q, J = 7.0 Hz, 1 H), 4.87 ($^1/_2$AB q, J = 7.0 Hz, 1 H), 4.68 (s, 2 H), 4.20 (ddd, J = 6.5, 6.7, 7.1 Hz, 1 H), 4.01 (dd, J = 6.5, 8.4 Hz, 1 H), 3.94 (dd, J = 3.4, 6.7 Hz, 1 H), 3.81 (dd, J = 7.1, 8.4 Hz, 1 H), 2.26 (s, 3 H), 2.04 (s, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR δ 197.47, 169.47, 140.16, 137.66, 132.15, 128.45, 127.75, 127.65, 109.64, 95.03, 78.70, 76.24, 73.11, 69.96, 65.98, 27.19, 26.35, 25.40, 20.81. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.50; H, 7.30.

(*E*)-(2*R*,3*S*,4*R*)-3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (32). Under the same reaction conditions as for the preparation of **29**, compound **30** afforded diacetate **32** (75% yield) as a colorless oil: $[\alpha]_D$ cf. Table I; IR (film) 2980, 2930, 1750, 1685, 1640, 1375, 1220, 1070 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.75 (dd, J = 5.7, 16.1 Hz, 1H), 6.22 (dd, J = 1.4, 16.1 Hz, 1 H), 5.56 (ddd, J = 1.4, 5.0, 5.7 Hz, 1 H), 5.16 (dd, J ; 4.4, 5.0 Hz, 1 H), 4.30 (ddd, J = 4.4, 5.7, 6.8 Hz, 1 H), 4.03 (dd, J = 6.8, 8.6 Hz, 1 H), 3.75 (dd, J = 5.7, 8.6 Hz, 1 H), 2.28 (s, 3 H), 2.11 (s, 3 H), 2.10 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H; ^{13}C NMR δ 197.35, 170.17, 169.34, 139.66, 132.38, 110,03, 74.14, 72.83, 71.76, 65.83, 27.17, 26.03, 25.39, 2×20.75. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.44; H, 7.25.

General Procedure for Preparation of Reference Compounds 23, 26, and 29 from 33,[29] 34,[30] and 35,[31] Respectively. The preparation of **23** is described as an illustrative case. To a solution of dithioacetal **33** (761 mg, 2 mmol) in a mixture of acetone–water (9 mL, 8:1 v/v), were added yellow mercury oxide (1.0 g, 4.6 mmol) and mercury chloride (1.0 g, 3.7 mmol). The mixture was allowed to stir while the temperature was raised to 60 °C over 3 h. At this moment TLC showed the absence of starting material. Then, the mixture was cooled to room temperature and filtered through a short pad of Celite and the solvents were evaporated. To the residue was added toluene (10 mL), and solids were filtered off. Then, the solution was treated with acetonyltriphenylphosphorane (830 mg, 2.6 mmol), and the reaction mixture was stirred at 60 °C for 4 h. After the mixture was cooled to room temperature, ethyl acetate (10 mL) and hexane (20 mL) were added, the precipitated triphenylphosphine oxide was removed by filtration, and the solvents were evaporated. The crude product was purified by flash chromatography (H-EA 3:2 v/v). When this procedure was used compounds **23**, **26**, and **29** were obtained in 70, 68, and 60% yield, respectively. Optical rotations of these compounds are presented in Table I. All spectral data were superimposable with those obtained for compounds synthesized from ketones **15**, **19**, and **16**, respectively.

Acknowledgment. Financial support from the Polish Academy of Sciences (Grants MR-I.12 and CPBP-01.13) is gratefully acknowledged.

Registry No. 3, 15186-48-8; **5**, 534-22-5; **6**, 103061-82-1; **8**, 103061-83-2; 9, 107941-07-1; **10**, 107941-08-2; **11**, 107941-09-3; **12**, 104731-95-5; **13**, 107941-10-6; **14**, 107959-94-4; **15**, 107941-11-7; **16**, 107941-12-8; **17**, 107941-13-9; **18**, 104731-97-7; **19**, 107941-14-0; **20**, 104731-99-9; **21**, 104732-00-5; **22**, 107941-15-1; **23**, 104732-01-6; **24**, 108031-86-3; **25**, 108031-87-4; **26**, 108031-88-5; **27**, 104732-02-7; **28**, 107941-16-2; **29**, 104760-54-5; **30**, 108031-89-6; **31**, 107941-17-3; **32**, 108031-90-9; **33**, 107941-18-4; **34**, 107941-19-5; **35**, 100423-67-4; Ph_3P=CHCOMe, 1439-36-7.

Synthesis of the 1,3-Dioxolane Ring System of the Trichothecenes Sambucinol and Sporol via a Stereoselective Claisen Rearrangement[1]

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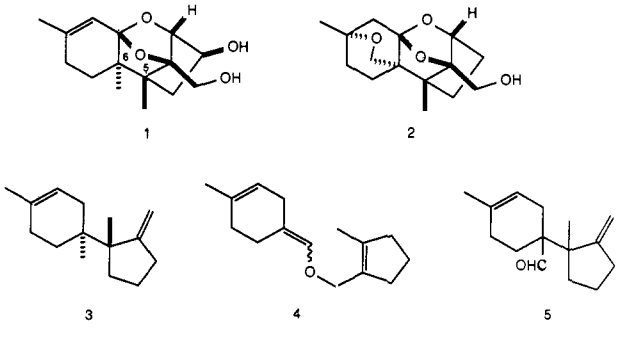
Abstract: The major stereoisomer from the Claisen rearrangement of allyl vinyl ether **10** was shown to be keto nitrile **12** by an X-ray crystallographic analysis on the derived hydroxy nitrile **15**. In a similar fashion, allyl vinyl ether **22** produced keto nitrile **23a**. This substance was converted into hydroxymethyl ketal **25**, which bears the 1,3-dioxolane ring system present in sambucinol **1** and sporol **2**.

Sambucinol **1**[3] and sporol **2**[4] represent recently discovered, unique trichothecenes that are postulated to have trichodiene **3** as their biosynthetic progenitor.[3] While stereocontrolled strategies for the synthesis of trichodiene have been reported,[5] routes employing the Claisen rearrangement for the stereoselective formation of the C_5–C_6 bond bearing the stereogenic centers have been disappointing. Thus, Suda reported[6] that Claisen rearrangement of stereoisomeric vinyl ethers **4** of undefined composition afforded a 1:1 mixture of aldehydes **5**, which, upon Wolff–Kishner reduction gave rise to trichodiene **3** and its stereoisomer, bazzanene. In a reinvestigation of the rearrangement, Gilbert[7] demonstrated that the selectivity for the chair transition state was 85% for vinyl ethers **4**, and that the general lack of stereoselectivity was a result of the inability to control the enol ether double bond stereochemistry. In a related *O*-silyl ester enolate Claisen rearrangement of ester **6**, Kraus[8] realized a 1:1 mixture of carboxyic acids **7**. Finally,



1 2 3 4 5

[†] Sterling Chemistry Laboratory.
[‡] Chemical Instrumentation Center.

(1) Dedicated to Professor George Büchi on the occasion of his 65th birthday.
(2) Crystallographer to whom inquires should be addressed concerning the X-ray analysis.
(3) Mohr, P.; Tamm, C.; Zuercher, W.; Zehnder, W. *Helv. Chim. Acta.* **1984**, *67*, 406.
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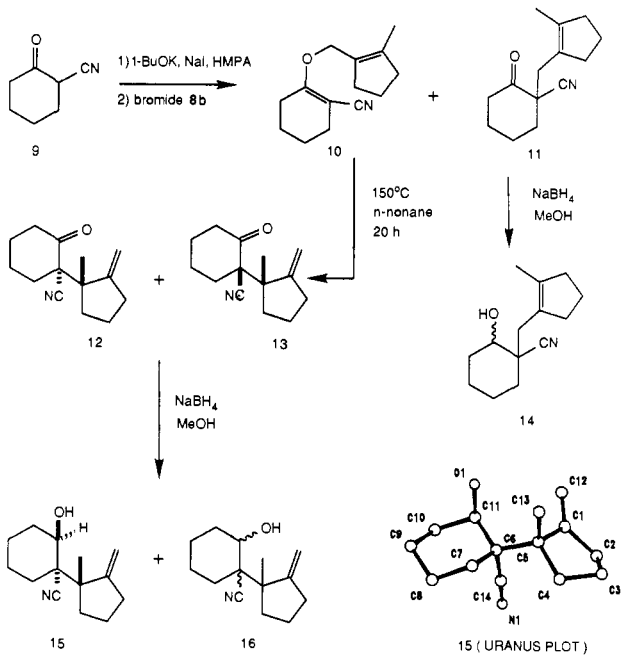
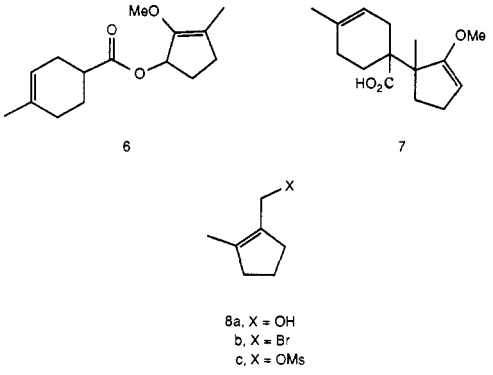
Scheme I



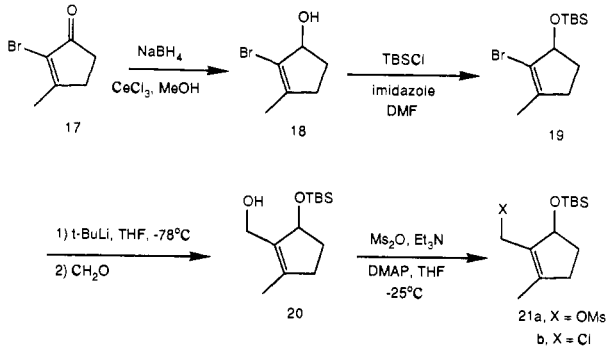
Ponaras has employed hydrazone anions to facilitate stereocontrolled Claisen rearrangements in the trichothecene series.[9]



In this paper we reveal a stereoselective Claisen rearrangement route to the formation of the C_5–C_6 bond and further elaboration of the rearrangement products into models for the synthesis of trichothecenes **1** and **2**.

Alkylation of 2-oxocyclohexanecarbonitrile (**9**) with 1-(bromomethyl)-2-methyl-1-cyclopentene (**8b**) under conditions expected to optimize *O*-alkylation (Scheme I) provided a 1:1 mixture of inseparable O- and C-alkylated products **10** and **11** in 87% yield as determined by ^{13}C NMR and IR.[10,11] Reduction of the mixture with $NaBH_4$ in MeOH permitted chromatographic separation of the pure O-alkylated product. Rearrangement of allyl vinyl ether **10** in refluxing *n*-nonane provided a 6:1 ratio of keto nitriles **12** and **13**, respectively, in 92% yield.[12] The ratio was readily determined by ^1H NMR integration of the vinyl protons or quaternary methyl signals. The stereochemistry of the major component was solved by using single-crystal X-ray analysis. Thus, reduction of the mixture of keto nitriles **12** and **13** ($NaBH_4$/MeOH) gave a 75% yield of hydroxy nitriles **15** and **16**, in which the ratio of axial to equatorial alcohols was 6:1.[13] The signals for the downfield, equatorial, hydroxyl methine protons (δ 4.25–4.40) were present in a ratio of 1:5. Flash chromatography afforded the major axial alcohol **15** (δ 4.40) in 48% yield whose NMR spectrum was identical with the spectrum of a crystalline sample that had been prepared for X-ray analysis.[14] Oxidation of alcohol **15** with pyridinium dichromate (PDC)[15] gave keto nitrile **12**. The rearrangement of vinyl ether **10** occurs preferentially through a chair transition that is favored over its boat counterpart by 1.5 kcal/mol.

Scheme II



Having established the stereochemical course of the reaction, we sought to explore the rearrangement with a more highly oxygenated substrate. Accordingly, the reactive allylic mesylate **21a** was prepared as a suitable alkylating agent (Scheme II).

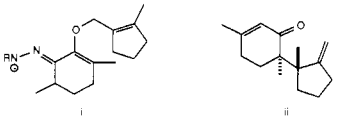
Allylic alcohol **20** proved to be moderately unstable but could be successfully converted to the reactive allylic mesylate **21a** at −25 °C employing methanesulfonic anhydride (Ms_2O)/Et_3N. When a solution of the potassium enolate of 2-oxocyclohexanecarbonitrile in HMPA containing 18-crown-6 and an additional equivalent of *t*-BuOK to neutralize triethylamine methanesulfonate was added to the mesylate at −25 °C and brought to 0 °C, the sole product, obtained in 55% yield, was O-alkylated carbonitrile **22**.

When methanesulfonyl chloride[16] was employed in the formation of mesylate **21a**, the O-alkylation product was obtained in only 25% yield in addition to the isolation of allylic chloride **21b**. The chloride is relatively inert under the reaction conditions that permit alkylation of the mesylate.

Interestingly, when the chloride **21b** was subjected to alkylation in the presence of added NaI under the conditions that had optimized O-alkylation, C-alkylation predominated over O-alkylation (5:1). In an attempt to optimize the O-alkylation of Scheme I, the mesylate **8c** was prepared and subjected to the reaction conditions that optimized O-alkylation with mesylate **21a**. Only a slight increase (~60:40) of O- vs. C-alkylation could be realized relative to the alkylation with bromide **8b**. The more hindered mesylate **21a** may be considered more biased than mesylate **8c** toward O- vs. C-alkylation because C–O bond formation with the enolate of 2-oxocyclohexanecarbonitrile is seemingly less congested than C–C bond formation, the latter instance generating a quaternary substituted carbon.

The cyclopentene ring of silyl ether **22** has diastereotopic faces that can produce, in principle, four diastereomeric Claisen re-

(9) The selective transformation of hydrazone anion i has been reported to provide enone ii: Ponaras, A. A. *Abstracts of Papers*, 187th National Meeting of the American Chemical Society, St. Louis, MO; American Chemical Society: Washington, DC, 1984; ORGN 29. Cf. Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866.



(10) The ratio was determined by integration of carbonyl signal vs. the α-vinyl ether carbon. See Experimental Section.

(11) Methyl 2-oxocyclohexanecarboxylate gave only C-alkylation.

(12) For an allyl phenyl ether variation of this rearrangement, see: Inouye, Y.; Ishihara, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 208.

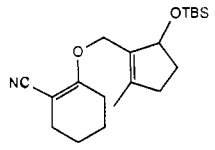
(13) The hydroxynitriles are assumed to be conformationally rigid, having the nitrile group axial and the methylene cyclopentane ring equatorially disposed, independent of their stereochemistry.

(14) The methods used to solve the structure are presented in the Experimental Section. Fractional coordinates and isotropic parameters (Table I), bond distances and angles (Table II), bond angles (Table III), torsional angles (Table IV), and anisotropic temperature factors (Tabel V) are provided in the Supplementary Material.

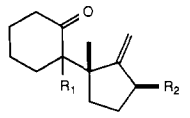
(15) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1978**, 399.

(16) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

arrangement products. Because bond formation is expected to occur on the face of the cyclopentene ring that is remote from the (*tert*-butyldimethylsilyl)oxy group, the number of possible diastereomers would be reduced to two.



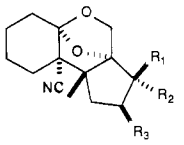
22



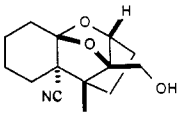
23a, R_1 = α-CN, R_2 = OTBS
b, R_1 = β-CN, R_2 = OTBS
c, R_1 = α-CN, R_2 = OH

Substrate **22** proved to be sensitive to elimination reactions when the rearrangement was conducted in refluxing *n*-nonane. Undesirable olefinic byproducts could be avoided by initial treatment of the reaction flask with bis(trimethylsilyl)acetamide. A 16:1 mixture of carbonitriles **23a,b** was produced from which could be isolated a single, crystalline diastereomer **23a** in 49% yield. The stereochemistry was assigned as arising from a chair transition state in analogy with the model study.[17]

Our next goal was the formation of the 1,3-dioxolane ring system present in sambucinol **1** and sporol **2**. To this end, carbonitrile **23a** was desilylated[18] in high yield with aqueous HF/CH_3CN providing allylic alcohol **23c**. The hydroxyl-directed epoxidation of allylic alcohol **23c** proved troublesome. *m*-Chloroperbenzoic acid (*m*-CPBA) failed to epoxidize allylic alcohol **23c** under ambient reaction conditions. When epoxidation was conducted with *m*-CPBA in refluxing 1,2-dichloroethane,[19] the 1,3-dioxolane **24a**, whose infrared spectrum was devoid of



24a, R_1 = OH, R_2 = R_3 = H
b, R_1, R_2 = O, R_3 = H
c, R_1 = R_3 = H, R_2 = OH
d, R_1 = H, R_2 = R_3 = OH



25

carbonyl absorption and whose NMR spectrum displayed an AB pattern at δ 3.56 and 4.03 (J_{AB} = 7.0 Hz)[20] for the methylene group of the 1,3-dioxolane ring, was formed directly, ostensibly arising from acid-catalyzed opening of the epoxide and participation of the ketone in ketal formation.[21] The stereochemistry of the ketal is assigned based upon α-face attack of the carbonyl oxygen on the transient β-epoxide. Moreover, structure **24a** has the tetrahydrofuran and cyclopentane rings in the more stable cis fused stereochemistry.

The 1,3-dioxolane structure of the target molecules is formed from a C_2-α-OH not the β-configuration present in alcohol **24a**. Accordingly, alcohol **24a** was oxidized under Swern[22] conditions to produce cyclopentanone **24b** (IR, 1753 cm^{-1}). Reduction of ketone **24b** with lithium aluminum tri-*tert*-butoxyhydride occurred with high exo face selectivity (12:1) producing endo alcohol **24c**. Exposure of the alcohol **24c** to BF_3·Et_2O in CH_2Cl_2 at 0 °C afforded the isomeric hydroxy ketal **25**, which clearly revealed the presence of the hydroxymethyl group in its NMR spectrum at δ 4.05 (1 H, dd, J = 12.4, 2.6 Hz) and δ 3.73 (1 H, dd, J = 12.4, 7.4 Hz). Both of the smaller couplings were removed by exchange with D_2O.

The highly stereoselective addition of hydride from the exo (β) face of ketone **24b** suggests that ketone **24b** should permit α-hydroxylation from the exo face and subsequent reduction to afford diol **24d**, a necessary requirement for the synthesis of sambucinol **1**. The carbonitrile moiety can function as a source of either a methyl or hydroxymethyl group. Studies are currently under way to explore these possibilities and to create the necessary oxidation level in ring A of the target substrates.

Experimental Section

(2-Methyl-1-cyclopentenyl)methanol (8a). To a solution of 12.9 g of crude 2-methylcyclopentene-1-carboxaldehyde, prepared from 0.1 mol of 1-methylcyclohexene by the procedure of Hudlicky,[23] in 250 mL of dry ether at −78 °C was added 4.6 g (0.12 mol) of $LiAlH_4$ over 20 min. After the addition was complete, the reaction mixture was maintained at −78 °C for 15 min and then allowed to warm to 0 °C. After 1 h at 0 °C, the reaction mixture was decomposed by the slow, successive addition of 4.6 mL of H_2O, 4.6 mL of 15% aqueous NaOH, and 9 mL of H_2O. After workup, distillation (bp 53 °C, 1.1 torr) provided 5.5 g (49% from 1-methylcyclhexene) of alcohol **8a**, whose ^1H NMR and IR were in agreement with literature values.[12]

1-(Bromomethyl)-2-methyl-1-cyclopentene (8b).[24] To a solution of alcohol **8a** (3.03 g, 27 mmol) in 65 mL of pentane at 0 °C was added 48% HBr 5.9 mL (54 mmol, 9.1 g) over 10 min. After having been stirred for an additional 30 min, the reaction mixture was washed successively with brine, saturated aqueous $NaHCO_3$, and brine. Workup afforded 3.6 g (76%) of crude bromide **8b**. The crude product was suitable for alkylation without further purification: ^1H NMR δ 4.11 (s, 2 H), 2.55–2.40 (m, 2 H), 2.40–2.28 (m, 2 H), 1.92–1.75 (m, 2 H), 1.71 (s, 3 H).

Allyl Vinyl Ether 10. A solution of 2-oxocyclohexanecarbonitrile (**9**)[25] (1.85 g, 15 mmol) in 30 mL of HMPA was treated with 1.68 g (15 mmol) of potassium *tert*-butoxide. After having been stirred for 1 h at 25 °C, a solution of bromide **8b** (3.6 g, 20 mmol) in 5 mL of HMPA and then 2.7 g (18 mmol) of solid NaI were added. After having been stirred an additional 4 h at 25 °C, the reaction mixture was diluted with brine, acidified to pH 4 with 5% HCl, extracted with ether, and worked up to afford 4.27 g of crude material. Flash chromatography (10% EtOAc/hexanes) afforded 2.83 g (87%) of O- and C-alkylation isomers **10** and **11**, respectively. Inspection of the ^{13}C NMR indicated a 1:1 mixture of the 2 isomers: R_f 0.27 (10% EtOAc/hexanes); ^1H NMR (partial) δ 4.60 (s, $-O-CH_2-$), 1.70 (s, $-CH_3$); ^{13}C NMR (partial) 202.6 (1 C, C=O), 167.5 (1 C, α-vinyl ether carbon); IR 2946, 2845, 2209, 1729, 1634, 1159 cm^{-1}.

To a mixture of O and C isomers **10** and **11** (2.5 g, 11.5 mmol) in 30 mL of MeOH at 0 °C was slowly added 660 mg (17.3 mmol) of $NaBH_4$. After having been stirred for 3 h at 0 °C, the excess $NaBH_4$ was decomposed with acetone. The reaction mixture was acidified to pH ~ 3 with 5% HCl and extracted with ether. Workup followed by flash chromatography (10% EtOAc/hexanes) afforded 750 mg (30%) of allyl vinyl ether **10**: R_f 0.27 (10% EtOAc/hexanes); ^1H NMR δ 4.60 (s, 2 H), 2.52–2.40 (m, 2 H) 2.40–2.20 (m, 6 H), 1.90–1.76 (m, 2 H) 1.74–1.62 (m, 2 H), 1.70 (s, 3 H), 1.60–1.40 (m, 2 H); ^{13}C NMR δ 167.7, 137.7, 130.4, 118.8, 86.0, 65.1, 38.7, 34.2, 26.2, 25.9, 21.8, 21.4 (2 carbons), 13.8; IR 2949, 2854, 2206, 1633, 1158, 908 cm^{-1}.

Ketones 12 and 13. A solution of allyl vinyl ether **10** (400 mg, 1.84 mmol) in 5 mL of *n*-nonane was purged with dry N_2 and heated at reflux under an atmosphere of N_2 for 20 h. The solvent was removed under reduced pressure, and the residue was chromatographed (10% EtOAc/hexanes). The inseparable ketones **12** and **13** (370 mg, 92%) were determined to be a 6:1 mixture, respectively, upon NMR integration of the vinyl and methyl signals: R_f 0.35 (10% EtOAc/hexanes); ^1H NMR (**12**) δ 5.20 (d, J = 2.7 Hz, 1 H), 5.08 (d, J = 2.4 Hz, 1 H), 2.93 (td, J = 13.7, 6.1 Hz, 1 H), 2.48–2.33 (m, 3 H), 2.20–1.85 (m, 6 H), 1.84–1.60 (m, 3 H), 1.56–1.44 (m, 1 H), 1.41 (s, 3 H); ^{1}NMR (**13**, partial) 5.08 (s, 1 H), 5.00 (s, 1 H), 1.24 (s, 3 H); ^{13}C NMR (**12**) δ 202.0, 156.9, 119.6, 107.6, 59.2, 47.1, 40.1, 37.3, 36.8, 33.4, 26.9, 25.8, 22.9, 22.2; IR 3083, 2949, 2871, 2229, 1732, 1648, 905 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.27; H, 8.86; N, 6.43.

(17) The reason for the small, but synthetically favorable, selectivity of the rearrangement of **10** (6:1) and **22** (16:1) is not known at this time. The energy difference between a ratio of 6:1 and 16:1 at 150 °C is ~0.8 kcal/mol. The ratios were determined by NMR integration of the vinyl region of the crude, but clean, reaction mixtures.

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(24) We thank Professor A. A. Ponaras (Catholic University, Washington, DC) for making this procedure available to us.

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Axial Alcohol 15. To a solution of diastereomeric ketones **12** and **13** (168 mg, 0.77 mmol) in 2 mL of MeOH at 0 °C was slowly added 44 mg (1.16 mmol) of $NaBH_4$. After having been stirred for 3 h, the excess $NaBH_4$ was decomposed with acetone, and the reaction mixture was acidified to pH ~3 with 5% HCl and worked up to afford 125 mg (75%) of crude material. The ^1H NMR spectrum showed methine proton signals at δ 4.25–4.40 (equatorial methine protons) and δ 3.60–3.70 (axial methine protons) in a 6:1 ratio, respectively. Flash chromatography (5%, then 10% EtOAc/hexanes) yielded 60 mg (48%) of pure axial alcohol **15**. Recrystallization from ether/hexanes afforded crystals satisfactory for single-crystal X-ray analysis: R_f 0.26 (10% EtOAc/hexanes); mp 67–68 °C; ^1H NMR δ 5.19 (s, 1 H), 5.15 (s, 1 H), 4.40 (s, 1 H), 2.49–2.38 (m, 2 H), 2.30–2.16 (m, 1 H), 2.12–1.91 (m, 2 H), 1.86–1.63 (m, 7 H), 1.60–1.45 (m, 3 H), 1.32 (s, 3 H); IR 3609, 3508, 2941, 2866, 2229, 1646, 1449, 999, 903 cm^{-1}.

1-Bromo-2-methyl-5-[(*tert*-butyldimethylsilyl)oxy]-1-cyclopentene (19). To a solution of bromo ketone **17**[26] (17.88 g, 0.10 mol) in 225 mL of MeOH at 0 °C was added 37.2 g (0.10 mol) of $CeCl_3 \cdot 7H_2O$ in 1 portion. When all the $CeCl_3 \cdot 7H_2O$ had dissolved (15–20 min), $NaBH_4$ (3.9 g, 0.102 mol) was added in small portions.[27] After having been stirred for an additional 30 min, excess $NaBH_4$ was decomposed with 50 mL of acetone, and the reaction mixture was acidified to pH ~3 with 5% HCl. Extraction with ether (5 × 100 mL) and workup provided 17.0 g (95%) of crude allylic alcohol **18**: R_f 0.45 (30% EtOAc/hexanes); ^1H NMR δ 4.72 (br s, 1 H), 2.56–2.17 (m, 3 H), 2.05 (br s, 1 H), 1.92–1.80 (m, 1 H), 1.80 (s, 3 H). The peak at δ 2.05 disappears on exchange with D_2O. IR 3591, 3410, 3010, 2974, 2920, 2853, 1717, 1661, 1438, 1236, 1041 cm^{-1}.

To the crude allylic alcohol (17.0 g, 0.096 mol) dissolved in 35 mL of dry DMF was added over 15 min imidazole (16.39 g, 0.24 mol) and *tert*-butyldimethylsilyl chloride (TBSCl) (17.4 g, 0.015 mol).[28] After having been stirred for 3 h at 25 °C, the reaction mixture was poured into 300 mL of brine. Extraction with ether and workup provided crude material, which was purified by flash chromatography (1% EtOAc/hexanes) giving 24.5 g (88%) of pure bromo silyl ether **19**: R_f 0.24 (hexanes); ^1H NMR δ 4.75 (br s, 1 H), 2.52–2.12 (m, 3 H), 1.88–1.78 (m, 1 H), 1.78 (s, 3 H), 0.93 (s, 9 H), 0.17 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR δ 140.1, 120.8, 80.2, 34.2, 32.5, 25.8 (3×), 18.3, 16.0, −4.6, −4.7; IR 2958, 2933, 2855, 1471, 1250 cm^{-1}. Anal. Calcd for $C_{12}H_{23}BrOSi$: C, 49.48; H, 7.96; Br, 27.43. Found: C, 49.53; H, 7.99; Br, 27.36.

{2-Methyl-5-[(*tert*-butyldimethylsilyl)oxy]-1-cyclopentenyl}methanol (20). A solution of bromo silyl ether **19** (2.91 g, 10.0 mmol) in 20 mL of dry THF containing a few crystals of 2,2′-dipyridyl as an indicator was cooled to −78 °C. *tert*-Butyllithium (13 mL, 22.0 mmol, 1.7 M in pentane) was added over 15 min, and the reaction mixture was stirred at −78 °C for 1 h. Paraformaldehyde (dried over P_2O_5, 0.5 torr/25 °C, 8 h) was cracked, and gaseous HCHO was purged through the reaction mixture until the bright red color disappeared. The mixture was decomposed at −78 °C by the addition of 10 mL of saturated NH_4Cl and allowed to warm to 25 °C. Extraction with ether and workup gave 3.2 g of crude material. Flash chromatography (15% EtOAc/hexane) afforded 2.18 g (90%) of pure allylic alcohol. The alcohol proved to be unstable and was not stored for more than 3 days at −20 °C: R_f 0.26 (15% EtOAc/hexanes); ^1H NMR δ 4.98 (br s, 1 H), 4.22 (m, 2 H), 2.47–2.36 (m, 2 H), 2.30–2.18 (m, 2 H), 1.75 (s, 3 H), 1.70–1.60 (m, 1 H), 0.94 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H). Upon exchange with D_2O: δ 4.22 (m, 2 H) → 4.26 (d, J = 12.5 Hz, 1 H, CH_2OH), and 4.15 (d, J = 12.5 Hz, 1 H, CH_2OH); δ 2.47–2.36 (m, 2 H) → 2.47–2.36 (m, 1 H, OH); ^{13}C NMR δ 139.2, 135.7, 81.1, 57.8, 35.6, 33.1, 25.8 (3×), 18.0, 14.2, −4.3, −4.9; IR 3495, 2958, 2928, 2855, 1471, 1250 cm^{-1}.

Allyl Vinyl Ether 22. To a solution of 2-oxocyclohexanecarbonitrile (9)[25] (2.12 g, 17.25 mmol) in 35 mL of dry HMPA at 10 °C was added potassium *tert*-butoxide (3.9 g, 34.5 mmol) in small portions. After 30 min, the K-enolate was treated with 6.1 g (23.0 mmol) of 18-crown-6 and stirred another 30 min.

A solution of alcohol **20** (2.78 g, 11.5 mmol), Et_3N (2.4 mL, 17.25 mmol, 1.75 g), and 4-(dimethylamino)pyridine (140 mg, 1.15 mmol) in 30 mL of dry THF was chilled to −25 °C. Methanesulfonic anhydride (2.6 g, 14.95 mmol, recrystallized from Et_2O prior to use) was added over 10 min. After stirring for an additional 10 min at −20 °C, the reaction mixture was treated with the K-enolate of **9**. The mixture was maintained at 0 °C for 2 h and then acidified to pH ~4 with 5% HCl. Dilution with brine, extraction with ether, and workup gave 8.1 g of crude material. Purification on silica gel (8% EtOAc/hexanes) afforded 2.1 g (53%) of ether **22**: R_f 0.36 (10% EtOAc/hexanes); mp = 54–56 °C (ether/pentane); ^1H NMR: δ 4.99 (br s, 1 H), 4.64 (d, J = 10.7 Hz, 1 H), 4.53 (d, J = 10.7 Hz, 1 H), 2.50–2.20 (m, 7 H), 1.78 (s, 3 H), 1.73–1.68 (m, 1 H), 1.68–1.55 (m, 4 H), 0.93 (s, 9 H) 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR 166.8, 141.2, 132.4, 118.3, 85.3, 76.0, 61.6, 35.4, 32.3, 25.9, 25.6, 25.3 (3×), 21.4, 21.0, 17.5, 13.9, −5.0, −5.4; IR 3020, 2951, 2933, 2854, 2208, 1635, 1367. Anal. Calcd for $C_{20}H_{33}NO_2Si$: C, 69.11; H, 9.57. Found: C, 69.16; H, 9.58.

Silyloxy Ketone 23a. A 25-mL flask was silylated with bis(trimethylsilyl)acetamide (BSA)/pentane (1 mL/2 mL) by swirling gently for 5 min. The pentane was evaporated by gentle warming (~40 °C), and BSA was concentrated under vacuum. The flask was rinsed with pentane (4–5 times) and dried in a stream of N_2. The allyl vinyl ether **22** (1.25 g, 3.6 mmol) was dissolved in 18 mL of *n*-nonane, purged with N_2, and immersed in a preheated oil bath (165 °C). The solution was heated at reflux for 6 h. The *n*-nonane was removed under reduced pressure. NMR integration of the vinyl proton signals of the crude residue showed a mixture of two diastereomers in a 16:1 ratio. The residue was chromatographed (7% EtOAc/hexanes) to yield 611 mg (49%) of ketone **23a**: R_f 0.40 (10% EtOAc/hexanes); mp = 77–78 °C (ether/pentane); ^1H NMR δ 5.26 (d, J = 2.6 Hz, 1 H), 5.22 (d, J = 2.4 Hz, 1 H), 4.37 (m, 1 H), 2.93 (td, J = 13.6, 6.0 Hz, 1 H), 2.46–2.24 (m, 2 H), 2.20–2.00 (m, 2 H), 2.00–1.81 (m, 4 H), 1.70–1.47 (m,3 H), 1.44 (s, 3 H), 0.95 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR δ 202.1, 157.6, 119.5, 108.4, 76.3, 59.1, 45.3, 40.3, 33.8, 31.9, 31.7, 27.3, 26.6, 25.8 (3×), 22.4, 18.1, −4.7, −4.9; IR 2956, 2933, 2855, 2231, 1730, 1648, 1450, 1253, 1097. Anal. Calcd for $C_{20}H_{33}NO_2Si$: C, 69.11; H, 9.57. Found: C, 69.20; H, 9.60.

Allylic Alcohol 23c. To a solution of silyl ether **23a** (347 mg, 1.0 mmol) in 3 mL of CH_3CN at 0 °C was added 3 mL of aqueous 48% HF/CH_3CN (1:20).[18] After 3 h at 0 °C, the reaction mixture was diluted with brine, extracted with ether, and worked up to provide 228 mg (98%) of solid allylic alcohol **23c**, which was used in subsequent operations without further purification. A sample from an independent experiment was purified by flash chromatography to obtain analytical data:[29] R_f 0.29 (40% EtOAc/hexanes); mp 65–67 °C (ether/pentane); ^1H NMR δ 5.34 (d, J = 2.6 Hz, 1 H), 5.28 (d, J = 2.4 Hz, 1 H), 4.41 (m, 1 H), 2.93 (td, J = 13.6, 6.0 Hz, 1 H), 2.47–2.28 (m, 2 H), 2.23–2.00 (m, 3 H), 2.00–1.78 (m, 3 H), 1.75–1.55 (m, 4 H), 1.46 (s, 3 H). Upon exchange with D_2O: δ 1.75–1.55 (m, 4 H) → δ 1.75–1.55 (m, 3 H); ^{13}C NMR 202.0, 158.4, 119.3, 108.2, 75.5, 59.0, 45.8, 40.2, 33.6, 31.9, 31.6, 27.1, 26.4, 22.4, 22.2; IR 3587, 3455, 3004, 2971, 2949, 2872, 2234, 1733, 1453, 1063, 914 cm^{-1}.

Cyclopentanone 24b. To a solution of allylic alcohol **23c** (202 mg, 0.87 mmol) in 4.5 mL of dry 1,2-dichloroethane was added 245 mg (1.12 mmol) of 80% *m*-chloroperbenzoic acid (*m*-CPBA) and 5 mg (2% weight of *m*-CPBA) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide.[19] The reaction flask was immersed in a preheated oil bath (95 °C), and the solution was heated at reflux for 3 h. The reaction mixture was cooled to room temperature, diluted with excess 15% aqueous $NaHSO_3$ solution, and stirred for 10 min. The aqueous layer was extracted with ether, and the organic layer was washed with aqueous 15% K_2CO_3 and brine. Workup afforded 200 mg (92%) of crude β-hydroxy ketal **24a**, which was used without further purification. A sample from an independent experiment was purified by flash chromatography to obtain analytical data:[29] R_f 0.34 (40% EtOAc/hexanes); mp = 114–116 °C (ether/pentane); ^1H NMR δ 4.61 (br s, 1 H), 4.03 (d, J = 7.0 Hz, 1 H), 3.56 (d, J = 7.0 Hz, 1 H), 2.53–2.40 (m, 1 H), 2.35–2.17 (m, 2 H), 2.04–1.90 (m, 3 H), 1.90–1.75 (m, 6 H), 1.65 (s, 1 H), 1.22 (s, 3 H); ^{13}C NMR δ 120.7, 109.0, 101.0, 72.1, 66.1, 58.4, 50.6, 37.0, 35.5, 28.1, 28.0, 22.4, 21.5, 19.4; IR 3611, 3468, 3009, 2942, 2904, 2870, 2229, 1378, 1030 cm^{-1}.

To a solution of oxalyl chloride (117 μL, 1.35 mmol, 171 mg) in 1.5 mL of dry CH_2Cl_2 at −78 °C was added a solution of Me_2SO (192 μL, 2.7 mmol, 210 mg) in 0.5 mL of CH_2Cl_2. After 15 min, a solution of β-hydroxy ketal **24a** (200 mg, 0.8 mmol) in 2 mL of CH_2Cl_2 was added. After having been stirred for 15 min at −78 °C, the reaction mixture was warmed to −30 °C (for 1 min). The reaction mixture was recooled to −78 °C and treated with 750 μL (5.4 mmol, 546 mg) of Et_3N. The reaction mixture was warmed to room temperature over 30 min, diluted with brine, and extracted with ether. Workup afforded 243 mg of crude material. Flash chromatography (30% EtOAc/hexanes) yielded 121 mg (60%) of cyclopentanone **24b**: R_f 0.31 (30% EtOAc/hexanes); mp 133–135 °C (ether/pentane): ^1H NMR δ 3.87 (d, J = 7.2 Hz, 1 H), 3.63 (d, J = 7.2 Hz, 1 H), 2.88–2.52 (m, 3 H), 2.32 (td, J = 12.5, 5.2 Hz), 2.11–1.79 (m, 7 H), 1.70–1.55 (m, 1H), 1.20 (s, 3 H); ^{13}C NMR δ 206.8, 120.1, 111.9, 93.0, 64.2, 58.7, 49.7, 38.3, 34.1, 28.3, 27.7, 22.2, 21.4, 16.5; IR 2945, 2908, 2872, 2233, 1753, 1447, 1374 cm^{-1}. Anal.

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(29) The crude and crystallized material had identical ^1H and ^{13}C NMR spectra.

Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93. Found: C, 68.09; H, 6.95.

Hydroxymethyl Ketal 25. To a solution of cyclopentanone **24b** (69.0 mg, 0.28 mmol) in 2 mL of THF at 0 °C was added $LiAl(O\text{-}t\text{-}Bu)_3H$ (143 g, 0.56 mmol). The reaction mixture was stirred for 5 h, diluted with brine, extracted with ether, and worked up to provide 59 mg (85%) of crude alcohols. NMR integration of methine proton signals showed a 12:1 ratio of hydroxy ketals **24c** and **24a**, respectively, which were inseparable on TLC: R_f 0.34 (40% EtOAc/hexanes); ^1H NMR (**24c**) δ 4.16 (m, 1 H), 3.85 (d, J = 6.9 Hz, 1 H), 3.59 (d, J = 6.9 Hz, 1 H), 2.47–2.18 (m, 3 H), 2.12–1.91 (m, 4 H), 1.90–1.70 (m, 4 H), 1.70–1.42 (m, 2 H), 1.09 (s, 3 H); IR 3583, 3446, 3015, 2947, 2903, 2868, 2232, 1449, 1081, 1062 cm^{-1}.

The mixture of ketals (55 mg, 0.22 mmol) was dissolved in 2 mL of CH_2Cl_2, cooled to 0 °C, and treated with 54 μL (0.44 mmol, 63 mg) of boron trifluoride etherate. After stirring for 2 h at 0 °C, the reaction mixture was diluted with brine, extracted with ether, and worked up to afford 49 mg of crude, isomerized ketal. Flash chromatography (20% EtOAc/hexanes) afforded the hydroxymethyl ketal **25** (36 mg, 66%): R_f 0.28 (20% EtOAc/hexanes); mp = 122–123 °C (ether/pentane); ^1H NMR δ 4.27 (d, J = 4.3 Hz, 1 H), 4.05 (dd, J = 12.4, 2.6 Hz, 1 H), 3.73 (dd, J = 12.4, 7.4 Hz, 1 H), 2.50 (ddd, J = 14.6, 8.4, 4.1 Hz, 1 H), 2.22–2.08 (m, 2 H), 2.05–1.67 (m, 7 H), 1.67–1.50 (m, 3 H), 1.12 (s, 3 H). Upon exchange with D_2O: δ 4.05 (dd, J = 12.4, 2.6 Hz, 1 H) → δ 4.05 (d, J = 12.4 Hz, 1 H); δ 3.73 (dd, J = 12.4, 7.4 Hz, 1 H) → δ 3.73 (d, J = 12.4 Hz, 1 H); δ 1.67–1.50 (m, 3 H) → δ 1.67–1.50 (m, 2 H); ^{13}C NMR δ 120.2, 105.5, 96.9, 81.5, 58.2, 57.1, 51.9, 35.6, 32.0, 27.3, 26.5, 22.6, 22.5, 16.5; IR: 3595, 3477, 2947, 2869, 2238, 1467, 1043. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68. Found: C, 67.52; H, 7.73.

Methods for the X-ray Solution of Structure 15. A crystal of dimensions 0.37 × 0.25 × 0.25 mm was mounted on a glass rod. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer by using graphite monochromatized Mo Kα radiation (λ = 0.710 73 Å). The unit cell was found by using 24 randomly selected reflections, and the indexing procedure produced the following monoclinic cell: a = 7.103 (2) Å, b = 10.998 (3) Å, and c = 16.142 (5) Å, with β = 95.44 (3). The volume is 1255 (1) Å^3, and the calculated density is 1.160 g/cm^3 for Z = 4. Systematic extinctions and an estimated density were the criterions used to uniquely establish the space group as $P2_1/c$ with 1 molecule of composition $C_{14}H_{21}ON$ comprising the asymmetric unit.

There were 2597 reflections collected with $2\theta \leq 52°$, with 749 (29%) observed ($I \geq 3\sigma I$). The structure was solved by direct methods, by using MULTAN80.[30] Eleven of the 16 non-hydrogen atoms were observed on the electron density map based on the phasing of 264 reflections ($E_{min} \geq 1.47$). The remaining five non-hydrogen atoms were located by using the weighted Fourier option in MULTAN80.

The carbon, oxygen, and nitrogen atoms were refined anisotropically. Hydrogen atoms were calculated by using SDP program HYDRO and added to the structure factor calculations. Full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement of their positions, has resulted in convergence to a standard crystallographic residual of 0.054 and a weighted residual of 0.049. All intramolecular bond distances and angles are within normal range.

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Registry No. 1, 90044-33-0; **2**, 101401-88-1; **8a**, 81328-62-3; **8b**, 99439-91-5; **9**, 4513-77-3; **9** (potassium enolate), 108060-96-4; **10**, 108060-88-4; **11**, 108060-89-5; **12**, 108060-90-8; **13**, 108060-91-9; **15**, 108060-92-0; **17**, 80963-36-6; **18**, 108060-93-1; **19**, 108060-94-2; **20**, 108060-95-3; **22**, 108060-97-5; **23a**, 108060-98-6; **23c**, 108060-99-7; **24a**, 108061-00-3; **24b**, 108061-01-4; **24c**, 108146-37-8; **25**, 108061-02-5; 2-methyl-1-cyclopentene-1-carboxaldehyde, 81328-61-2.

Supplementary Material Available: Tables I–V (ref 14) contain X-ray data (5 pages). Ordering information is given on any current masthead page,

(30) All data were generated on a VAX 11/750 (Digital Equipment Corporation) by using the Enraf-Nonius SDP-PLUS programs and MULTAN80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data: Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Wolfson, M. M. The programs URANUS and SKKPUB, programs to generate plot and tables, respectively, were written by Simon Kay Kearsley, Yale University, 1985.

2,5-Cyclohexadien-1-one to Bicyclo[3.1.0]hexenone Photorearrangement. Development of the Reaction for Use in Organic Synthesis

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Abstract: 2,5-Cyclohexadien-1-ones (**8–14**) were prepared from derivatives of benzoic acid and benzonitrile by a Birch reductive alkylation–oxidation sequence. Photorearrangement of **9a** at 366 nm gave phenols **17** and **18** in a product ratio of 3:1, respectively; bicyclo[3.1.0]hexenone **15** was not detected even at short reaction times. Intermediate bicyclohexenone **15** presumably undergoes rapid photoisomerization to zwitterion **16**, which suffers competitive 1,2-migrations of the carbomethoxy group to give phenols **17** and **18**. In contrast, irradiation of **8a–e** produced a mixture of bicyclohexenones **19a–e** and **20a–e** in good to excellent yields. Continued irradiation (366 nm) of the mixtures of **19** and **20** gave predominately the diastereoisomeric series **19a–e** (~9:1 for the composition of **19** and **20**). None of the regioisomeric bicyclohexenones **22a–e** were detected. The photostabilizing effect of the enone β-methoxy group also was demonstrated in the context of 2,5-cyclohexadienone photochemistry; the 3,5-dimethoxy-substituted **12** was found to be photostable at 366 nm despite the fact that light is absorbed by **12**. 2,5-Dimethoxy-substituted **11** underwent slow photoconversion to phenol **35**, presumably via loss of formaldehyde in intermediate zwitterion **34**. Irradiation of the 2,6-dimethyl-substituted **10** gave phenol **38**. Replacement of the 4-carbomethoxy group with a cyano group provides a control element which allows isolation of bicyclohexenones from photorearrangement of 4,4-disubstituted 2,5-cyclohexadienones. Thus, **13a** photorearranged to **40a** and **41a** (**40a**:**41a**, 9:1) with no trace of phenolic byproducts; as expected, 3-methoxy-substituted **14** gave mainly **40b** (**40b**:**41b**, >95:5). Stereochemical studies with an enantiomerically pure 2,5-cyclohexadien-1-one **53a** demonstrated that photochemical interconversions of bicyclo[3.1.0]hexenones occur by external cyclopropane bond cleavage (bond "b" in structure **54**). These studies also demonstrated that there is a pathway for return of the excited state or primary photoproduct to racemized 2,5-cyclohexadienone, e.g., **53a** + **53b**. Bicyclohexenone **19b** was converted to lactone **63** (~quantitative yield) on treatment with $NaBH_4$ followed by acidification.

The most intensively studied photoreaction of 2,5-cyclohexadien-1-ones **1** is the rearrangement to bicyclo[3.1.0]hexenones **3** via intermediate zwitterions **2**. Although a great deal is known about the mechanism[1] of this photoconversion, there are relatively

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