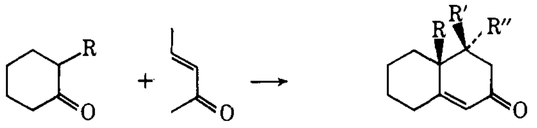
A Remarkably Stereoselective Robinson Annulation Reaction

Sir:

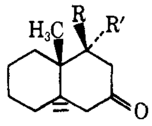
The Robinson annulation reaction has long been employed as a convenient route to fused ring ketones.[1] Using *trans*-3-penten-2-one (**3**) as the Michael acceptor, this method has recently been employed as the first step in synthetic sequences leading to mixtures of dimethyloctalones exemplified by structures **4** and **5**.[2] Unfortunately, this reaction proceeds poorly, if at all, when unactivated cyclohexanones (*e.g.*, **1** or its homologs) are used.[1,3] All successful reports[4] of the Robinson annulation reaction with *trans*-3-penten-2-one (**3**) have necessitated the use of activated cyclohexanones such as **2**[2a,d,f] or derivatives of 2-methyl-1,3-cyclohexanedione.[2b,e] The problems associated with the conversion of the resulting carbomethoxyoctalones (*e.g.*, derivatives of **6**) to the desired *cis*-4,10-dimethyl-1(9)-octal-2-one ring system (**4**) are well documented.[2a,d,f]



1, R = CH_3
2, R = CO_2CH_3
3
4, R = R′ = CH_3; R″ = H
5, R = R″ = CH_3; R′ = H
6, R = CO_2CH_3; R′ = CH_3; R″ = H
7, R = CO_2CH_3; R″ = CH_3; R′ = H

We wish to report a remarkably stereoselective, high-yield, one-step synthesis of both octalones **4** and **5**. Treatment of a suspension of the sodium enolate of 2-methylcyclohexanone (**1**) in dioxane[5] with 1 equiv of *trans*-3-penten-2-one (**3**)[6] at room temperature for 100 hr[7] afforded octalone **4** [$\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.08 ppm (s, 3 H, $\mathrm{CC}\mathit{H}_3$), 65%]. Alternatively, treatment of a solution of the enolate of **1** in dimethyl sulfoxide (DMSO)[8] with 1 equiv of *trans*-3-penten-2-one (**3**) under similar conditions for 3 hr gave octalone **5** [$\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.27 ppm (s, 3 H, $\mathrm{CC}\mathit{H}_3$), 72%]. In both cases the isomeric purity of the products was greater than 95%.[9]

The stereochemistry of octalones **4** and **5** was determined by reducing each isomer (Li, liquid NH_3, *tert*-BuOH,[10] followed by Jones reagent[11]) to the corresponding trans-fused decalones **8** and **9**. The nmr and richly detailed ir spectra of **8** and **9** were identical with spectra of authentic samples.[12]



8, R = CH_3; R′ = H
9, R = H; R′ = CH_3

Annulations of substituted 2-carbomethoxycyclohexanones with *trans*-3-penten-2-one (**3**), in which the stereochemistry of the secondary methyl group is presumably determined in the initial Michael addition step, have been shown to give predominately the cis isomer (*i.e.* **6** and its homologs).[2a,d,f] In these cases, the choice of solvent appears to affect the cis–trans ratio although neither the nature nor the magnitude of the effect has been reported.[13,13a] A transition state in which steric and electronic factors appear to favor the cis isomer has been proposed.[2a] In addition, the suggestion that the transition state leading to the cis isomer might be stabilized by nonpolar solvents and somewhat destabilized by polar solvents has also been made, but this suggestion has not yet been verified.[2f]

None of the above postulates appears satisfactory to explain the complete reversal of stereochemistry we observed in changing solvents from dioxane to DMSO. One possible explanation is that in the relatively nonpolar solvent dioxane, the mechanism proposed by Marshall[2a] is operative, thus leading to the cis isomer. In the case of the highly polar solvent DMSO, however, in which proton transfers of even carbon acids are extremely rapid (in some cases the rates are apparently diffusion controlled)[14] the sequence outlined in Scheme I may well explain the high degree of stereoselectivity observed in this solvent. This sequence involves an aldol condensation followed by a thermally[15] allowed

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[1] E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

[2] (a) J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); (b) R. L. Hale and L. H. Zalkow, *ibid.*, 1249 (1968); (c) H. C. Odom and A. R. Pinder, *ibid.*, 26 (1969); (d) J. A. Marshall and R. A. Ruden, *Tetrahedron Lett.*, 1239 (1970); (e) R. M. Coates and J. E. Shaw, *J. Amer. Chem. Soc.*, 92, 5657 (1970); (f) L. W. Piszkiewicz, Ph.D. Thesis, California Institute of Technology, 1967; *Diss. Abstr. B*, 27, 3865 (1967).

[3] (a) J. K. Coombs, M.S. Thesis, Iowa State University, 1970. (b) J. A. Marshall and W. I. Fanta [*J. Org. Chem.*, **29**, 2501 (1964)] have reported a modification of the annulation reaction with methyl vinyl ketone by which 10-methyl-1(9)-octal-2-one (**4**, R = CH_3; R′ = R″ = H) can be obtained in 45–50% yield. Comparable yields, using a twofold excess of 2-methylcyclohexanone (**1**), have also been reported by N. C. Ross and R. Levine [*J. Org. Chem.*, **29**, 2341 (1964)].

[4] The work of Odom and Pinder[2c] describing the Robinson annulation of 4-isopropenyl-2-methylcyclohexanone with *trans*-3-penten-2-one has recently been retracted (footnote 1 of ref 2d).

[5] Prepared by heating to reflux an equimolar mixture of NaH and **1** in dioxane for 3 hr.

[6] A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.*, **68**, 1715 (1946).

[7] Optimum reaction conditions have not yet been determined but preliminary results indicate that shorter reaction times or elevated temperatures lead to significantly lower yields.

[8] Prepared by stirring at room temperature an equimolar mixture of NaH and **1** in DMSO until hydrogen evolution ceased (*ca.* 3 hr).

[9] Determined from the integrated nmr spectra of **4** and **5**.

[10] (a) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964); (b) C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, Chapter 7, and references cited therein.

[11] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

[12] (a) Decalone **8** was prepared by the method outlined by L. H. Zalkow, F. X. Markley, and C. Djerassi [*J. Amer. Chem. Soc.*, **82**, 6354 (1960)]. (b) Decalone **9** was prepared by treatment of 3-bromo-10-methyl-*trans*-2-decalone [M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956)] with a solution of LiBr and Li_2CO_3 in DMF [E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, **87**, 5736 (1965)] followed by conjugate addition of $Li(CH_3)_2Cu$ to the resulting 10-methyl-*trans*-3-octal-2-one [see J. A. Marshall and N. H. Anderson, *J. Org. Chem.*, **31**, 667 (1966), and M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Commun.*, 1152 (1968), and references cited therein for discussions of the stereoelectronic requirements of the conjugate addition reaction]. While this work was in progress Coates and Shaw[2e] reported the preparation of decalones **8** and **9** from significantly different precursors.

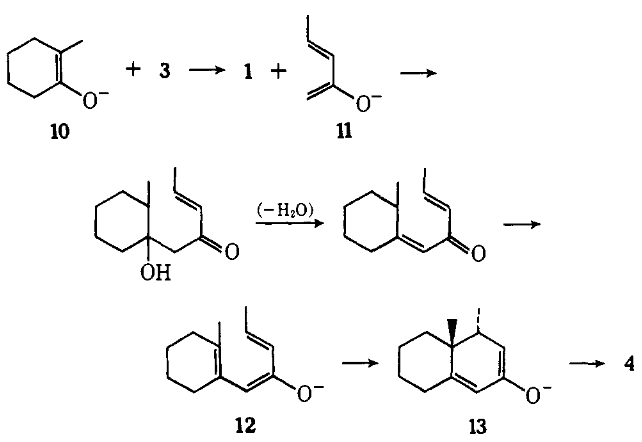
[13] Footnote 4 of ref 2d.

[13a] NOTE ADDED IN PROOF. Since submission of this manuscript, a detail report of the solvent effect discussed above has appeared: J. A. Marshall and T. M. Warne, Jr., *J. Org. Chem.*, **36**, 178 (1971).

[14] C. D. Ritchie, *J. Amer. Chem. Soc.*, **91**, 6749 (1969), and references cited therein.

[15] Thermal cyclizations of hexatrienes to cyclohexadienes have been observed at temperatures as low as 25° [E. J. Corey and A. G. Hortmann, *ibid.*, **87**, 5736 (1965)]. Typically, temperatures of *ca.* 130° have been employed [E. N. Marvell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965), and E. Vogel, W. Grimme, and E. Dinné, *ibid.*, 391 (1965)] although much higher temperatures (275°) have been used.[16c] Our experiments were performed at room temperature although the reaction mixture warmed noticeably (to *ca.* 60°) after **3** had been added.

Scheme I



disrotatory cyclization[16] of 12 to 13, essentially the reverse of the normally accepted steps in the Robinson annulation reaction.[1,17] Since enolates derived from homologs of 2-carbomethoxycyclohexanone (2) are considerably more stable than the enolate of 3, Scheme I would not be expected to be operative in those cases. In the above case, however, the cross-conjugated enolate 11[18] is probably more stable than the enolate derived from 2-methylcyclohexanone (10). Moreover, initial Michael addition of 10 to 3 would be expected to be retarded significantly due to increased steric congestion (relative to methyl vinyl ketone) at the β-carbon atom of 3. Further experiments designed to verify the validity of the steps proposed in Scheme I are currently in progress in our laboratories.

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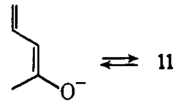
(16) (a) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinham/Bergstr., Germany, 1970, Chapter 5. (b) It is of interest that the conversion 10 → 11 is analogous in many respects to the cyclization described by Woodward [R. B. Woodward, *Chem. Soc. Spec. Publ.*, No. 21, 217 (1967)] which ultimately led to the concepts of the conservation of orbital symmetry. (c) The *trans*-1,9-dimethyldecalin ring system has recently been prepared *via* cyclization of a related triene system [R. Ramage and A. Sattar, *Chem. Commun.*, 173 (1970)].

(17) That the steps in the Robinson annulation reaction might be an aldol condensation followed by an intramolecular Michael reaction, instead of the reverse, has been alluded to previously [R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.*, 72, 494 (1950)].

(18) The formation of the alternative enolate i probably occurs even more readily than 11. Since products derived from i are not observed, its formation does not affect the above argument as long as a rapid equilibrium between the two enolates is established.[14]



i

(19) A. J. Speziale, J. A. Stephens, and Q. E. Thompson, *J. Amer. Chem. Soc.*, 76, 5011 (1954).

Charles J. V. Scanio,* Richmond M. Starrett
Department of Chemistry, Iowa State University
Ames, Iowa 50010

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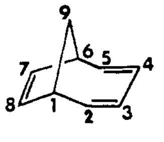
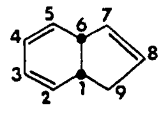
Pyrolytic Transformation of Bicyclo[4.2.1]nona-2,4,7-triene to Bicyclo[4.3.0]nona-2,4,7-triene (*cis*-8,9-Dihydroindene). The "Hydrogen-Rebound" Pathway of Thermal Rearrangement[1]

Sir:

The pyrolysis of bicyclo[4.2.1]nona-2,4,7-triene (**1**) at temperatures above 290° in either the gas phase or dodecane solution causes rearrangement to bicyclo-[4.3.0]nona-2,4,7-triene (*cis*-8,9-dihyrdoindene, **2**).[2] Most of the plausible hypothetical mechanisms for this reaction fall into two categories: (i) an all-carbon sigmatropic process, such as [1,3]- or [1,5]-sigmatropic rearrangement to *cis*-bicyclo[6.1.0]nona-2,4,6-triene (**3**), which is known[3] to rearrange readily to **2**, or isomerization of **1** to its tricyclic valency tautomer **4**[4] followed by sigmatropic rearrangement of the type recently reported in another system;[5] (ii) a process initiated by an intramolecular Diels–Alder reaction (**1** → **5**)[2b] and completed by overall hydrogen shift (**5** → **2**).



1



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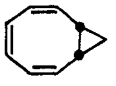

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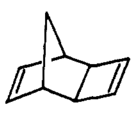

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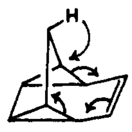

5

Experiments with the deuterium-labeled substance 1-$7,8$-d_2 permit in principle a distinction between these two mechanistic categories. Category i gives product **2** with at least one olefinically bound deuterium, whereas category ii gives **2** with deuterium bound exclusively to paraffinic carbon. Pyrolyses of two samples of 1-$7,8$-d_2[6] give product **2** with olefinic–paraffinic proton magnetic resonance intensity ratios of 2.07 and 2.21, as compared to theoretical values of 1.310 and 1.325 for mechanistic category i and 2.727 and 2.567 for

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[1] Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We are also grateful to the National Science Foundation for partial support through an institutional grant (No. GU-3282).

(2) (a) Side products include indan, indene, β-methylstyrene, and allylbenzene, all of which are formed in the pyrolysis of **2** itself. Prolonged pyrolysis leads to extensive polymerization. (b) For a rearrangement of 9-phenyl-9-acetoxybicyclo[4.2.1]nona-2,4,7-triene to 2-phenylindene, see T. S. Cantrell and H. Shechter, *J. Amer. Chem. Soc.*, 89, 5868 (1967).

(3) (a) E. Vogel and H. Kiefer, *Angew. Chem.*, 73, 548 (1961); (b) references to several other examples of this rearrangement in substituted derivatives of **3** are given by: S. W. Staley and T. J. Henry, *J. Amer. Chem. Soc.*, 91, 1239 (1969), and P. Radlick and W. Fenical, *ibid.*, 91, 1560 (1969).

(4) For the reverse of this (**4** → **1**), see (a) L. G. Cannell, *Tetrahedron Lett.*, 5967 (1966); (b) H. M. Frey, J. Metcalfe, and J. M. Brown, *J. Chem. Soc. B*, 1586 (1970).

(5) E. Vedejs, *Tetrahedron Lett.*, 4963 (1970).

(6) (a) Prepared by treatment of *exo-trans-endo*-dinorbornadiene[6b] (kindly supplied by Dr. D. J. Trecker of Union Carbide Co., Inc.) with *n*-butyllithium in cyclohexylamine-N,N-d_2 and pyrolysis[4a] of the resulting olefinically deuterated[7] dimer. (b) *Cf.* D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Amer. Chem. Soc.*, 87, 2596 (1965).

(7) H. E. Zimmerman, R. W. Binkley, R. S. Givens, G. L. Grunewald, and M. A. Sherwin, *ibid.* 91, 3316 (1969).