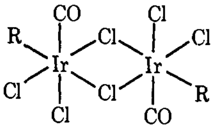

4a, R = $CH(CH_3)_2$
b, R = $CH_2CH_2CH_3$
c, R = $CH(CH_3)CH_2CH_3$
d, R = $CH_2CH_2CH_2CH_3$

methylpropanoyl chloride reacts with **3** in hot benzene to give the isopropyl complex (**4a**, R = $CH(CH_3)_2$) as white crystals: ir (Nujol) 2130, 2070 cm^{-1} [ν(CO)]; nmr ($CDCl_3$) δ 1.45 (d, 6, CH_3), 3.28 (septet, 1, CH, J = 7.5 Hz), but after 90 min in refluxing benzene, the solution contains approximately equal amounts of the isopropyl and *n*-propyl complexes, as shown by nmr. The pure *n*-propyl complex **4b** is obtained as white crystals by treating **3** with butanoyl chloride {ir (Nujol) 2135, 2085 cm^{-1} [ν(CO)]; nmr ($CDCl_3$) δ 1.00 (t, 3, CH_3, J = 8 Hz); 1.68 (sextet, 2, CH_2CH_2), 2.66 (m, 2, CH_2CH_2)}, but this also undergoes isomerization in refluxing benzene for 90 min to give the equilibrium mixture of isopropyl and *n*-propyl complexes. The *sec*-butyl complex **4c**, obtained from **3** and 2-methylbutanoyl chloride, isomerizes over a 3-hr period at ~30° to give an equilibrium mixture consisting almost entirely of the *n*-butyl complex **4d**. In both cases, isomerization is accompanied by formation of the insoluble hydride complex $[IrHCl_2(CO)_2]_n$,[5] which probably arises by competing decomposition of an intermediate hydrido–olefin complex.

Isomerization of π-$C_5H_5Fe(CO)_2CH_2CH_2CH_3$ to π-$C_5H_5Fe(CO)_2CH(CH_3)_2$ has been effected indirectly *via* an intermediate cationic propene complex $[\pi\text{-}C_5H_5\text{-}Fe(CO)_2CH_2{=}CHCH_3]^+$ by successive H^- abstraction and addition,[7] but so far as we are aware, the present work provides the first example of isomeric transition metal alkyls which are in thermal equilibrium. The observations may bear on the mechanisms proposed for reactions involving intermediate transition metal alkyls, such as hydroformylation, and particularly on the tendency of phosphine-modified cobalt–carbonyl catalysts to favor formation of straight-chain aldehydes in this reaction.[8]

(7) M. L. H. Green and P. L. I. Nagy, *J. Organometal. Chem.*, **1**, 58 (1963).

(8) L. H. Slaugh and R. D. Mullineaux, *ibid.*, **13**, 469 (1968).

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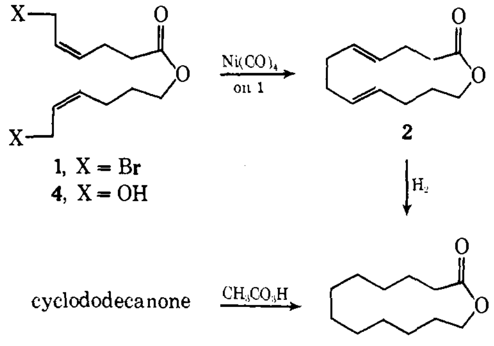
A New Method for the Synthesis of Macrolides

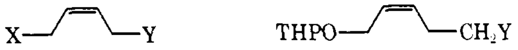
Sir:

The cyclization of allylic dibromides by nickel carbonyl has previously been applied to the synthesis of carbocycles of 9–18 members, including the naturally occurring sesquiterpene humulene.[1–5] It has now been found that this procedure is also highly effective for the formation of macrocyclic lactones, an important class of organic substances (*e.g.*, in the antibiotic field) for which there exists only a very limited synthetic methodology.

Gradual addition (over 3.5 hr) of the dibromo ester **1**[6] (***Z,Z*** isomer) to 6 equiv of nickel carbonyl in *N*-methylpyrrolidone[3,4] (*ca.* 0.2 *M* in $Ni(CO)_4$) with stirring at 50° under argon effected cyclization to the (*E,E*)-diene macrolide **2** as the major product.[7] Removal of excess nickel carbonyl[9] from the reaction by codistillation with ether, addition of water, extraction with pentane, concentration, and isolation by preparative layer chromatography (plc) on silica gel afforded **2**[6,7] (70–75% yield) having infrared max (CCl_4) due to C=O at 5.77 μ and due to *trans*-CH=CH at 10.33 μ and lacking absorption characteristic of *cis*-HC=CH at 14.2 μ. Hydrogenation of the mixture of stereoisomeric lactones[7] in ethanol over palladium/charcoal catalyst produced ω-hydroxydodecanoic acid lactone (**3**) as the sole product (by gas-chromatographic and thin-layer chromatographic analysis), identical with an authentic sample[10] prepared by the action of peroxyacetic acid–sulfuric acid on cyclododecanone.



The dibromide **1** was prepared in 83% yield from the corresponding diol **4**[6a] by reaction with phosphorus tribromide in ether at 0° for 12 hr. The synthesis of **4** was carried out *via* the intermediates **5–12** as follows.



5, X = AcO; Y = OTs
6, X = AcO; Y = $CH(COOC_2H_5)_2$
7, X = HO; Y = $CH(COOC_2H_5)_2$
8, X = THPO; Y = $CH(COOC_2H_5)_2$

9, Y = $COOC_2H_5$
10, Y = COOH
11, Y = CH_2OH
12, Y = CH_2I

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(1) E. J. Corey and E. Hamanaka, *J. Amer. Chem. Soc.*, **86**, 1641 (1964).

(2) E. J. Corey and M. F. Semmelhack, *Tetrahedron Lett.*, 6237 (1966).

(3) E. J. Corey and E. K. W. Wat, *J. Amer. Chem. Soc.*, **89**, 2757 (1967).

(4) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).

(5) For a synthesis of the divinylcyclohexane sesquiterpene elemol by this reaction, see E. J. Corey and E. A. Broger, *Tetrahedron Lett.*, 1779 (1969).

(6) Satisfactory (a) infrared and nuclear magnetic resonance data and (b) high-resolution mass spectral data were obtained for this liquid substance using samples which were homogeneous by thin-layer chromatographic analysis.

(7) In addition to **2**, two isomeric substances were produced (ratio 90:4:6) as ascertained by gas-chromatographic analysis (300 × 0.32 cm column of 5% diethylene glycol succinate on Chromosorb W at 190°). These by-products are considered to be stereoisomers of **2**, but their exact structures have not been determined. The predominating formation of the *E,E* product (even starting from the (*Z,Z*)-dibromide **1**) was expected on the basis of previous results[1,3,4,8] which show that the nickel carbonyl reaction results in the formation of the same stereoisomeric cyclization product(s) starting with (*E,E*)- or (*Z,Z*)-allylic dibromides.

(8) E. J. Corey, M. F. Semmelhack, and L. S. Hegedus, *J. Amer. Chem. Soc.*, **90**, 2416 (1968).

(9) All operations involving the toxic nickel carbonyl must be conducted in a well-ventilated hood.

(10) K. Kosswig, W. Stumpf, and W. Kirchhof, *Justus Liebigs Ann. Chem.*, **681**, 28 (1965).

Reaction of 2,5-dihydrofuran with acetic–toluenesulfonic mixed anhydride[11] in acetonitrile at reflux for 16 hr produced the acetoxy tosylate[6a] **5** (90%) which was treated with sodiomalonic ester in tetrahydrofuran (THF)–hexamethylphosphoric triamide at 25° for 2 hr to afford 63% of the acetoxy malonic ester derivative **6**.[6] Deacetylation (K_2CO_3 in ethanol at 75° for 2 hr) gave **7** which was converted *via* **8**[6a] (dihydropyran–toluenesulfonic acid in ether) to monoester **9**[6] (sodium cyanide in dimethyl sulfoxide at 160° for 4 hr,[12] 64% from **6**). From **9**, the acid **10**[6] was prepared by saponification (>95% yield), and the alcohol **11**[6] was formed by reduction (70% yield) with lithium aluminum hydride. The iodide **12**[6a] was obtained from the alcohol **11** by sequential reaction with toluenesulfonyl chloride–pyridine (0°, 12 hr) and displacement of tosylate by iodide (sodium iodide–acetone, 25°, 0.5 hr, and 50°, 1 hr) (92% overall yield). Finally, reaction of the iodide **12** with the sodium salt of the acid **10** (from NaH) in dimethylformamide provided in 64% yield the bistetrahydropyranyl[6] derivative of the ester diol **4**, and the free diol **4** was obtained by cleavage of the tetrahydropyranyl groups at 25° in methanol–THF containing a small amount of toluenesulfonic acid.

The efficacy of the synthesis of **2** by the allylic dihalide–nickel carbonyl cyclization process depends in part on the unreactivity of σ- and π-allylnickel intermediates toward the ester function. Our previous experience with this method of cyclization leads to the expectation that the efficient synthesis of macrolides of larger ring size than **2** is possible and, further, that a variety of functional groups on the substrate dihalide can be tolerated. Further, it seems probable that the method should be applicable to macrocyclic lactams. We hope to provide additional information on these points in due course.

Acknowledgment. This research was supported by the National Science Foundation and the National Institutes of Health.

[11] M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971).

[12] A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).

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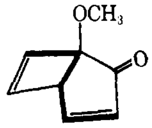
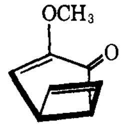
The Thermal Rearrangement of 1,4,4-Trimethylbicyclo[3.2.0]hepta-2,6-diene to 2,2,6-Trimethylbicyclo[3.2.0]hepta-3,6-diene

Sir:

Two distinct mechanistic interpretations of the apparent antara,antara Cope rearrangements of bicyclo[3.2.0]hepta-2,6-dienes and bicyclo[4.2.0]octa-2,7-dienes have been advanced.

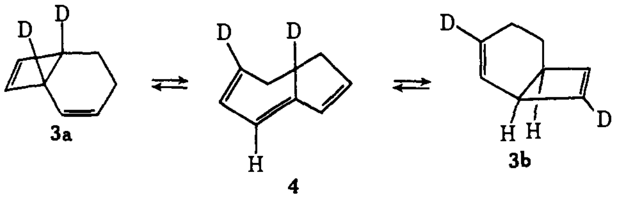


1



2

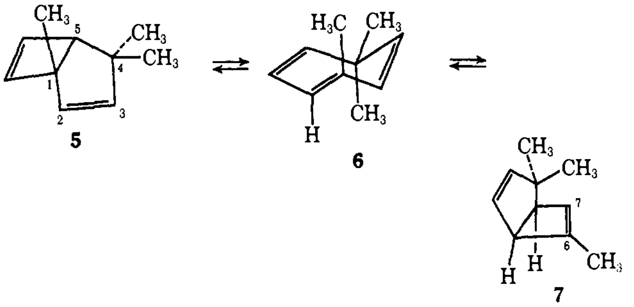
According to the first,[1] isomerizations like **1** → **2** are concerted $_{\pi}2_a + {}_{\sigma}2_s + {}_{\pi}2_a$ intramolecular cycloreactions permitted to occur in a fashion conserving orbital symmetry.[2]



According to the second,[3] isomerizations like the degenerate bicyclo[4.2.0]octa-2,7-diene equilibration (**3a** $\rightleftarrows$ **3b**) involve an intermediate cis,trans,cis cyclic triene, **4**, formed and collapsing through conrotatory electrocyclic valence isomerizations of the cyclobutene $\rightleftarrows$ butadiene variety.

An argument in support of the second view,[3] based on the failure of bicyclo[3.3.0]octa-2,6-diene to achieve this equilibration even at much higher temperatures,[4] has been countered by the observation that, in bicyclo[3.2.0] systems, a methoxy group at C-1 and the carbonyl group at C-2 are essential.[1] These functions are able to stabilize the concerted antara,antara transition state electronically or geometrically, and hence the lack of reactivity in a bicyclo[3.3.0]hydrocarbon is not surprising.[1]

We now report that 1,4,4-trimethylbicyclo[3.2.0]hepta-2,6-diene (**5**), a hydrocarbon lacking the oxygen functionality previously considered essential,[1] but possessing the cyclobutene moiety absent in bicyclo[3.3.0]octa-2,6-diene and necessary for production of the postulated cis,trans,cis cyclic triene intermediate **6**, undergoes the apparent antara,antara Cope rearrangement quite readily.



Hydrocarbon **5** was synthesized through treating the tosylhydrazone derivative (mp 118–121°; m/e = 318.140) of 1,4,4-trimethylbicyclo[3.2.0]hept-6-en-2-one, a photoisomer of eucarvone,[5,6] with methyllithium in ether.[7,8] The diene **5** was purified by glpc on an SE-30 column; m/e 134.109; nmr ($CDCl_3$) 3 H singlets at δ 1.03, 1.08, and 1.29, and 1 H absorptions at 2.58 (broad), 5.27 (dd, $J \cong 6$ and 1 Hz), 5.59 (d, $J \cong 6$ Hz), 6.02 (d, $J = 3$ Hz) and 6.48 (d, $J = 3$ Hz, C(7)–H).

Pyrolysis of **5** in the gas phase at 200° gave the known 3,7,7-trimethylcycloheptatriene[9] and diene **7**, having

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[3] J. E. Baldwin and M. S. Kaplan, *Chem. Commun.*, 1560 (1970); *J. Amer. Chem. Soc.*, **93**, 3969 (1971).

[4] J. E. Baldwin and M. S. Kaplan, *Chem. Commun.*, 1354 (1969).

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[6] H. Hart and T. Takino, *ibid.*, **93**, 720 (1971).

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[9] J. A. Berson and R. M. Willcott, III, *ibid.*, **88**, 2494 (1966).