuran (87%). The oxetane **11** was obtained as a colorless liquid: bp 110 °C (bath temp, 1 mm); NMR ($CDCl_3$) 1.23 (s, 3 H), 3.87–4.23 (m, 3 H); IR (liquid film) 1370, 990–980 cm^{-1}; mass *m/e* 210 (M^+).

(28) For the oxetane rearrangement reactions, diethylaluminum *N*-methylanilide was found to be a superior reagent to diethylaluminum 2,2,6,6-tetramethylpyperidide, with which the rearrangement required the longer period of reflux, see ref 31.

(29) Bp 50 °C (bath temp, 1 mm); NMR ($CDCl_3$) 1.00 (s, 6 H), 3.27 (s, 2 H), 5.35–5.46 (m, 2 H); IR (liquid film) 3350, 1040, 970 cm^{-1}; mass *m/e* 142 (M^+); homogeneous by TLC, $AgNO_3$–silica gel TLC, and GLC ($AgNO_3$–Carbowax 20M) (>99% pure). The *E,Z*-mixture of the alcohol **12** was prepared independently by the Wittig reaction (butylidenetriphenylphosphorane and 2,2-dimethyl-3-hydroxypropanal).

(30) Bp 145 °C (bath temp, 1 mm); NMR ($CDCl_3$) 1.01 (s, 3 H), 3.17–3.53 (m, 2 H), 5.30–5.44 (m, 2 H); IR (liquid film) 3350, 1035, 980 cm^{-1}; mass *m/e* 210 (M^+).

(31) A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 6513 (1974); see also S. Tanaka, A. Yasuda, H. Yamamoto, and H. Nozaki, *ibid.*, **97**, 3252 (1975).

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Cyclizations via Organopalladium Intermediates. Macrolide Formation

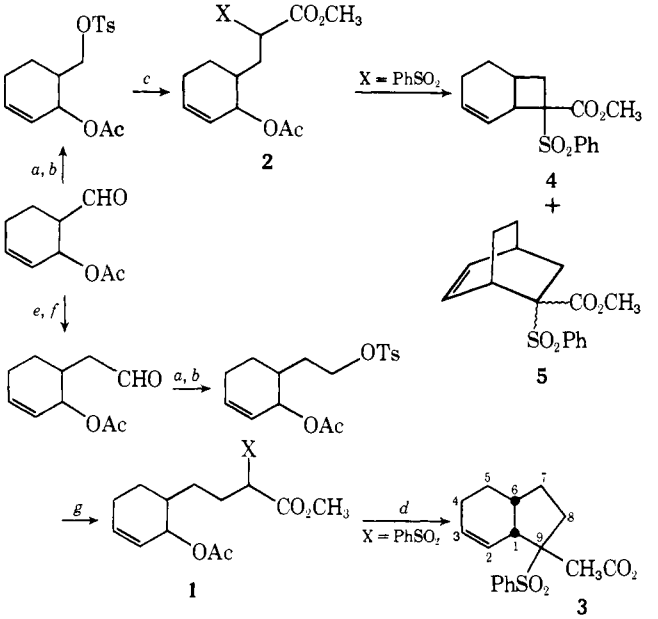
Sir:

Formation of C–C bonds in a cyclization reaction varies in efficiency as a function of the ring being formed among other factors. While great strides have been made in developing methods for formation of three- to seven-membered rings, larger rings such as those of 14 and 16 members are not very accessible by C–C bond formation.[1] For example, while progress in macrolactonization has been forthcoming, formation of macrolides by C–C bond formation is very limited.[1,2] The importance of the macrolide antibiotics[2] led us to identify such ring systems as our target. We wish to report a new approach to cyclizations that includes access to large rings and is exemplified by a synthesis of exaltolide.[3]

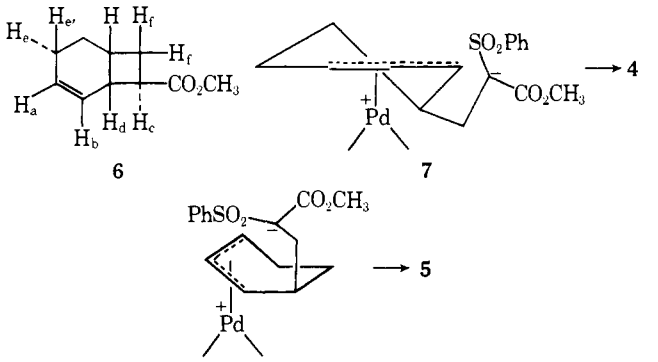
Initial attention focused on allylic acetates **1**[4] and **2**[4] (Scheme I) which are available from the Diels–Alder adduct of 1-acetoxybutadiene and acrolein[5] by straightforward methods as outlined in Scheme I. Conversion of **1** (X = $PhSO_2$) to its anion in THF and addition of the resultant solution to a refluxing THF solution of 2–6 mole % of tetrakis(triphenylphosphine)palladium led to a 75% isolated yield of the desired cyclized product **3**[4] as a 4:1 mixture which is isomeric at C(9).[6] While the addition of the substrate to the catalyst could be performed by rapid addition, improvement in yield was observed by slow addition utilizing a mechanically driven syringe pump. Cyclization times were on the order of 4–10 h. It is important that if any excess sodium hydride is used to generate the anions, it must be removed by filtration prior to the addition to the palladium catalyst.

Cyclization of **2** (X = $PhSO_2$) proved to be most interesting in light of our previous results in which a nitrogen nucleophile was employed.[6a] In contrast to that case, the major product was the [4.2.0] compound **4**. For characterization, the sample was desulfonylated[7] (6% Na(Hg), Na_2HPO_4, CH_3OH) and analyzed by VPC. The minor product (20%) was identified as the bicyclo[2.2.2]octene by comparison to an authentic sample prepared by the Diels–Alder reaction between 1,3-cyclohexadiene and ethyl acrylate followed by transesterification. The major product (80%) was identified as **6**. Most noteworthy is the NMR spectrum which establishes the structural relationship of protons a–d at δ 5.81, 5.55, 3.31, and 3.03 with J_{ab} = 10 Hz, $J_{ad} = J_{bd}$ = 4.5 Hz, and J_{cd} = 9 Hz, J_{ae} = 5.5 Hz, $J_{ae'}$ = 2.5 Hz, and J_{cf} = 9 Hz. The contrast in regiochemistry between the case of carbon and nitrogen nucleophiles may reflect kinetic and thermodynamic control. Conformational considerations suggest that cyclization via **7** (bulky group pseudoequatorial on a half-chair ring) should be kinetically preferred over that via **8** (bulky group pseudoaxial on a twist boat ring). With carbon as the nucleophile, cyclization is irreversible. When the nucleophile is nitrogen, the initial azetine may undergo palladium catalyzed isomerization to the thermodynamically more stable isoquinuclidine.[8]

Scheme I. Cyclizations of Allylic Acetates **1** and **2**



[a] $NaBH_4$, CH_3OH, or C_2H_5OH, 0 °C, 95%. [b] TsCl, pyridine, 0 °C, 73%. [c] $KOH(SO_2Ph)CO_2CH_3$, NaI, HMPA, 55 °C, 62%. [d] NaH, THF, $(Ph_3P)_4Pd$, reflux, 67–75%. [e] $Ph_3P^+CH_2OCH_3Cl^-$, *t*-C_4H_9Li, THF, 0 °C → room temperature, 87%. [f] $(CO_2H)_2$, THF, H_2O, room temperature, 94%. [g] $NaCH(SO_2Ph)CO_2CH_3$, NaI, HMPA, 50 °C, 95%.



Utilizing a similar scheme, allylic acetates **1** and **2** (X = CO_2CH_3) are also available. Interestingly, cyclization of these compounds led to very poor yields of products.

Scheme II outlines the formation of 14- and 16-member macrolides and the conversion of the latter to exaltolide. The preparation of the carboxylic acid **9** was achieved from ethyl adipate as outlined. Tetrahydrofuran and 1,6-hexanediol served as the precursors to the requisite alcohols **10** and **11**. Conversion of acid **9** to its acid chloride and condensation with the alcohols led to the desired cyclization substrates **12**[4] and **13**.[4] Conversion to the anion with sodium hydride in THF and addition of the resultant solution via a syringe pump to a refluxing solution of 2–6 mole % of Pd(0) catalyst produced regiospecifically the medium ring compounds **14**[4] and **15**[4] (mp