Control Elements in the Intramolecular Diels-Alder Reaction. Synthesis of (±)-Torreyol

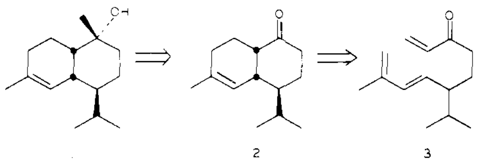
Sir:

The crystalline sesquiterpene alcohol torreyol[1] **1** was first isolated in 1922.[2] After considerable effort, the correct structure was finally established about 10 years ago.[3] No synthesis has yet been reported. We report our retrosynthetic analysis of **1** and the resultant stereoselective synthesis. These results strongly suggest that, in the transition state of an intramolecular Diels-Alder reaction[4] leading to a carbocyclic 6,6 system, the elements bridging the diene and dienophile adopt the most stable cyclohexane conformation. Thus, conformational information derived from the study of substituted cyclohexanes can be used to predict the geometric arrangement of substituents on the bridge relative to the ring fusion.[5]

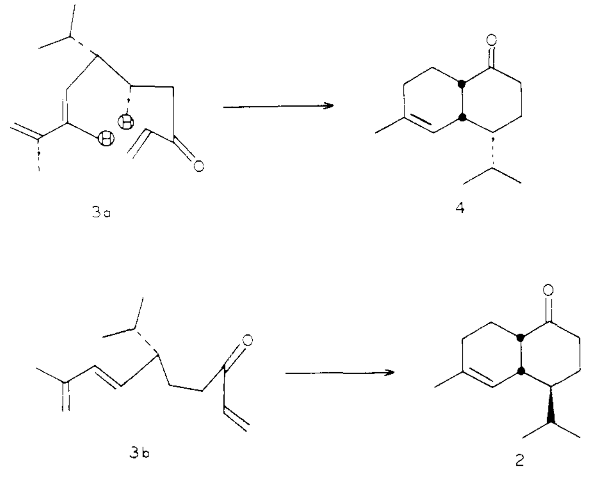
Our retrosynthetic scheme (Scheme I) was based on ketone **2.** Thus, it seemed reasonable that addition of methyllithium to the less hindered face of ketone **2** should give **1.** It also seemed reasonable that intramolecular cyclization of **3** in the endo sense[4] should give the cis ring fusion of **2.** Finally, we predicted that the ring fusion would occur such that the isopropyl group would largely be syn to the angular hydrogens, as shown. This prediction was based on the likelihood, suggested by models, that due to a severe nonbonding interaction in chair transition state conformation **3a,** boat conformation **3b** should be the more stable (Scheme II). If such were the case, more of **2** should be formed than **4.** We have prepared **3,** and have found that cyclization indeed substantially favors **2.**

The synthetic plan (Scheme III) was centered on **8,** prepared by a modification of the method of Vig.[6] Thus, addition[7] of the piperidine enamine[8] of isovaleraldehyde to ethyl acrylate, followed by hydrolysis, gave aldehyde **7** [bp 83-85 °C (0.5 mm); 85%; NMR ($CDCl_3$) δ 0.98 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.4-2.8 (m, 6 H), 4.18 (q, J = 7, 2 H), 9.8 (d, J = 3, Hz, 1 H)]. Condensation of **7** with methallyltriphenylphosphonium chloride[9] (NaH, Me_2SO, room temperature, 1 h, then 50 °C, 2 h) gave **8** [oil; R_f (20%[10] EtOAc-hexane) 0.59; 53%; NMR ($CDCl_3$) δ 0.85 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.1 (t, J = 7 Hz, 3 H), 1.8 (s, 3 H), 1.4-2.7 (m, 6 H), 4.1 (q, J = 7 Hz, 2 H), 4.9 (br s, 2 H), 5.4 (dd, J = 9, 16 Hz, 1 H), 6.1 (d, J = 16 Hz, 1 H)]. Ester **8** so prepared appeared (NMR) to be exclusively the *E* isomer.

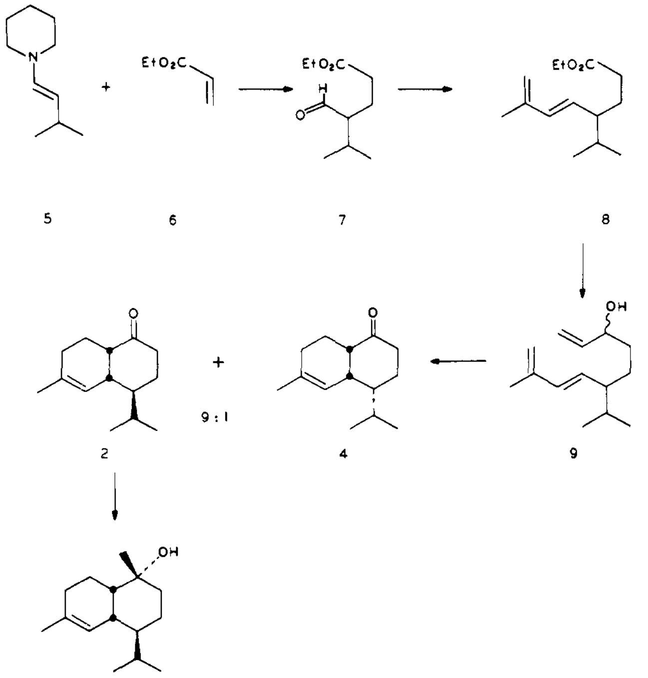
Scheme I



Scheme II



Scheme III



Ester **8** was elaborated ($LiAlH_4$[11] Et_2O, room temperature, 1 h; Me_2SO, DCC,[12] benzene, dichloroacetic acid, room temperature, 15 min; vinylmagnesium bromide, ether, 0 °C for 5 min) to triene **9** [R_f (20% EtOAc/hexane) 0.47; 40% from **8** (74%/step); NMR ($CDCl_3$) δ 0.85 J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.85 (s, 3 H), 1.0-2.2 (m, 7 H), 4.1 (m, 1 H), 4.9 (s, 2 H), 5.0-6.2 (m, 5 H); IR (CCl_4) 3615, 3080, 1638, 1608, 1452, 1368, 972, 925, 888 cm^{-1}; MS *m/e* (%) 208 (10), 165 (25), 147 (34), 136 (44), 105 (51), 93 (100)]. On oxidation ($H_2Cr_2O_7$,[13] ether, 0 °C, 25 min), **9** spontaneously cyclized to a ketone mixture [bp 130-150 °C (0.5 mm) (Aldrich Kugelrohr); 87%; R_f (20% EtOAc-hexane) 0.59; NMR ($CDCl_3$) δ 0.95 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H), 1.75 (s, 3 H), 1.2-2.8 (m, 12 H), 5.5 (br s, 1 H); IR (CCl_4) 2960, 2935, 2880, 1705, 1448, 1370, 1253, 1129, 1094, 940 cm^{-1}; MS *m/e* (%) 206 (100), 163 (42), 145 (52), 121 (71), 136 (69)]. On the basis of GLC analysis,[14] it was concluded that the cyclization gave **2** and **4** in an initial ratio of 89.7:10.3, and that the distillate was 87% **2.** Addition of methyllithium (Me_3CuLi_2,[16] ether, −70 °C, 5 min) to the mixture gave (±)-torreyol [R_f (20% EtOAc-hexane) 0.28; 64% based on the amount of **2** in the distilled mixture; mp 108.5-109 °C; NMR ($CDCl_3$) δ 0.80 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H), 1.1-1.6 (m, 13 H), 1.75 (s, 3 H), 2.0 (br s, 3 H), 5.6 (br s, 1 H); IR (CCl_4) 3615, 2935, 2895, 2875, 1449, 1375, 1102, 1046, 948, 917, 876 cm^{-1}; MS *m/e* (%) 222 (<1), 204 (42), 189 (8), 161 (100), 119 (42), 105 (29), identical (NMR, IR, TLC) with natural material].

The utility of stereochemically unambiguous intramolecular Diels-Alder reactions has been amply documented.[4] If analysis of steric interactions in the transition state, as outlined here, can be shown to in general have predictive power, this reaction should find widespread application in the field of complex natural product synthesis.

Acknowledgments. We wish to express our appreciation to Professor William G. Dauben for supplying a sample of natural torreyol. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American

0002-7863/79/1501-3992$01.00/0

Chemical Society, and to the National Institutes of Health (GM 15431), DHEW, for partial support of this work.

References and Notes

(1) Torreyol has also been known as δ-cadinol, sesquigoyol, albicaulol, and pilgerol: Westfelt, L. *Acta Chem. Scand.* **1966**, *20*, 2893.

(2) Shinozaki, E. *J. Soc. Chem. Ind. Jpn.* **1922**, *25*, 768; cited ref 1.

(3) (a) Nagasampagi, B. A.; Yankov, L.; Dev, S. *Tetrahedron Lett.* **1968**, 1913. (b) Westfelt, L. *Acta Chem. Scand.* **1970**, *24*, 1618.

(4) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289.

(5) Wilson[4b] has observed some partitioning between diastereomeric transition states which he has rationalized by a similar analysis. The key to the success of the approach outlined here is the use of an activated dienophile, thus allowing the cyclization to occur below room temperature.

(6) Ketone **2** has evidently previously been prepared, as one component of a mixture[14] of **2**, **4**, and **11** that was thought by the authors to be pure **11**: Vig, O. P.; Chugh, O. P.; Matta, K. L. *Indian J. Chem.* **1970**, *8*, 29.

(7) Pettit, G. R.; Fessler, D. C.; Paull, K. D.; Hofer, P.; Knight, J. C. *J. Org. Chem.* **1970**, *35*, 1398.

(8) Dulou, R.; Elkik, E.; Veillard, A. *Bull Soc. Chim. Fr.* **1960**, 967.

(9) Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775.

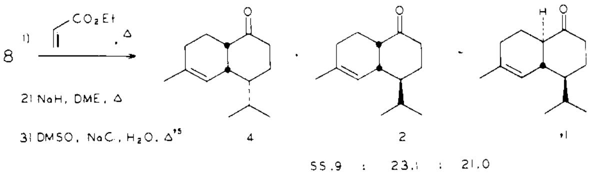
(10) "20% EtOAc–hexane" refers to a solvent mixture prepared by diluting 20 mL of EtOAc to a total volume of 100 mL with hexane.

(11) Micovic, V. M.; Mihailovic, M. L. J. *J. Org. Chem.* **1953**, *18*, 1190.

(12) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.

(13) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387.

(14) The distilled material showed three peaks on GLC (1/8 in. × 6 ft, 3% OV-17, 160 °C, 25 mL/min; retention times 7.25, 8.00, and 9.50 min) in a ratio of 10.3:86.9:2.8. These were assigned structures **4**, **2**, and **11**, respectively,



on the basis of the following: The three gave quite similar but distinct mass spectra. A comparison sample (which should have roughly equal isopropyl isomers from the initial addition) was prepared by a modification of the method of Vig.[6] This procedure gave the same three GLC peaks, having superimposable mass spectra, in the ratio indicated. Finally, refluxing the initial mixture from the oxidation of **9** in methanolic sodium methoxide gave again the same three peaks, this time in a ratio of 10.1:47.2:42.7.

(15) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.

(16) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280.

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Received December 18, 1978

Electron-Transfer Reactions in the "Abnormal" Free-Energy Region

Sir:

For an outer-sphere electron-transfer reaction, the rate constant can be written as

$$k = \nu_{\mathrm{et}}K \exp[-(\Delta G^*/RT)] \qquad (1)$$

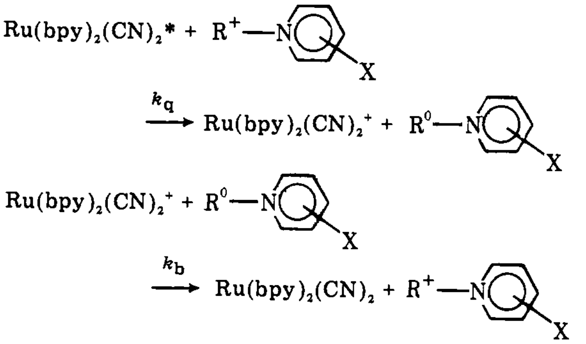
where ν_{et} is the frequency factor for electron transfer within an ion pair or association complex of the reactants and K is the formation constant for the association complex. From their classical treatments of ΔG^*, Marcus[1] and Hush[2] have derived eq 2, where ΔG is the free-energy change on electron transfer within the association complex and λ is the optical or vertical vibrational barrier to electron transfer. Combining eq 1 and 2 gives eq 3:

$$\Delta G^* = \frac{\lambda}{4}\left(1 + \frac{\Delta G}{\lambda}\right)^2 \qquad (2)$$

$$k = \nu_{\mathrm{et}}K \exp\left(\left[\frac{-\lambda}{4RT}\left(1 + \frac{\Delta G}{\lambda}\right)^2\right]\right) \qquad (3)$$

This has been tested repeatedly in different forms (e.g., see ref 3 and 4). Equation 3 successfully predicts an increase in k as $-\Delta G$ increases and approaches λ, but makes the remarkable prediction that, for reactions in the "abnormal" or "inverted" free-energy region where $-\Delta G > \lambda$[5], k should decrease as ΔG becomes even more favorable.

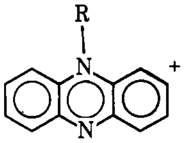
To date, studies of reactions in the abnormal free-energy region have been based on excited-state quenching experiments.[6-8] The results show that there is at best a slight decrease in k as ΔG becomes even more favorable in contrast to the prediction made by eq 3. A second experimental approach to the problem is the use of the flash photolysis technique, where a reaction in the abnormal free energy can be induced by an initial excited-state quenching step (eq 4, 5).[9]



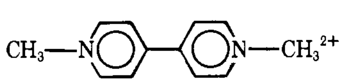
(4)

(5)

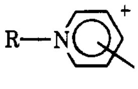
We have measured both quenching (k_q, eq 4)[10] and back electron-transfer (k_b, eq 5)[11] rate constants in acetonitrile ($I = 2.0 \times 10^{-3}$–5.0×10^{-1} M using $[\mathrm{NEt_4^+}](\mathrm{ClO_4^-})$)[12] at room temperature for a series of reactions involving the dicyano complexes $\mathrm{Ru(bpy)_2(CN)_2}$ (bpy is 2,2′-bipyridine) and $\mathrm{Ru(phen)_2(CN)_2}$ (phen is 1,10-phenanthroline) and the pyridinium type ions:



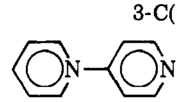
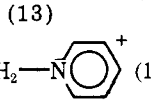
R = $\mathrm{CH_3}$ (1), $\mathrm{C_2H_5}$ (2)



(3)



R = $\mathrm{CH_3}$; X = 4-CN (4), 4-C(=O)$\mathrm{OCH_3}$ (5), H (14),
3-C(=O)$\mathrm{NH_2}$ (11), 4-C(=O)$\mathrm{NH_2}$ (8)
R = $\mathrm{C_2H_5}$; X = 4-C(=O)$\mathrm{OCH_3}$ (6), 4-C(=O)$\mathrm{NH_2}$ (7),
3-C(=O)$\mathrm{NH_2}$ (10), H (13)

 (9), $\mathrm{BrCH_2CH_2CH_2}$—  (12)

The numbers in parentheses identify the quenchers used to obtain the data shown in Figure 1.

The reactions involve a series of structurally related reactants, where ΔG varies widely but λ, K, and ν_{et} are expected to be nearly the same. The reactions are also attractive from the interpretive point of view because they are free of electrostatic effects arising from charge–charge interactions (eq 4, 5).

Values for k_q referred to as "quenching" in Figure 1 were obtained by luminescence quenching[10] and for k_b by flash photolysis. The data are shown in Figure 1 as a plot of $RT \ln k_{\mathrm{obsd}}$ (k_q or k_b) against ΔG. The ΔG values were calculated from redox potentials for the couples involved.[13]

Assuming that $\nu_{\mathrm{et}}K$ and λ are reasonably constant for the series of quenching reactions, eq 3 in logarithmic form

$$RT \ln k = RT \ln \nu_{\mathrm{et}}K - \frac{\lambda}{4}\left(1 + \frac{\Delta G}{\lambda}\right)^2 \qquad (3a)$$

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