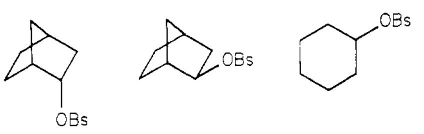
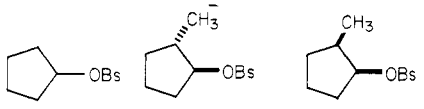
Scheme II



	1	3	6
RR ($Q^+N_3^-$, 27.5 °C)	0.026	0.014	1.0
RR (trifluoroacetolysis, 25 °C)[12]	1.5	1730	1.0



	7	8	9
RR ($Q^+N_3^-$, 27.5 °C)	56	2.6	12.3
RR (trifluoroacetolysis, 25 °C)[12]	8.9	24	

Q^+OTs^- had the same effect as increasing the concentration of $Q^+N_3^-$. Analogous observations with other substrates[7,10] have been attributed to association of the quaternary salts in weakly polar solvents.

exo-2-Norbornyl brosylate (**3**) and $Q^+N_3^-$ yielded 77–83% of *endo*-2-norbornyl azide (**4**) (contaminated with <3% of the exo-isomer **2**[8]) and 17–23% of nortricyclene (**5**). Only traces of norbornene were found. Substitution and elimination were treated as parallel second-order reactions; the rate constants in the table refer to the formation of **4**. The proton abstraction from **3** was explored with the aid of 6-position *d* labels. With the assumptions $(k_H/k_D)_{exo} = (k_H/k_D)_{endo} = Y$ and $k_{H,endo}/k_{H,exo} = k_{D,endo}/k_{D,exo} = p$, we obtain $Y = 1.6$ and $p = 1.3$. Our results agree closely with Nickon's data ($Y = 1.6$, $p = 1.5$) for the *tert*-butoxide-induced 1,3-elimination.[11]

So that the reactivity of **1** and **3** in direct displacement reactions with $Q^+N_3^-$ could be assessed, the brosylates **6**–**9** were included in our study (Scheme II and Table I). Cyclohexyl brosylate (**6**) reacted ca. 50 times faster than the 2-norbornyl brosylates, quite in contrast to the relative rates of trifluoroacetolysis.[12] The superiority of cyclopentyl over cyclohexyl derivatives in S_N2 reactions[13] was confirmed with **7** and $Q^+N_3^-$. For an evaluation of steric effects we studied *trans*- and *cis*-2-methylcyclopentyl brosylates (**8**, **9**). Both **8** and **9** showed clean inversion and depressed rates, as compared to **7**. The cis-isomer **9** (in which departure of the brosylate is sterically hindered) was ca. 5 times faster than the trans-isomer **8** (where the methyl group is in the way of the approaching nucleophile). These effects appear to balance more evenly in the reactions of **1** and **3** with $Q^+N_3^-$, whose rates differ by a factor less than 2.

The S_N2 reactivity of the 2-norbornyl brosylates (**1**, **3**) is moderate if compared to sterically unhindered substrates (**6**, **7**). On the other hand, **1** and **3** react at least 500 times faster than the seriously congested 2-adamantyl brosylate (**10**). An upper limit[14] for the reaction of **10** with $Q^+N_3^-$ in toluene at 65 °C is $k = (4.4 \pm 0.6)10^{-6}$ M s^{-1}. Inspection of Scheme II strongly suggests that the deviant behavior of **1** and **3** in solvolyses is not due to large differences in k_s but to the fast unimolecular ionization (k_c or k_Δ) of **3**.

Registry No. 1, 840-89-1; **2**, 22526-51-8; **3**, 840-88-0; **4**, 81940-38-7; **5**, 279-19-6; **6**, 18939-93-0; **7**, 4596-40-1; **8**, 36367-81-4; **9**, 81940-39-8; **10**, 38680-00-1; *endo*-2-norbornylamine, 31002-73-0; *exo*-2-norbornylamine, 7242-92-4.

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(11) Nickon, A.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3914, 1915, 3917.

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(14) The reaction of 2-adamantyl brosylate with $Q^+N_3^-$ was second order but afforded 82% of 2-adamantyl azide and 18% of 2-adamantyl bromide. The most probable source of bromide ion is nucleophilic displacement at the para position of the brosylate. Therefore the rate constant contains an unknown contribution of S_NAr. These complications are avoided with 2-adamantyl tosylate which, however, requires elevated temperatures: $k \approx 9.5 \times 10^{-5}$ M s^{-1} at 111 °C in toluene; $k = (1.48 \pm 0.02) \times 10^{-4}$ M s^{-1} at 114 °C in ethylbenzene. The stereochemistry of these reactions remains to be elucidated.

Stereochemical Control of Intramolecular Conjugate Addition. A Short, Highly Stereoselective Synthesis of Adrenosterone

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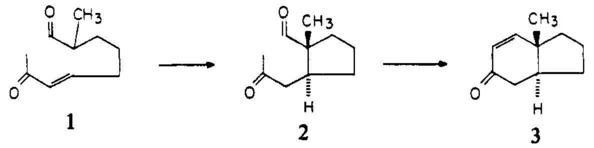
Received March 11, 1982

We have recently demonstrated the use of the intramolecular Michael addition to control vicinal stereochemistry in the construction of trans-fused hydrindans, i.e., **1** → **3**.[1]



1 **2** **3**

We report here the application of this method to a short synthesis of adrenosterone. The synthesis of the key intermediate, *trans*-hydrindenone **10**, is outlined below (Scheme I).

Alkylation of the dianion of ethyl 2-methylacetoacetate[2] with allyl bromide (tetrahydrofuran, 0 °C → room temperature) provided **5** (68% yield, bp 76–78 °C (12 mmHg)), which was ketalized (ethylene glycol, *p*-toluenesulfonic acid, benzene, 74% yield) to give **6**, bp 64–66 °C (0.05 mmHg).[3] Ozonolysis of **6** (methanol, −78 °C, triphenylphosphine, 93% yield) afforded aldehydo ester **7**, which was treated with dimethyl 3-methoxy-2-(oxopropyl)phosphonate[4] (K_2CO_3, benzene, room temperature, 79% yield) to provide enone ester **8**.[5] Reduction of **8** (lithium aluminum hydride, tetrahydrofuran, −40 °C → room temperature, 95% yield) furnished the corresponding unsaturated diol, which was oxidized by using the Ratcliffe modification[6] of the Collins oxidation[7] to produce **9** in 70–80% yield.

Cyclization of **9** with 1.5 equiv of zirconium tetra-*n*-propoxide (0.04 M in benzene, room temperature) followed by treatment with 2 equiv of sodium methoxide furnished *trans*-hydrindenone **10**, mp 80–81 °C (ether/petroleum ether), in 63% yield (found: C, 65.40; H, 7.55). ^{1}H NMR and VPC analysis of the reaction product showed a 25:1 trans/cis ratio of hydrindenone **10** and its cis-fused isomer.[8,9]

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(1) Stork, G.; Shiner, C.; Winkler, J. *J. Am. Chem. Soc.* **1982**, *104*, 310.

(2) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(3) Infrared data are listed in cm^{-1}. ^{1}H NMR data are reported in δ, downfield from Me_4Si. ^{13}C NMR data are reported in δ, with $CHCl_3$ as a reference standard. **6**: IR (film) 1720, 1640; ^{1}H NMR (80 MHz) 1.18 (d, J = 7 Hz, 3 H), 1.24 (t, J = 7 Hz, 3 H), 1.6–2.3 (m, 4 H), 2.80 (q, J = 7 Hz, 1 H), 3.96 (s, 4 H), 4.13 (q, J = 7 Hz, 2 H), 4.92 (br d, J = 10 Hz, 1 H), 5.03 (br d, J = 8 Hz, 1 H), 5.6–6.1 (m, 1 H); ^{13}C NMR (20.1 MHz) 12.26, 13.90, 27.13, 34.11, 46.91, 60.01, 65.35, 110.97, 113.95, 138.34, 172.92; MS (CI–ME) 229 (M + 1).

(4) Corey, E. J.; Kwiatkowsky, G. *J. Am. Chem. Soc.* **1966**, *88*, 5652.

(5) **8**: IR (film) 1735, 1695, 1630; ^{1}H NMR (80 MHz) 1.18 (d, J = 7 Hz, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.8–2.5 (m, 4 H), 2.80 (q, J = 7 Hz, 1 H), 3.41 (s, 3 H), 3.97 (br s, 4 H), 4.15 (s, 2 H), 4.14 (q, J = 7 Hz, 2 H), 6.24 (d, J = 16 Hz, 1 H), 6.99 (dt, J = 7, 16 Hz, 1 H); MS (CI–ME) 301 (M + 1).

(6) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(7) Collins, J.; Hess, W. *Org. Synth.* **1972**, *52*, 5.

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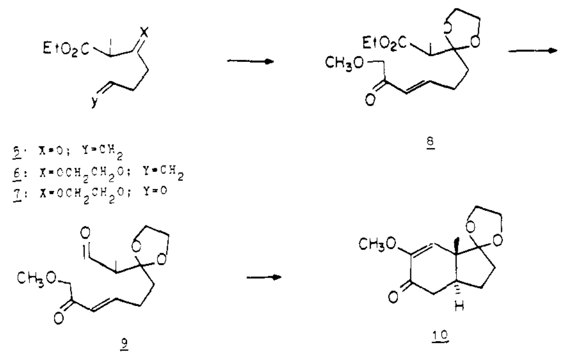
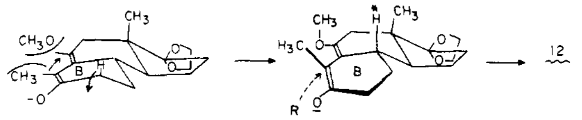
Scheme I



Scheme II

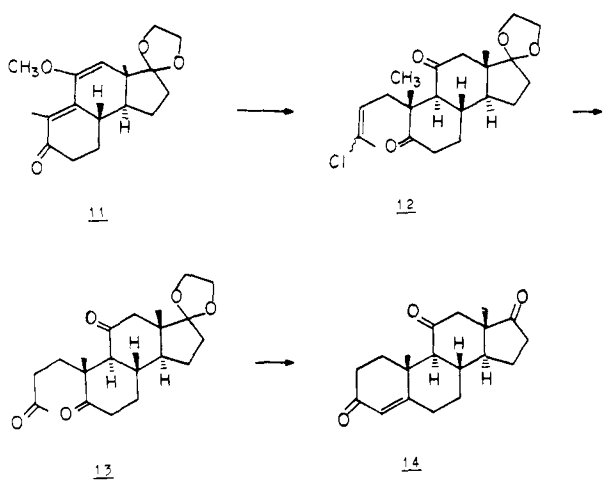


Treatment of the anion corresponding to *trans*-**10** (lithium diisopropylamide, tetrahydrofuran, −78 °C) with 3-(trimethylsilyl)-3-penten-2-one,[10] followed by cyclization of the crude reaction product with sodium methoxide in refluxing methanol, afforded **11**,[11] mp 87–88 °C, in 62% yield (found: C, 70.65; H, 7.76).

Previous work from these laboratories[12] suggested that "equatorial alkylation" would occur in our system to provide the correct stereochemistry at C-10. In the case of the dienolate corresponding to **11**, the B ring must be twisted into a half-boat conformation to alleviate the severe interaction between the C-10 methyl and the methoxyl group at C-11. This results in increased accessibility of the α face. At the same time, the starred hydrogen (Scheme II) would hinder alkylation from the β face. β alkylation would also force the C-10 methyl group to move past the C-11 methoxyl through a fully eclipsed position.

Reaction of **11** (Scheme III) with 3 equiv of lithium in tetrahydrofuran/liquid ammonia (1:2) containing 0.9 equiv of water, at −33 °C, followed by treatment of the resulting dienolate with 1-bromo-3-chloro-2-butene[12] and acid hydrolysis (10% aqueous hydrochloric acid, tetrahydrofuran, room temperature) of the crude product afforded a 70% yield of **12**, obtained as a mixture of double-bond isomers.

Scheme III



Hydrolysis of the vinyl chloride ($Hg[OCOCF_3]_2$, dichloromethane, room temperature, 70% yield)[13] gave **13**,[14] which was cyclized (potassium hydroxide, aqueous methanol, room temperature, 80% yield) to provide (±)-adrenosterone, mp 167–169 °C (ethyl acetate), whose spectral (250-MHz ^1H NMR, ^{13}C NMR, IR, MS) properties were identical with those of an authentic sample.[15,16]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

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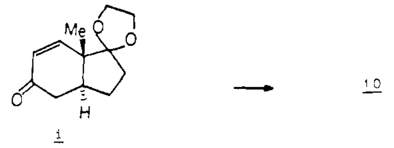
(8) Authentic samples of cis- and trans-fused **10** were prepared from the corresponding *cis*- and *trans*-hydrindenones i (reference 1), respectively, by



reduction (DIBAL-H, diethyl ether, −78 °C), epoxidation (*m*-CPBA, dichloromethane, room temperature), oxidation (Collins reagent, dichloromethane, 0 °C), methoxide opening, and dehydration (sodium methoxide, methanol, room temperature). ^1H NMR: CH_3 trans 1.06, cis 1.12; vinyl H trans 5.91, cis 5.70. VPC (3%FFAP, 1/8 in. × 10 ft, 200 °C) cis 8.9 min, trans 11.9 min.

(9) **10**: VPC (3% FFAP/200 °C) cis 8.6 min, trans 11.9 min. *trans*-**10**: IR (CH_2Cl_2) 1690, 1615; ^1H NMR (80 MHz) 1.06 (s, 3 H), 1.5–2.1 (m, 5 H), 2.52 (m, 2 H), 3.58 (s, 3 H), 3.96 (s, 4 H), 5.91 (s, 1 H); ^{13}C NMR (20.1 MHz) 15.48, 23.31, 33.56, 38.05, 40.84, 46.42, 54.07, 63.53, 64.62, 117.16, 120.68, 151.02, 192.70; MS (CI-ME) 239 (M + 1). *cis*-**10**: IR (CH_2Cl_2) 1690, 1630; ^1H NMR (80 MHz) 1.12 (s, 3 H), 1.5–2.1 (m, 5 H), 2.59 (m, 2 H), 3.58 (s, 3 H), 3.95 (s, 4 H), 5.70 (s, 1 H); MS (CI-ME) 239 (M + 1).

(10) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181.

(11) **11**: IR ($CHCl_3$) 1655, 1600; ^1H NMR (80 MHz) 1.00 (s, 3 H), 2.08 (d, *J* = 2 Hz, 3 H), 1.3–2.9 (m, 10 H), 3.55 (s, 3 H), 3.96 (s, 4 H), 5.36 (s, 1 H); ^{13}C NMR (20.1 MHz) 13.30, 17.42, 22.09, 26.46, 34.17, 37.56, 46.91, 47.03, 54.19, 64.14, 65.11, 112.79, 117.95, 131.30, 147.80, 154.54, 200.04; MS (CI-ME) 305 (M + 1).

(12) Stork, G.; Logusch, E. *J. Am. Chem. Soc.* **1980**, *102*, 1218, 1219.

(13) Yoshioka, H.; Takahashi, K.; Kobayashi, M. *Tetrahedron Lett.* **1979**, 3489.

(14) **13**: IR ($CHCl_3$) 1740, 1710; ^1H NMR (80 MHz) 0.89 (s, 3 H), 1.32 (s, 3 H), 2.11 (s, 3 H), 1.7–2.9 (m, 17 H); MS (CI-ME) 319 (M + 1).

(15) Obtained from the Sigma-Aldrich Chemical Co.

(16) **14**: IR ($CHCl_3$) 1740, 1710, 1660, 1620; ^1H NMR (250 MHz) 0.86 (s, 3 H), 1.41 (s, 3 H), 1.0–3.0 (m, 17 H), 5.72 (br s, 1 H); ^{13}C NMR (62.8 MHz) 14.66, 17.49, 21.61, 31.08, 32.04, 33.73, 34.92, 35.89, 36.48, 38.42, 50.05, 50.31, 50.51, 63.53, 124.83, 167.39, 198.88, 207.12, 216.02; MS (CI-ME) 301 (M + 1).

On the Structure of the Hypothetical Common Tetramethylene Biradical Intermediate

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Received November 16, 1981

1,4-Biradicals are postulated as intermediates in a variety of thermal[1-5] and photochemical[6] reactions. For the parent compound, tetramethylene, Segal[7] reported *two* stable conformers—the gauche (**1a**) and the anti (**2a**)–in his ab inito configuration interaction study of the singlet potential-energy surface. Data from the thermolyses of 1,2-dimethylcyclobutanes[1] and the cyclic azo compounds **3b**[2a] have been interpreted by assuming[2a] that there

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† Samuel B. Silbert Fellow, 1981–1982.

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(4) Berson, J. In "Rearrangements in Ground and Excited States", de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 311–391.

(5) Gajewski, J. J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1981; pp 61–67.

(6) (a) Wagner, P. *Acc. Chem. Res.* **1971**, *4*, 168. (b) Jones, G. *Org. Photochem.* **1981**, *5*, 1. (c) Engel, P. *Chem. Rev.* **1980**, *80*, 99–150.

(7) Segal, G. *J. Am. Chem. Soc.* **1974**, *96*, 7892–8.

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