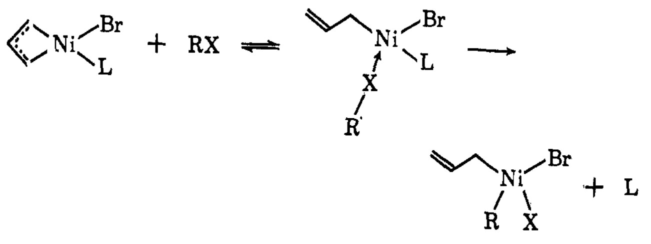

8

L=*e.g.*, DMF

The behavior of allylic halides toward π-allylnickel(I) derivatives, which contrasts sharply with that of nonallylic halides such as those appearing in Table I, will be detailed in due course.[19]

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The Synthesis of Large-Ring 1,5-Dienes by Cyclization of Allylic Dibromides with Nickel Carbonyl

Sir:

The method for forming cycloolefins from allylic dihalides and nickel carbonyl which has recently been reported[1,2] has now been examined in order to ascertain its scope with a series of dibromides of structure **1**. The results which have been obtained suggest that this

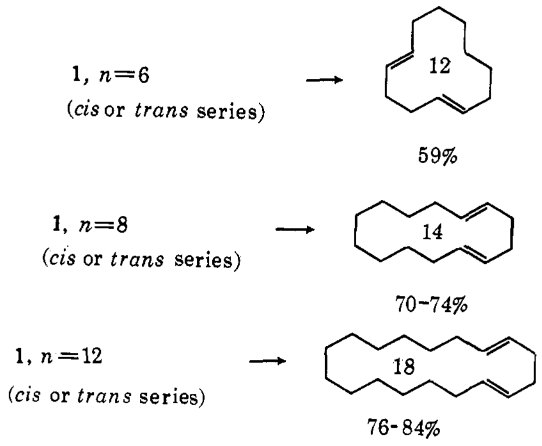
$$\underset{\mathbf{1}}{BrCH_2CH{=}CH(CH_2)_nCH{=}CHCH_2Br}$$

$$\underset{\mathbf{2}}{HOCH_2C{\equiv}C(CH_2)_nC{\equiv}CCH_2OH}$$

cyclization process provides an unusually efficient route for the formation of large rings. In addition, because it leads to cyclic 1,5-dienes, it makes available a wide variety of cyclic structures which are not obtainable in a practical way *via* the acyloin reaction, currently the only commonly used general approach to large rings.

The dibromides **1**, n = 2, 4, 6, 8, and 12, were synthesized in both *cis,cis* and *trans,trans* forms from the acetylenic diols **2**, n = 2, 4, 6, 8, and 12, by selective reduction to the corresponding *cis,cis*-[3] or *trans,trans*-ethylenic[4] diols[5] followed by reaction with phosphorus tribromide.[6] The required acetylenic diols **2**, n = 4, 6, and 8, were made by alkylation of a dibromide, $Br(CH_2)_nBr$, with the sodio derivative of propargyl alcohol tetrahydropyranyl ether[7] in liquid ammonia–ether[8] (n = 4, 6, 8) or in tetrahydrofuran–dimethyl sulfoxide (n = 12), and the diol **2**, n = 2, was obtained from 1,5-hexadiyne[9] and formaldehyde.[10]

The cyclization experiments were conducted by slow addition (motor-driven syringe, 12-hr period of addition) of the allylic dibromide (1 mmole) in dimethylformamide (1 ml) to a solution of nickel carbonyl (5 mmoles) in dimethylformamide (*ca.* 40 ml) under argon at 50°. In the cases of the dibromides **1**, n = 6, 8, and 12, the same cyclization product was obtained starting with either *cis,cis* or *trans,trans* isomer.



In each of these cases the cyclization product was principally (95–98%) the *trans,trans*-1,5-diene, but small amounts of an isomeric compound, probably the *cis,trans* isomer, could be detected by vapor phase chromatography.[11] The major product from **1**, n = 6, was identified as *trans,trans*-1,5-cyclododecadiene by spectroscopic comparison with the known substance;[12] the infrared spectrum manifested absorption at 10.4 μ due to CH=CH (*trans*) and no absorption at *ca.* 14.2 μ which would be expected for CH=CH (*cis*), and hydrogenation afforded cyclododecane, identical with an authentic sample. The principal products from **1**, n = 8, and **1**, n = 12, were identified by their infrared spectra (*e.g.*, absorption at 10.4 μ but not at 14.2 μ), mass spectra, nmr spectra, and hydrogenation to cyclotetradecane, mp 54–55°,[13] and cyclooctadecane, mp 71–72°,[13] respectively. The predominant course of cyclization with the dibromides **1**, n = 2, and **1**, n = 4, was formation of six-membered ring structures by 1–6 and 3–8 coupling, respectively; again the product composition was essentially independent of the geometry of the starting dibromide. With nickel carbonyl, **1**, n = 2, afforded 4-vinylcyclohexene (42%) and *cis,cis*-1,5-cyclooctadiene (5%); the same products were also obtained using triphenylphosphinenickel tricarbonyl,[14] but the relative amount of 1,5-cyclooctadiene was somewhat greater (*ca.* 20% of the mixture). In the case of dibromide **1**, n = 4, with either nickel carbonyl or triphenylphosphinenickel tricarbonyl, only

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

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

(3) Using Lindlar catalyst; see H. Lindlar and R. Dubuis, *Org. Syn.*, **46**, 89 (1966).

(4) Using lithium aluminum hydride in tetrahydrofuran; see K. R. Bharucha and B. C. L. Weedon, *J. Chem. Soc.*, 1584 (1953).

(5) Satisfactory analytical and spectroscopic (infrared and nmr) data have been obtained for the new compounds reported herein. The stereochemical assignments to the *cis,cis*- and *trans,trans*-dibromides **1** and the corresponding diols rest not only on the methods of synthesis (previously shown to be stereospecific) but also on the occurrence of infrared absorption at 10.4 or 10.3 μ for the *trans,trans*-dihalides or diols and at 13.1–13.4 μ for all the *cis,cis*-dibromides.

(6) J. M. Osbond, *J. Chem. Soc.*, 5270 (1961).

(7) R. G. Jones and M. J. Mann, *J. Am. Chem. Soc.*, **75**, 4048 (1953).

(8) H. Bader, L. C. Cross, I. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 619 (1949).

(9) R. A. Raphael and F. Sondheimer, *ibid.*, 120 (1950).

(10) F. Sondheimer, *J. Am. Chem. Soc.*, **74**, 4040 (1952).

(11) Using a column packed with Carbowax 20M (10%) on Chromosorb P at 200°.

(12) Reference spectra were furnished by Dr. Masaji Ohno, Toyo Rayon Co., Kamakura, Japan.

(13) L. Ruzicka, M. Stoll, M. W. Huyser, and H. A. Boekenoogen, *Helv. Chim. Acta*, **13**, 1152 (1930).

(14) See ref 2 for an example of ligand control of product using this reagent.

cis- and *trans*-1,2-divinylcyclohexane[15] were observed, with the former reagent giving a preponderance of the *cis* isomer and the latter favoring the *trans* isomer with a ratio of *ca.* 1:2; no 1,5-cyclodecadiene[15,16] could be detected spectroscopically or by vpc.

Although it has not yet been shown experimentally that the cyclization of allylic dibromides by nickel carbonyl can be used for the synthesis of ring sizes larger than 18, the efficiency of cyclization in the 18-membered case strongly suggests that it can.[17] The formation of essentially the same cyclization product from *cis–trans* isomeric dibromides is not surprising in view of earlier findings and similar results in intermolecular coupling reactions,[18] and it can be explained simply by allylic isomerization either because of allylic halogen–nickel exchange[18] or allylic rearrangement within the organonickel complexes *via* σ-allylnickel structures.[19]

The fact that the cyclization of **1**, $n = 2$ and 4, leads mainly to six-membered ring structures indicates that the formation of this ring size relative to the alternative eight- and ten-membered structures is sufficiently favorable to overcome the marked preference for the joining of primary over secondary over tertiary carbons in allylic coupling.[18,20,21]

It is noteworthy that the efficiency of cyclization of the substrates **1**, $n = 2$, 4, 6, 8, and 12, is strongly dependent on the solvent which is used; solvents such as dimethylformamide and N-methylpyrrolidone are much superior to, *e.g.*, tetrahydrofuran or glyme solvents. A discussion of these effects and detailed considerations of the mechanism of the cyclization process will be presented in due course.

It is apparent that the cyclization discussed herein is a very useful synthetic method. In principle it is applicable, for example, to a synthesis of elemol,[22] β-maaliene,[23] or cembrene.[24] A total synthesis of humulene has already been accomplished using this method.[25,26]

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[15] Authentic samples of *cis*-1,2-divinylcyclohexane and *cis,trans*-1,5-cyclodecadiene were kindly provided by Dr. P. Heimbach, Max-Planck Institut, Mülheim, Germany; see P. Heimbach, *Angew. Chem. Intern. Ed. Engl.*, **3**, 702 (1964); **5**, 595 (1966).

[16] It was shown by a control experiment that *cis,trans*-1,5-cyclodecadiene was recovered unchanged after being subjected to cyclization conditions.

[17] A study of the cyclization of 1,40-dibromo-2,38-tetracontadiene which could give a 40-membered ring is now under way. The yields given for the cyclization of **1**, $n = 6$, 8, 12, are probably not optimal, since only one set of reaction conditions was tried.

[18] E. J. Corey and M. F. Semmelhack, to be published.

[19] The intervention of allylnickel(I) bromide complexes in these cyclizations is clear from the development of the deep red color characteristic of such complexes during reaction. This color develops rapidly as the addition of dibromide to nickel carbonyl is started, and at the end of the addition it fades and gives way to the characteristic green color of nickel(II) bromide in dimethylformamide solution.

[20] I. D. Webb and G. T. Borcherdt, *J. Am. Chem. Soc.*, 73, 2654 (1951).

[21] E. J. Corey and M. F. Semmelhack, *ibid.*, **89**, 2755 (1967).

[22] V. Sykora, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, 20, 220 (1955).

[23] V. Herout, *et al.*, Abstracts, IUPAC Congress on Natural Products, Stockholm, Sweden, 1966, p 57.

[24] W. G. Dauben, W. E. Thiessen, and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962).

[25] E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).

[26] This work was generously supported by the National Institutes of Health (fellowships to E. Wat) and the National Science Foundation

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Total Synthesis of Humulene

Sir:

We describe herein a total synthesis of humulene, **7** (2,6,6,9-tetramethyl-*trans,trans,trans*-cycloundeca-1,-4,8-triene),[1–4] a fundamental monocyclic triisoprenoid structure which is a likely precursor of a number of other naturally occuring sesquiterpenes.[5] The key step in the synthesis is formation of the 11-membered ring by cyclization of a 1,11-dibromo-2,5,9-undecatriene derivative using nickel carbonyl.[6]

One important intermediate in the synthesis is the phosphonium ylide **1** which was obtained starting with dimethyl *trans*-3-methylglutaconate[7] by a sequence involving (1) reduction to the corresponding diol (**2**, U = V = OH) using lithium aluminum hydride–aluminum chloride (3:1)[8] in ether; (2) conversion to the dibromide **2**, U = V = Br,[9] then selective displacement of the allylic bromine with trimethylbenzylammonium dichloroacetate in acetone to give **2**, U = Br, V = $OCOCHCl_2$; (3) basic hydrolysis to the bromohydrin **2**, U = Br, V = OH; (4) acid-catalyzed addition to dihydropyran to form **2**, U = Br, V = OTHP (THP = 2-tetrahydropyranyl ether), and (5) reaction with triphenylphosphine in acetonitrile at 80° for 24 hr to form the phosphonium (bromide), U = $P^+(C_6H_5)_3$, V = OTHP.

A second key intermediate is the aldehyde **3**, the synthesis of which proceeded from 1-chloro-2-methyl-4-acetoxy-2-butene,[10] **4**, W = Cl, X = OAc, as follows: (1) displacement of chloride from **4**, W = Cl, X = OAc, by trimethylbenzylammonium mesitoate in ethanol at 80° for 24 hr to form **4**, W = mesitoyloxy, X = OAc; (2) selective alkaline hydrolysis to **4**, W = mesitoyloxy, X = OH; and (3) reaction with phosphorus tribromide[11] in ether to give **4**, W = mesitoyloxy, X = Br, which was used to alkylate the magnesium derivative formed from N-(2-methylpropylidine)cyclohexylamine[12,13] to afford an imine which yielded **3** by hydrolysis with aqueous oxalic acid at 25° for 4 hr.

Wittig condensation of the ylide **1** with the aldehyde **3** in dimethyl sulfoxide[14] afforded the triene **5**, Y =

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[1] S. Dev, *Tetrahedron*, **9**, 1 (1960).

[2] M. D. Sutherland and O. J. Waters, *Australian J. Chem.*, **14**, 596 (1961).

[3] A. T. McPhail, R. I. Reed, and G. A. Sim, *Chem. Ind.* (London), 976 (1964).

[4] J. A. Hartsuck and I. C. Paul, *ibid.*, 977 (1964).

[5] For example: (a) caryophyllene: E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964), and references therein cited; (b) zarumbone: S. Dev, *Tetrahedron*, **8**, 171 (1960); (c) humulene mono- and dioxide: S. K. Ramaswami and S. C. Bhattacharyya, *ibid.*, **18**, 575 (1962); (d) humulenol: N. P. Damodaren and S. Dev, *Tetrahedron Letters*, 1941 (1963).

[6] See (a) E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **86**, 1641 (1964); (b) E. J. Corey and M. F. Semmelhack, *Tetrahedron Letters*, 6237 (1966); (c) E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.*, **89**, 2757 (1967).

[7] Obtained from a commercially available mixture of *trans* and *cis* isomers (ratio 45:55) by fractional distillation; any *cis* isomer remaining as an impurity in this starting material could easily be removed in the transformation to **2**. U = Br, V = OH.

[8] M. J. Jorgenson, *Tetrahedron Letters*, 559 (1962).

[9] Procedure of I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 843 (1958).

[10] W. Oroshnik and R. Mallory, *J. Am. Chem. Soc.*, 72, 4608 (1950).

[11] J. M. Osbond, *J. Chem. Soc.*, 5270 (1961).

[12] G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2179 (1963).

[13] G. Wittig, H. D. Frommeld, and P. Suchaneck, *Angew. Chem. Intern. Ed. Engl.*, 2, 693 (1963).

[14] R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).