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^+).

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Yoshizo Kitagawa, Akira Itoh, Shinsuke Hashimoto
Hisashi Yamamoto,* Hitosi Nozaki
Department of Industrial Chemistry, Kyoto University
Yoshida, Kyoto 606, Japan

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Cyclizations via Organopalladium Intermediates. Macrolide Formation

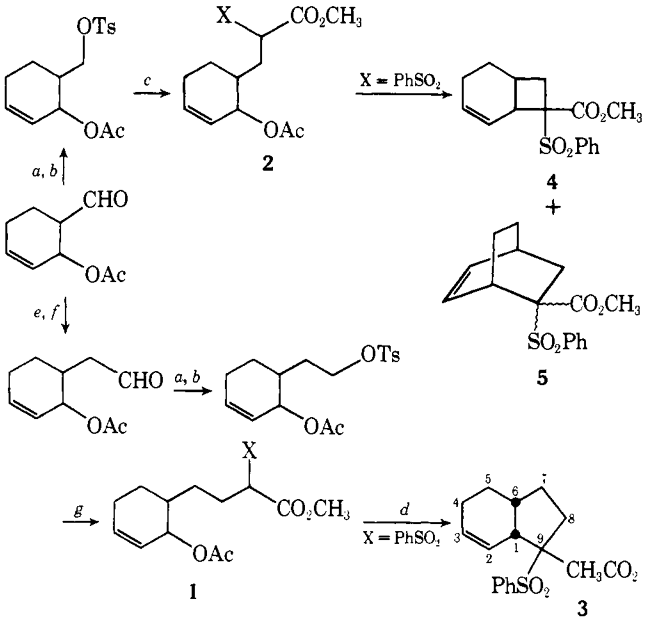
Sir:

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]

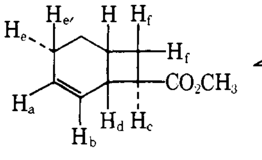
Initial attention focused on allylic acetates **1**[4] and **2**[4] (Scheme I) which are available from the Diels–Alder adduct of 1-acetoxybutadiene and acrolein[5] by straightforward methods as outlined in Scheme I. Conversion of **1** (X = $PhSO_2$) to its anion in THF and addition of the resultant 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]

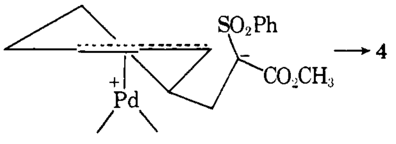
Scheme I. Cyclizations of Allylic Acetates **1** and **2**



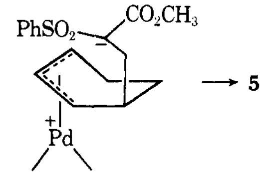
[a] $NaBH_4$, CH_3OH, or C_2H_5OH, 0 °C, 95%. [b] TsCl, pyridine, 0 °C, 73%. [c] $KOH(SO_2Ph)CO_2CH_3$, NaI, HMPA, 55 °C, 62%. [d] NaH, THF, $(Ph_3P)_4Pd$, reflux, 67–75%. [e] $Ph_3P^+CH_2OCH_3Cl^-$, *t*-C_4H_9Li, THF, 0 °C → room temperature, 87%. [f] $(CO_2H)_2$, THF, H_2O, room temperature, 94%. [g]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



6



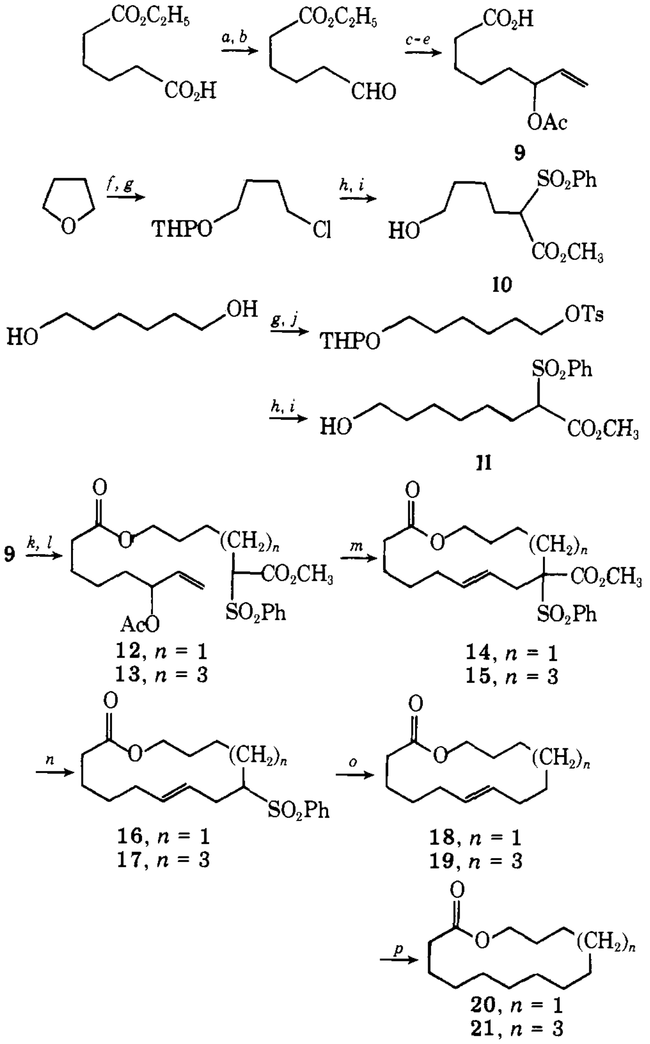
7



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

Scheme II. Macrolide Formation



[a] BH_3, THF, −15 °C → room temperature, 93%, ref 9. [b] $C_5H_5N^+ \cdot HClCrO_3^-$, NaOAc, room temperature, 75%. [c] $CH_2{=}CHLi$, ether, −78 → −20 °C, 78%. [d] KOH, 50% aqueous C_2H_5OH, [e] C_5H_5N, Ac_2O, room temperature, 70%. [f] References 10. [g] DHP,[11] CH_2Cl_2, TsOH, 40–83%. [h] $NaCH(SO_2Ph)CO_2CH_3$, NaI, DMF, 60 °C. [i] HCl, H_2O, THF, 50–69%. [j] TsCl, C_5H_5N, 0 °C, 93%. [k] $SOCl_2$, ether, reflux, [l] **10** or **11**, $(C_2H_5)_3N$, ether, 50 °C, 76 or 95%. [m] NaH, THF $[Ph_3P]_4Pd$, reflux, 49–69%. [n] $(CH_3)_4NOAc$, HMPA, 90–95 °C, 76–81%. [o] 6% Na(Hg), Na_2HPO_4, THF, C_2H_5OH, −20 °C, 70–89%. [p] H_2, 5% $Pd/BaCO_3$, 2 atm, room temperature, 95–99%.

105–106 °C) in 49–69% yield.[12] NMR examination of the crude material did not reveal the presence of any terminal vinyl group which would have resulted from reaction at the allylically related carbon. Further characterization was achieved by decarboxylation to **16** (mp 110–112.5 °C) and **17** (mp 91.5–92 °C) and desulfonylation to **18** (mp 25–33 °C) and **19** (mp 46–48 °C). Observation of a 15 Hz coupling constant between the vinyl protons in **14–17** indicates the major isomers in both rings have the *E* configuration. Detection of the *Z* isomer as a minor product in **18** was confirmed by irradiating the allylic protons at δ 2 and observing small peaks with the 10.8 Hz coupling constant in the vinyl region. Unfortunately, overlap of these absorptions with those for the *E* isomer precluded accurate determination of the isomeric ratio. The high regioselectivity and stereoselectivity make the cyclization particularly attractive.

Hydrogenation of **18** gives tridecanolide **20** (mp 24–6 °C)[13] and of **19** gives exaltolide **21** (mp 33–35 °C).[13] The flexibility of the sulfone ester moiety, in part illustrated by the transformations herein, makes the use of this group especially noteworthy. In contrast to the intermolecular versions,[6b-c] the malonates are considerably poorer in the alkylations, a specific advantage of the sulfone ester in this case. The success of this macrocyclization may be a result of a template effect but such speculation is postponed for subsequent publications. Further aspects of this new cyclization method are under active investigation in our laboratories.

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(4) **1** (X = $PhSO_2$): IR 1745 and 1735 cm^{-1}; NMR δ 7.86 (m, 2 H), 7.62 (m, 3 H), 5.80 (m, 2 H), 5.10 (m, 1 H), 4.12 (m, 1 H), 3.62 and 3.58 (two s, 3 H), 1.98 and 1.94 (two s, 3 H); ^{13}C NMR 170.5, 170.3, 166.2, 137.5, 137.1, 134.3, 134.2, 133.2, 132.5, 129.1, 124.5, 124.0, 68.8, 68.3, 67.8, 65.9, 52.9, 35.3, 28.0, 27.7, 25.2, 24.6, 24.2, 22.8, and 20.9. **2** (X = $PhSO_2$): IR 1735 cm^{-1}; NMR δ 7.90 (m, 2 H), 7.68 (m, 3 H), 5.86 (m, 2 H), 5.10 (m, 1 H), 3.95 (bt, *J* = 6 Hz, 1 H), 3.67 and 3.64 (two s, 3 H), and 2.00 (s, 3 H). **3** IR 1735 cm^{-1}; NMR δ 7.92 (m, 2 H), 7.61 (m, 3 H), 6.28 (dm, *J* = 10 Hz, 0.2 H), 5.96 (dm, *J* = 10 Hz, 0.2 H), 5.76 (dm, *J* = 10 Hz, 0.8 H), 5.29 (dm, *J* = 10 Hz, 0.8 H), 3.31 (m, 1 H). **12:** IR 1755 cm^{-1}; NMR δ 7.90 (m, 2 H), 7.66 (m, 3 H), 5.82 (ddd, *J* = 16, 10, 6 Hz, 1 H), 5.23 (m, 3 H), 4.05 (bt, *J* = 6 Hz, 3 H), 3.68 (s, 3 H), 2.06 (s, 3 H). **13:** IR 1750 cm^{-1}; NMR δ 7.90 (m, 2 H), 7.66 (m, 3 H), 5.80 (ddd, *J* = 17, 10.5, 6 Hz, 1 H), 5.18 (m, 3 H), 4.01 (m, 3 H), 3.62 (s, 3 H), 2.27 (bt, *J* = 7 Hz, 2 H), 2.03 (s, 3 H). **14:** IR 1730 cm^{-1}; NMR δ 7.85 (m, 2 H), 7.55 (m, 3 H), 5.79 (dt, *J* = 15, 6.5 Hz, 1 H), 5.56 (dt, *J* = 15, 7 Hz, 1 H), 4.09 (m, 2 H), 3.67 (s, 3 H), 2.87 (m, 2 H), and 2.35 (m, 2 H); ^{13}C NMR δ 172.6, 168.0, 136.2, 135.3, 134.0, 129.9, 128.6, 124.3, 75.7, 62.8, 52.7, 35.1, 33.4, 30.9, 29.8, 29.5, 28.8, 23.1, and 19.8. **15:** IR 1745 cm^{-1}; NMR δ 7.83 (m, 2 H), 7.77 (m, 3 H), 5.55 (dt, *J* = 15, 6.6 Hz), 5.43 (dt, *J* = 15, 6.4 Hz), 4.09 (bt, *J* = 6 Hz, 2 H), 3.65 (s, 3 H), 2.86 (dt, *J* = 15, 6.3 Hz), 2.71 (dd, *J* = 15, 6.7 Hz).

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(11) DHP = dihydropyran.

(12) To 524.2 mg (1.056 mmol) of **13** in 2 mL of dry THF was added 51 mg of a 60% oil dispersion of sodium hydride (1.275 mmol) and the mixture heated at 45 °C for 10 min. This mixture was diluted to a total volume of 13 mL and added through a glass wool plug to filter out excess sodium hydride utilizing a syringe pump at a rate of 1.5 mL/h to a refluxing solution of 42.4 mg (0.0367 mmol) of tetrakis(triphenylphosphine)palladium in 15 mL of dry THF. After completion of the addition, reflux was continued for 4 h. The reaction mixture was cooled to room temperature, partitioned between ether and aqueous saturated ammonium chloride, and extracted with ether. After drying, filtering, and concentrating in vacuo, 625.6 mg of yellow oil was obtained and purified by preparative TLC (3:1 V:V hexane:ethyl acetate, two elutions) to give 319.4 mg (69% yield) of **15** as a colorless oil which solidified upon standing, mp 105–106 °C (cyclohexane:ethanol). See ref 4 for spectral data.

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Barry M. Trost,* Thomas R. Verhoeven
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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