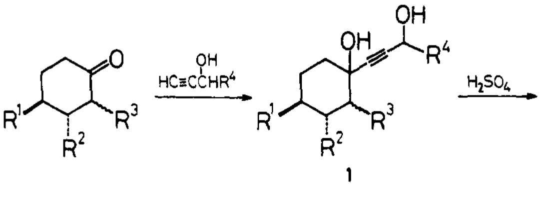
Regio- and Stereoselective Cyclopentenone Annulation by Means of Ketone–Propargyl Alcohol Adducts

Sir:

Much attention has been focused on the development of ring-forming reactions for constructing fused carbocyclic skeletons. Of particular significance is the regio- and the stereochemical outcome of the annulation. These aspects of the Robinson annulation have been extensively studied and are now well established.[1] The analogous problems with cyclopentenone-forming reactions[2] seem to remain still unsolved in spite of several attempts.[3,4] A process briefly noted by Raphael[5a] and others[5b,c] is found to provide the solution.

When 2-methylcyclohexanone–propargyl alcohol adduct **1a**[6] was treated with a mixture of concentrated sulfuric acid and methanol (1:1) at 0 °C for 30 min, hydrindanone **2a**[7] was produced in 70% yield as the sole product. This result strongly suggests a hydroxypentadienyl cation of thermodynamically favorable form **3a** as an intermediate. As the five-membered-ring formation is subject to the electrocyclic conrotatory rule,[8] we can easily obtain the *cis-vic*-dimethyl derivative **2b**[9] (67% yield) from **1b**,[10] along with its isomer **4**[11] (~10%). Thus, the geometrically favorable cation **3b** is the intermediate responsible for the formation of **2b**. The stereochemical outcome was readily confirmed by transforming **2b**[12,13] into **5** and by comparing the ^{1}H NMR spectra with the literature.[14] Application of the reaction to 2,3-dimethylcyclohexanone resulted in the formation of *trans-vic*-dimethylhydrindanone **2c**. Acid treatment of **1c**[15] gave a complex mixture of products, whereas monoacetylation (Ac_2O-pyridine, room temperature) of the diol, followed by treatment of the resulting hydroxyacetate with sulfuric acid–2,2,2-trifluoroethanol (1:2) at 0 °C, gave **2c**[16] (60% yield) as a single product. The trans relationship of the two methyl groups was demonstrated by converting **2c** into **6**.[17,18] Such stereochemical preference is easily understood by considering the transition state **3'c** of the electrocyclic reaction.[19] We can take advantage of these results for selective ring closure with concomitant selective arrangement of substituents.



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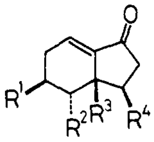

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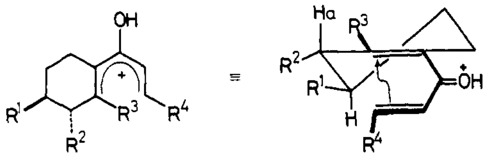
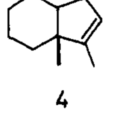
a: $R^1 = R^2 = R^4 = H, R^3 = Me$
b: $R^1 = R^2 = H, R^3 = R^4 = Me$
c: $R^1 = R^4 = H, R^2 = R^3 = Me$
d: $R^1 = i\text{-Pr}, R^2 = H, R^3 = R^4 = Me$



3 3'



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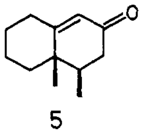

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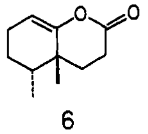

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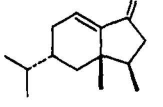
The glycol **1d**[21] was obtained from 4-isopropyl-2-methylcyclohexanone and 1-butyn-3-ol as a stereoisomeric mixture (87% yield). When this was exposed to the sulfuric acid–methanol conditions at 0 °C, **2d** and **7** were produced in a ratio of 83:17 in 64% yield.[22] In order to establish the stereochemistry of the substituents, the mixture of products was successively subjected to a ring-enlargement reaction[23] to give a mixture[24] of dihydro-7-epinootkatone (**8**)[25] and dihydronootkatone (**9**)[26] (82:18). It is noteworthy that three cis substituents are selectively disposed in a single reaction. The observed selectivity is, again, explained by the preferred transition state **3'd** wherein the bulky isopropyl group resides at an equatorial position and C–C bond formation develops under orbital control.[20] Accordingly, the present reaction provides a facile route to hydrindanone derivatives with high selectivity in the stereo- and regiochemical sense. This may find wide applicability in terpenoid synthesis, in particular of eremophilane derivatives,[27] when combined with the ring-enlargement reaction.



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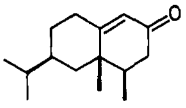

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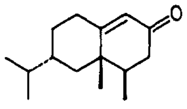

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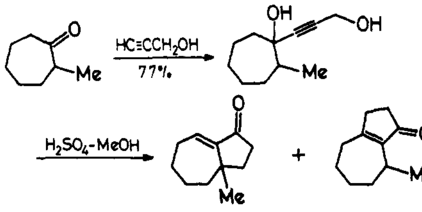
Application of the present reaction to 2-methylcycloheptanone afforded hydroazulenones **10**[3] (67%) and **11**[3] (14%). The regioselectivity here is in sharp contrast to the results of our previous study[3] of the adduct of the ketone and 1,1-dichloroallyllithium which afforded **11** exclusively.



10(67%) 11(14%)

In conclusion, the prominent feature of the present annulation procedure is the thermodynamically most favorable cation **3** intermediate. This feature is again recognized in an acyclic system as the adduct of 2-octanone and propargyl alcohol was converted exclusively to 2-methyl-3-pentyl-2-cyclopentenone[3] in 58% yield. Further synthetic application of this new method is now in progress.[28]

References and Notes

(1) M. E. Jung, *Tetrahedron*, **32,** 3 (1976); J. d'Angelo, *Ibid.*, **32,** 2979 (1976); R. E. Gawley, *Synthesis,* 777 (1976).

(2) R. A. Ellison, *Synthesis,* 397 (1973); B. M. Trost and D. E. Keeley, *J. Am. Chem. Soc.*, **98,** 248 (1976), and references cited therein.

(3) Previous efforts provide, to some extent, a solution to this problem: T. Hiyama, M. Shinoda, and H. Nozaki, *Tetrahedron Lett.*, 771 (1978).

(4) Regioselective cyclopentenone synthesis: M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **98,** 4679 (1976); Y. Hayakawa, K. Yokoyama, and R. Noyori, *Ibid.*, **100,** 1799 (1978).

(5) (a) A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 2247 (1953); G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor, and H.-J. Wild, *J. Chem. Soc., Perkin Trans. 1*, 410 (1976). (b) M. Karpf and A. S. Dreiding, *Helv. Chim. Acta,* **59,** 1226 (1976). (c) M. Baumann, W. Hoffmann, and N. Müller, *Tetrahedron Lett.*, 3585 (1976).

(6) Butyllithium–hexane solution (2.0 M, 15.8 mL, 32.0 mmol) was added dropwise to propargyl alcohol (0.845 g, 15.0 mmol) in tetrahydrofuran (THF) (40 mL) at −78 °C under a nitrogen atmosphere. After the mixture was stirred for 1 h at −78 °C, a THF solution (10 mL) of 2-methylcyclohexanone (1.12 g, 10.0 mmol) was added drop by drop, and the mixture was stirred at −78 °C for 1 h, then allowed to warm to room temperature, and stirred for a further 30 min. Usual workup followed by column chromatography on silica gel gave two isomeric adducts **1a** (totally 1.48 g, 88% yield, 58:42 ratio). Each isomer was subjected to cyclization affording **2a** in 62 and 66% yield, respectively. As both isomers can provide **2a** equally well, the mixture of the two isomers was directly used for the next reaction and the results are shown in the text.

(7) Following is a typical experimental procedure for the cyclization reaction. To a methanol (1.5 ml) solution of **1a** (162 mg, 0.96 mmol) was added 98% sulfuric acid (1.5 mL) drop by drop in 15 min at 0 °C and the mixture was

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stirred for 1.5 h at 0 °C. Workup was effected by addition of ether (10 mL), neutralization with aqueous sodium bicarbonate solution, and extraction. Concentration of the organic phase gave an oil (128 mg) which was purified by preparative TLC (Kiesel gel Merck PF_{254}, CH_2Cl_2, R_f 0.35–0.49) to afford **2a** (101 mg, 70% yield): bp 78–80 °C (0.04 Torr); IR (neat) 1716, 1646 cm^{-1}; ^1H NMR (CCl_4) δ 1.08 (s, 3 H), 6.37 (t, 1 H, $J = 3.6$ Hz); mass spectrum *m/e* 150 (M^+). Formation of the regioisomer of **2a** corresponding to **11** was <5% as revealed by GLC.

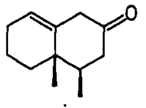
(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie GmbH, Weinheim-Berchstr., Germany, 1970, p 58; T. S. Sorensen and A. Rauk in "Pericyclic Reactions", Vol 2, A. P. Marchand and R. E. Lehr, Eds., Academic Press, New York, 1977, p 31.

(9) **2b:** bp 105–113 °C (bath temperature) (0.07 Torr); IR (neat) 1723, 1653 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (s, 3 H), 1.07 (d, 3 H, $J = 6.0$ Hz), 6.37 (t, 1 H, $J = 3.0$ Hz); mass spectrum *m/e* 164 (M^+).

(10) Potassium hydroxide (6.80 g, 121 mmol) was dissolved in an aqueous 55% solution (Tokyo Kasei Kogyo Co.) of 1-butyn-3-ol (5.74 g, 45 mmol). To this solution was added 2-methylcyclohexanone (3.36 g, 30 mmol) over a period of 2 h at 40 °C. The resulting mixture was stirred for 24 h. Usual workup followed by purification of the crude product by short column chromatography on silica gel gave the adduct **1b** (two of the four possible racemic isomers were separable, but the mixture of the isomers was used for the next reaction): 4.59 g, 84% yield; IR (neat) 3344 cm^{-1}; ^1H NMR (CCl_4) δ 0.91 (d, 3 H, $J = 6.0$ Hz), 1.02 (d, 3 H, $J = 6.0$ Hz), 4.3–4.7 (m, 1 H).

(11) **4:** IR (neat) 1700, 1619 cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (s, 3 H), 1.99 (d, 3 H, $J = 1.7$ Hz), 5.7–5.8 (m, 1 H); mass spectrum m/e 164 (M^+).

(12) Dibromomethyllithium addition (83% yield) followed by butyllithium treatment[13] gave i (41% yield; IR (neat) 1715 cm^{-1}; ^1H NMR (CCl_4) δ 0.94 (d, 3 H, $J = 6.0$ Hz), 1.10 (s, 3 H), 5.3–5.5 (m, 1 H); mass spectrum *m/e* 178 (M^+)) which was isomerized to **5** under acidic conditions (5% H_2SO_4–THF (1:1), room temperature, 2 h, 73%). The ^1H NMR spectrum ($CDCl_3$) of **5** showed a bridgehead methyl signal at δ 1.08 (s) identical with that of the authentic sample[14] and was clearly distinguished from that of the cis isomer.



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(13) H. Taguchi, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **50**, 1588, 1592 (1977).

(14) C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.*, **93**, 1539 (1971).

(15) Obtained in 89% yield. The two stereoisomers were separated chromatographically. Both gave **2c** equally well. The result in the text refers to that of the mixture.

(16) **2c:** IR (neat) 1718, 1654 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (d, 3 H, $J = 7.2$ Hz), 1.19 (s, 3 H), 6.46 (t, 1 H, $J = 3.6$ Hz); mass spectrum *m/e* 164 (M^+).

(17) Birch reduction (Li–NH_3), followed by enolate trap with acetic anhydride, ozonization, and acetic acid–sodium acetate treatment, gave **6:** IR (CCl_4) 1758, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 3 H, $J = 6.8$), 1.20 (s, 3 H), 5.30 (t, 1 H, $J = 7.0$ Hz); mass spectrum *m/e* 180 (M^+). The ^1H NMR data are completely consistent with those of the trans isomer and clearly different from those of the cis isomer of **6**.[18]

(18) E. Piers, R. W. Britton, and W. de Waal, *Can. J. Chem.*, **47**, 4307 (1969).

(19) A priori, four transition states (**3′c**, ii, iii, and iv) can lead to cyclopentenones. Transition state **3′c** or ii gives **2c** while iii or iv affords the cis isomer of **2c.** In the transition state iii or iv interaction of the two methyl groups grows severe as C–C bond formation develops, while in **3′c** or ii such interaction is not crucial as the two methyl groups are more farther apart during the course of C–C bond formation. Of the two transition states (**3′c** and ii) we prefer **3′c** for the reason that the methyl group on the six-membered ring takes a pseudoequatorial position and C–C bond formation occurs from the antiperiplanar direction of C–H_a bond under orbital control.[20]

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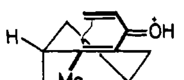

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(20) C. L. Liotta, *Tetrahedron Lett.*, 519 (1975).

(21) **1d:** IR (neat) 3346 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (d, 6 H, $J = 6.0$ Hz), 1.02 (d, 3 H, $J = 6.0$ Hz), 4.3–4.7 (m, 1 H); mass spectrum *m/e* 224 (M^+).

(22) The ratio was determined by ^1H NMR. The major product gave an olefinic proton signal at δ 6.53 (dd, $J = 7.7$, 3.0 Hz) and the minor component at δ 6.36 (t, $J = 3.3$ Hz); IR (neat) 1715, 1652 cm^{-1}; mass spectrum *m/e* 206 (M^+).

(23) Dibromomethyllithium addition (74% yield), butyllithium treatment (83% yield), and subsequent acidic isomerization (79% yield).

(24) **8–9:** IR (neat) 1663, 1627 cm^{-1}; ^1H NMR (CCl_4) of the major product δ 0.87 (d, $J = 6.0$ Hz), 0.97 (d, $J = 6.0$ Hz), 1.043 (s), 5.65 (br s, 0.82 H), and of the minor product gave peaks at δ 1.063 (s) and 5.59 (br s, 0.18 H); mass spectrum *m/e* 220 (M^+).

(25) An authentic specimen of 7-epinootkatone was prepared according to the literature: Y. Takagi, Y. Nakahara, and M. Matsui, *Tetrahedron*, **34**, 517 (1978). The sample was hydrogenated to **8** ($RhCl(PPh_3)_3$, H_2, benzene, room temperature, overnight): ^1H NMR (CCl_4) δ 1.046 (s), 5.65 (br s).

(26) Prepared according to the literature: H. C. Odom and A. R. Pinder, *J. Chem. Soc. Perkin Trans. 1*, 2193 (1972). We are indebted to Professor Pinder for his generous gift of a sample of (±)-nootkatone. ^1H NMR (CCl_4) spectra of dihydronootkatone gave peaks at δ 1.066 (s), 5.59 (br s).

(27) J. A. Marshall and R. A. Ruden, *J. Org. Chem.*, **36**, 594 (1971).

(28) This research was financially assisted by the Ministry of Education, Science and Culture, Japanese Government (Grant-in-aid No. 375462).

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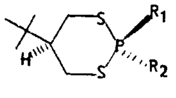
Nonchair Conformations in Phosphorus-Containing Cyclohexanes. Crystal and Molecular Structures of *cis*- and *trans*-2-Phenyl-2-oxo-5-*tert*-butyl-1,3,2-dithiaphosphorinanes and *cis*-2-Phenyl-5-*tert*-butyl-1,3,2-dithiaphosphorinane

Sir:

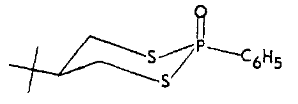
Saturated homocyclic and heterocyclic six-membered rings generally exhibit a strong preference for the chair conformation over nonchair forms ($\Delta H° = \sim 3–8$ kcal/mol).[1] Although special ring modifications or severe steric biasing influences afford a predisposition for the twist or other nonchair structures, molecules that inherently favor a twist conformation in unstrained situations are rare.[1a,2] In a recent ^1H NMR study on the stereochemical properties of **1a** and **1b** in solution, we found that, although **1b** assumes predominantly a chair conformation (**2**), **1a** populates considerably a twist form (**3**).[3]



1a; $R_1 = C_6H_5$; $R_2 = O$

b; $R_1 = O$; $R_2 = C_6H_5$

c; $R_1 = C_6H_5$; $R_2 =$ lone pair



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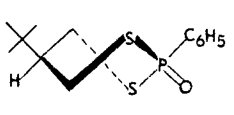

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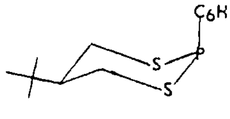

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Since the free-energy difference between the chair and twist forms was estimated to be as low as 0.5 kcal/mol,[3] the 1,3,2-dithiaphosphorinane ring system appeared to be a good candidate for obtaining unconstrained twist structures. To find out whether the twist conformation for **1a** would be manifested in the solid state, X-ray crystallographic analyses were performed on **1a** and, for comparison, on **1b** and **1c**. Surprisingly, *both* **1a** *and* **1b** *adopt a twist conformation* in the solid state, which represents an unusual case where two configurational isomers of a six-membered ring assume twist forms.

Crystals of **1a**, **1b**, and **1c** all belong to the monoclinic system, space group $P2_1/c$. All three crystal structures were solved by direct methods using MULTAN.[4] Atomic positional[5] and thermal parameters (anisotropic C, O, P, S; isotropic H) were refined by full-matrix least-squares calculations to $R =$ 0.054 (**1a**), 0.050 (**1b**), and 0.040 (**1c**) over 2433, 1876, and 1270, respectively, statistically significant ($I > 2.0\sigma(I)$) reflections measured on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu Kα radiation, $\lambda = 1.5418$ Å; θ–2θ scans).

Views of the solid-state conformations for **1a**[6] and **1b** are shown in Figures 1 and 2;[5a] endocyclic torsion angles defining the heterocyclic ring shapes of **1a–c** are in Table I. Although the endocyclic torsion angles for **1a** and **1b** depart significantly from ideal symmetry-related values characterizing a twist (D_2) form, it is quite apparent that the six-membered rings in each

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