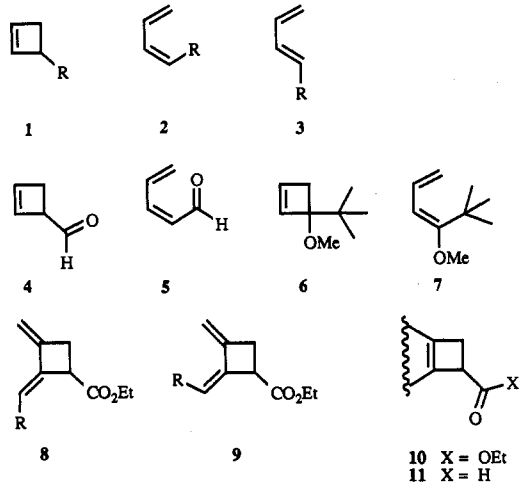
Stereochemistry of Thermal Ring Opening of Substituted 7-(Ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes and Related Substances

Summary: Thermally driven ring openings of the substituted 3-formylcyclobutenes **16** and **26** occur with exclusive inward rotation of the formyl group. Thermolysis of the ester **13** results in predominant formation of the ester diene **17** (outward rotation of CO_2Et), while heating of the ester **25** provides a 1:1 mixture of the isomeric esters **27** and **28**.

Sir: Theoretical[1-5] and experimental[1,3,4,6-9] studies concerning the thermally allowed conrotatory ring opening of 3-substituted cyclobutenes **1** have shown that the nature of R has a profound effect on the stereochemistry of the process. Groups that are strongly electron withdrawing favor inward rotation to provide **2**, while functions that are strong electron donors prefer outward rotation to give **3**. For example, thermolysis of 3-formylcyclobutene (**4**) affords *only* (*Z*)-2,4-pentadienal (**5**),[3] while heating of the substituted cyclobutene **6** results in *exclusive* outward rotation of the OMe function to give **7**.[4] Very recent calculations by Buda, Wang, and Houk[5] have predicted that the CO_2Me group favors outward rotation by about 1.7 kcal/mol.

Recently, we reported[10] an efficient, stereocontrolled method for the synthesis of ethyl 2-alkylidene-3-methylenecyclobutanecarboxylates **8** and **9**. Successful Diels-Alder reactions of these dienes would produce products possessing the part structure shown in **10**. Thus,



it appeared that we would have easy access to substituted 3-(ethoxycarbonyl)cyclobutenes, which could be employed as substrates to test experimentally the predictions of Buda, Wang, and Houk.[5] Furthermore, compounds **10** could readily be converted into the corresponding aldehydes **11** and, consequently, the stereochemistry of ring opening of 3-formylcyclobutenes more highly substituted than the parent substrate **4** could be investigated.

A Lewis acid catalyzed Diels-Alder reaction of the diene **12**[10] with 3-buten-2-one gave the keto ester **13**[11] as the sole product (Scheme I). Not unexpectedly, the cycloaddition reaction occurred via an endo transition state, with the dienophile approaching the diene from the side opposite the CO_2Et function. The stereochemistry of **13** was confirmed by ^1H NMR spectroscopy (coupling patterns, NOE difference experiments).

Reduction of **13** afforded a 4:1 mixture of epimeric diols **14** and **15**, from which pure **14** (mp 113-114 °C) could be obtained by fractional crystallization. Oxidation of the mixture of **14** and **15** gave the keto aldehyde **16**.

Thermolysis of **13** provided cleanly a mixture of the two geometrically isomeric keto esters **17** and **18**, in a ratio of 11:1, respectively (^1H NMR analysis). These substances, which could be separated by chromatography on silica gel, were shown in separate experiments to be stable under the conditions of their formation from **13**. In ^1H NMR NOE difference experiments, irradiation of the singlets due to H_a in compounds **17** and **18** (δ 5.84 and 5.72, respectively) caused, in each case, enhancement of the signal due to H_b (br t, δ 5.03, and m, δ 2.90-2.98, respectively). Furthermore, reduction of **17** afforded the diols **19** (11:1 mixture of epimers), the major isomer of which was found to be identical with the *single* product (mp 72.5-74 °C) derived from thermolysis of **14**. Thus, the stereochemistry of **17** and **18** was, in each case, unambiguously established.

Thermally induced ring opening of the substituted 3-formylcyclobutene **16** in refluxing C_6D_6 provided, on the basis of ^1H NMR analysis, a mixture of the keto aldehyde **21** and the keto ether **22**, in a ratio of 1:2, respectively. Clearly, **22** is formed by (reversible) electrocyclic ring closure of the initially formed dienal **21**. Compounds **21** and **22** could be partially separated by column chromatography on silica gel, but, due to the fact that these substances interconvert (slowly) at room temperature, they could not be obtained pure. However, the spectral data, particularly those derived from the ^1H NMR spectra,[12] unequivocally confirmed the structural assignments. Furthermore, the ^1H NMR spectrum of **21** is clearly different from that of the keto aldehyde **20**, which was obtained by oxidation of the diols **19**.

Thermolysis of **16** in PhMe, followed by cooling of the solution to -78 °C, addition of *i*-Bu_2AlH, and warming of the reaction mixture to room temperature, provided the diols **23** (10:3 mixture of epimers). The ^1H NMR spectrum of **23** is clearly different from that of **19**.

A Diels-Alder reaction similar to that described above (Scheme I, step a) effected conversion of the diene **24**[10] into the keto ester **25** (66%), which, upon subjection to a *i*-Bu_2AlH reduction-Swern oxidation sequence, was transformed into the keto aldehyde **26**. Substrates **25** and **26**

(1) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.
(2) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.
(3) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708.
(4) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125.
(5) Buda, A.; Wang, Y.; Houk, K. N. *J. Org. Chem.*, preceding paper in this issue.
(6) Jefford, C. W.; Boschung, A. F.; Rimbault, C. G. *Tetrahedron Lett.* **1974**, 3387.
(7) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871.
(8) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. *Tetrahedron Lett.* **1986**, *27*, 4387.
(9) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. L.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1987**, *109*, 219.
(10) Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1988**, *53*, 926.

(11) All compounds reported herein exhibited spectra in full accord with structural assignments. New, isolable compounds gave satisfactory molecular mass determinations (high-resolution mass spectrometry).
(12) In the ^1H NMR spectrum (400 MHz, $CDCl_3$) of **21**, the signals due to the dienal function appear at δ 5.02 (br t, $J \approx 1$ Hz), 5.31 (br t, $J \approx 1$ Hz), 5.99 (d, $J = 8$ Hz), and 9.83 (d, $J = 8$ Hz), while, for compound **22**, the alkene protons give rise to doublets ($J = 6$ Hz) at δ 5.10 and 6.40 and the CH_2O protons produce a multiplet at δ 4.39-4.48.

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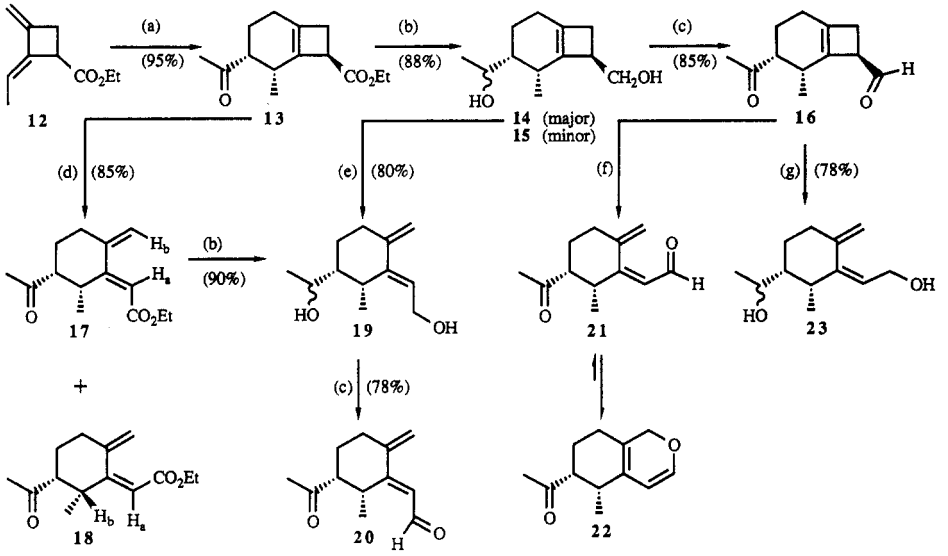
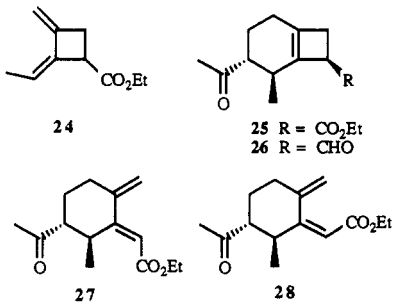
Scheme I[a]



[a] (a) 3-Buten-2-one, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C; (b) *i*-Bu_2AlH, Et_2O; (c) $(COCl)_2$, Me_2SO, CH_2Cl_2; Et_3N; (d) mesitylene, reflux, 1 h; (e) neat, 160 °C, 30 min; (f) C_6D_6, reflux, 3 h; (g) PhMe, reflux, 30 min; cool to −78 °C; add *i*-Bu_2AlH in PhMe; stir at −78 °C for 30 min, at 0 °C for 30 min, and at room temperature for 2 h.

are epimeric with the previously studied substances **13** and **16**, respectively.



Thermolysis of **26** produced results essentially identical with those described above for the ring opening of **16** (Scheme I, steps f and g). On the other hand, thermally induced ring opening of **25** gave a result significantly different from that derived from thermolysis of **13**. Thus, while ring opening of **13** produced a 11:1 mixture of **17** and **18**, treatment of **25** under identical conditions afforded a 1:1 mixture of the isomeric esters **27** and **28**.

The results summarized above show that functionalized 3-formylcyclobutene systems (e.g. **16**, **26**), like the parent compound **4**,[3] undergo electrocyclic ring opening with exclusive inward rotation of the formyl group. Interestingly, in accord with the theoretical predictions of Buda, Wang, and Houk,[5] thermolysis of the bicyclic ester **13** results in preferential outward rotation of the CO_2Et function. However, in the ring opening of **25**, the rates of inward and outward rotation of the ester group are equal. It is possible to rationalize the stereochemical difference between the ring openings of **13** and **25** as follows. Molecular models indicate that, in the conversion of **25** into **27** (outward rotation), it is necessary for the CO_2Et group to slide past the (pseudoequatorial) secondary Me group on the six-membered ring. The resultant steric strain, which is absent in the conversion of **13** into **17**, would cause an increase in the transition state energy for the **25** → **27** transformation relative to that for the **13** → **17** conversion. Thus, the stereochemistry of the thermal ring opening of **13** might be considered "normal", while that of the corresponding reaction involving substrate **25** can be classified as being somewhat "abnormal".

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Supplementary Material Available: Experimental procedures for the preparation of compound **13** and for the thermolysis of compounds **13** and **16**; spectral data for compounds **13**, **16**–**18**, and **21**–**23** (4 pages). Ordering information is given on any current masthead page.

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Intramolecular Radical Cyclizations of 2-Deoxy-2-iodohexopyranoside Derivatives: Routes to Densely Functionalized Carbocycles[1]

Summary: 2-Deoxy-2-iodohexopyranosides containing appropriate traps at C6 or C7 undergo radical cyclization to give oxabicyclo[2.2.1] or -[2.2.2] systems whose glycosidic bonds are readily cleaved to afford densely functionalized cyclopentanes or cyclohexanes.

Sir: The use of carbohydrates for the synthesis of carbocycles has been an area of protracted interest in our research group.[3] The well-documented annulation of carbohydrates through Diels–Alder methodology[4] and other techniques[5] has provided convenient access to optically

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