The coupling of the two optically active subunits **13** and **8a-c**[20] required a chelation-controlled aldol reaction[21] to achieve high levels of stereochemical efficiency. Although the reactions between the trimethylsilyl enol ether derived from the methyl ketone **13** and the protected aldehydes **8a-c** in the presence of $SnCl_4$ (CH_2Cl_2, -78 → -20 °C) provided mixtures of the adducts **14** and **15** in which the desired diastereoisomer **14** dominated by as much as 9:1, the yields observed for these transformations were uniformly less than 20%. Alternatively, when the lithium enolate of **13** (LDA, THF, -78 °C, 0.75 h) was allowed to react with freshly prepared **8c**[7] (THF, -78 °C, 1 h), an easily separable mixture (1.2:1) of **14** and **15** was obtained in 78% combined yield.[22] Since the stereochemistry at C(10) in the undesired adduct **15** could be efficiently corrected after glycoside formation (vide infra), the modest level of stereoselectivity obtained in this directed aldol reaction represents a temporary nuisance rather than a serious flaw.

The fluoride-induced removal [5% aqueous HF (2-3 equiv), MeOH, room temperature, 20 h; 70-80%)] of the silyl ether protecting group from the C(12) hydroxyl of **14** proceeded with concomitant formation of the methyl glycosides **16a,b** (1:2.7), and **15** was converted into **17** by the same protocol. At this juncture the inversion of the hydroxyl group at C(10) of **17** was achieved in a straightforward fashion by sequential oxidation and highly stereoselective hydride reduction of the intermediate ketone to provide **16a** exclusively [(a) Py-SO_3, Me_2SO, Et_3N, room temperature 0.5 h; (b) L-Selectride, THF, -78 °C 0.5 h; 73% overall].[23] Liberation of the latent β-hydroxy ketone array at C(5)-C(7) of the isoxazolines **16a,b** [H_2 (55 psi), W-2 Raney Ni, $B(OH)_3$ (5 equiv), 15% aqueous MeOH, room temperature, 20 h; 82-89%] followed by a kinetically controlled, acid-catalyzed spiroketalization [CF_3SO_3H (5 mol %), CH_2Cl_2, room temperature, 2 h; 78%] delivered a separable mixture (18:1) of the spiro ketal **3** and a substance tentatively identified as **18**. The spiro ketal **3**, which was spectroscopically identical with Williams' intermediate,[6,24] was then subjected to sequential methylenation [$Me_2S(O)=CH_2$, THF, 0 °C, 0.5 h] of the C(7) carbonyl function and O-cinnamoylation (PhCH=CHCOCl, DMAP, CH_2Cl_2, reflux, 48 h)[6] to furnish synthetic (+)-phyllanthocin (**1**) that was spectroscopically identical with an authentic sample.[25]

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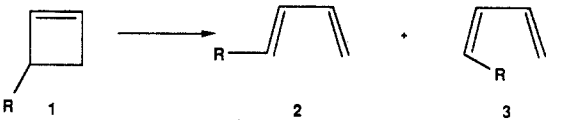
Prediction and Experimental Verification of the Stereoselective Electrocyclization of 3-Formylcyclobutene

Summary: 3-Formylcyclobutene has been synthesized from cyclobutene-1,1-dicarboxylic acid; it opens at 25-70 °C with an activation energy of 27 ± 1 kcal/mol to give exclusively (>98%) the *Z* product, in accord with predictions.

Sir: The thermally allowed conrotatory ring-opening of substituted cyclobutenes **1** may result in formation of either **2** or **3** (eq 1), the result of outward or inward rotation of the substituent. We previously developed a theory to



(1)

explain why the tendency for outward rotation increases as the substituent becomes a better donor.[1,2] In the case of a very strong acceptor, such as the BH_2 group, inward rotation was predicted to be favored.[1b] This theory has been used to rationalize other results which are clearly not sterically controlled.[2,3] We have now studied more conventional electron-withdrawing groups and report here the predictions stemming from these calculations, as well as an experimental test of the predictions.

The transition structures for inward and outward rotations of the CN group in 3-cyanocyclobutene and the CHO group in 3-formylcyclobutene were located with ab initio calculations involving full optimizations with the 3-21G basis set,[4] using Pople's GAUSSIAN 82 series of programs.[5] Harmonic frequency calculations verify that these are transition structures with only one imaginary frequency. Energies were evaluated with 6-31G* calculations[6] on the 3-21G geometries. We have found that substituent effects are correctly predicted with RHF theory, although correlation energy corrections are needed in order to obtain reasonable activation energies.[1a,b] Reactant and transition

(20) We thank Dr. Noal Cohen (Hoffmann-La Roche Inc.) for a generous sample of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid used for the preparation of **8a-c**.

(21) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96. (b) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (d) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327. (e) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.

(22) The corresponding directed aldol reactions of the lithium enolate of **13** with **8a,b** proceeded with comparable efficiency and diastereoselectivity (**14**/**15** = 1.1-1.8:1), but the removal of the benzyl and (benzyloxy)methyl protecting groups at later stages of the sequence proved difficult.

(23) Reduction of the intermediate ketone with sodium borohydride provided a mixture (9:1) of **16a** and **17**.

(24) We thank Professor D. R. Williams (University of Indiana) for providing spectral data of **3** for comparison.

(25) We thank Professor S. D. Burke (University of South Carolina) for providing the ^1H NMR spectrum of **1** and Professor A. B. Smith, III, (University of Pennsylvania) for generous quantities of an authentic sample of **1**.

(1) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.

(2) (a) Jefford, C. W.; Spellmeyer, D. C.; Houk, K. N., submitted for publication. (b) Spellmeyer, D. C.; Houk, K. N., manuscript in preparation.

(3) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. *Tetrahedron Lett.* **1986**, *27*, 4387.

(4) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(5) Binkley, J. S.; Frisch, M. J.; Krishnan, R.; DeFrees, D.; Schlegel, H. B.; Whiteside, R. A.; Fluder, E.; Seeger, R.; Pople, J. A. *GAUSSIAN 82*; Carnegie-Mellon University: Pittsburgh, PA; Releases E and H.

(6) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

0022-3263/87/1952-3708$01.50/0

Table I. 3-21G Activation Energies (in kcal/mol) of 3-Cyano- and 3-Formylcyclobutene Ring Openings

	CN		CHO			
			syn[a]		anti[a]	
	in	out	in	out	in	out
$\Delta E^{\ddagger}$(3-21G)[b]	43.9	39.3	40.9	39.9	34.7	39.2
$\Delta\Delta E^{\ddagger}_{rel}$(3-21G)[c]	+4.3	0.0	+6.8	+5.2	0.0	+4.5
$\Delta\Delta E^{\ddagger}_{rel}$(6-31G*//3-21G)[d]	+4.3	0.0	+6.4	+4.7	0.0	+4.6

[a] Anti indicates the oxygen is pointed away from the ring while syn indicates the oxygen pointed toward the ring. [b] Calculated activation energy at the fully optimized 3-21G level. Cyclobutene has an activation energy of 41.6 kcal/mol at this level. [c] Energies are relative to the lowest energy transition state. [d] 6-31G* energies at 3-21G geometries.

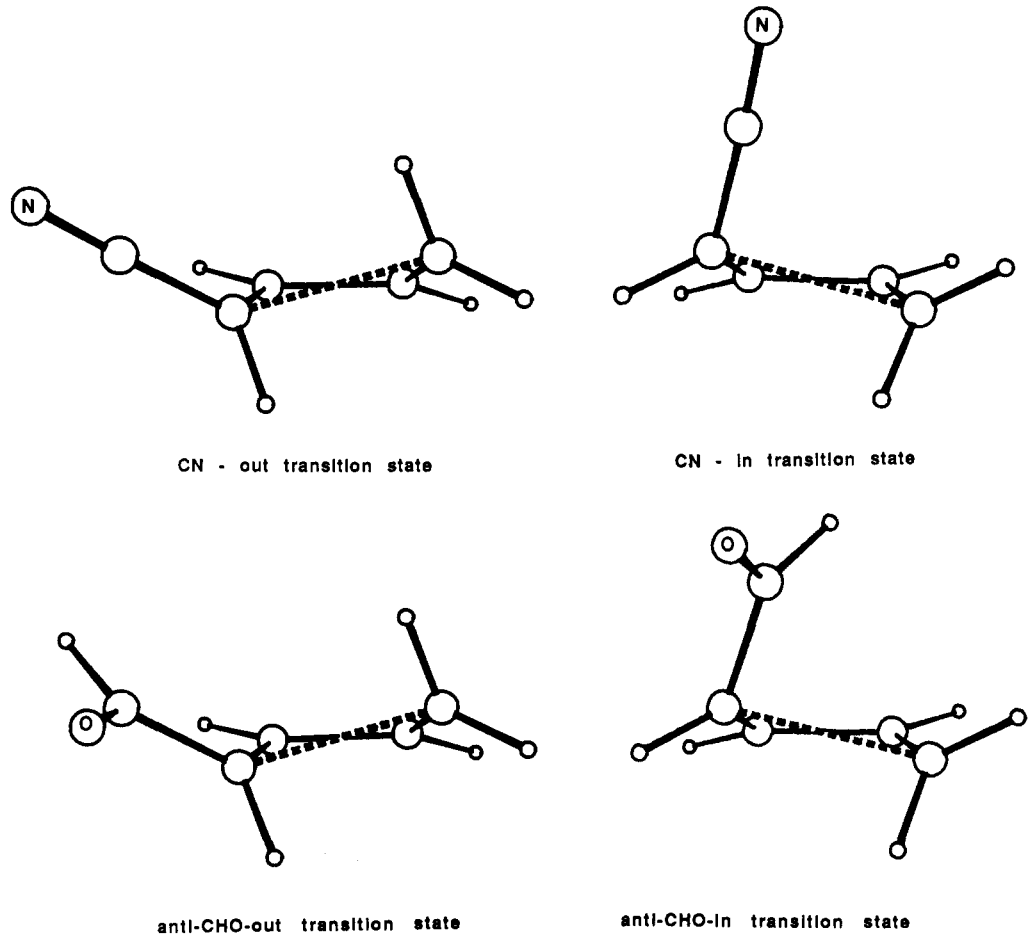


Figure 1. 3-21G optimized transition structures.

structures are shown in Figure 1, and energies are summarized in Table I.

The CN inward transition structure is 4.3 kcal/mol higher in energy than the outward transition structure. The activation energy of the outward transition structure is 2.3 kcal/mol lower than that calculated for the parent system.[1] This is the behavior expected for a very weak donor. However, the formyl group gave delightfully different results. Four transition structures for the interconversion of 3-formylcyclobutene to (*E*)- and (*Z*)-pentadienal were located. The two lowest are shown in Figure 1. These calculations predict that the formyl group prefers to rotate inward by 4.5 kcal/mol. The activation energy for the inward rotation of CHO is predicted to be 6.9 kcal/mol below that of the cyclobutene reaction, or 26 kcal/mol. The preference for inward rotation does not arise from product stabilities, since (*Z*)-2,4-pentadienal is predicted to be 3.1 kcal/mol less stable than the *E* isomer. Why does the formyl group prefer the sterically disfavored inward rotation?

The HOMO of the conrotatory transition state is largely the σ_{C-C} orbital of the breaking and twisting C–C bond, while the LUMO is the corresponding σ^*_{C-C} orbital (Figure 2). A substituent donor orbital stabilizes the transition state by mixing with the σ^*_{C-C} LUMO, while the interaction between the donor orbital and the HOMO is destabilizing. The overall effect of a donor is stabilization of the transition structure when the donor rotates outward. Upon inward rotation, the donor orbital overlaps better with the HOMO resulting in a larger destabilization. In addition, the interaction of the donor orbital with the LUMO is smaller upon inward rotation, because the LUMO has a node between the atoms. Thus, the activation energy for inward rotation is higher than for outward rotation.

An acceptor substituent has a low-lying vacant orbital capable of a two-electron stabilizing interaction with the HOMO of the transition structure. This stabilization is greater when the acceptor substituent rotates inward, since the overlap with the HOMO is greater for the inward than for the outward transition structure. This is, in effect, a two-electron cyclic aromatic transition structure.

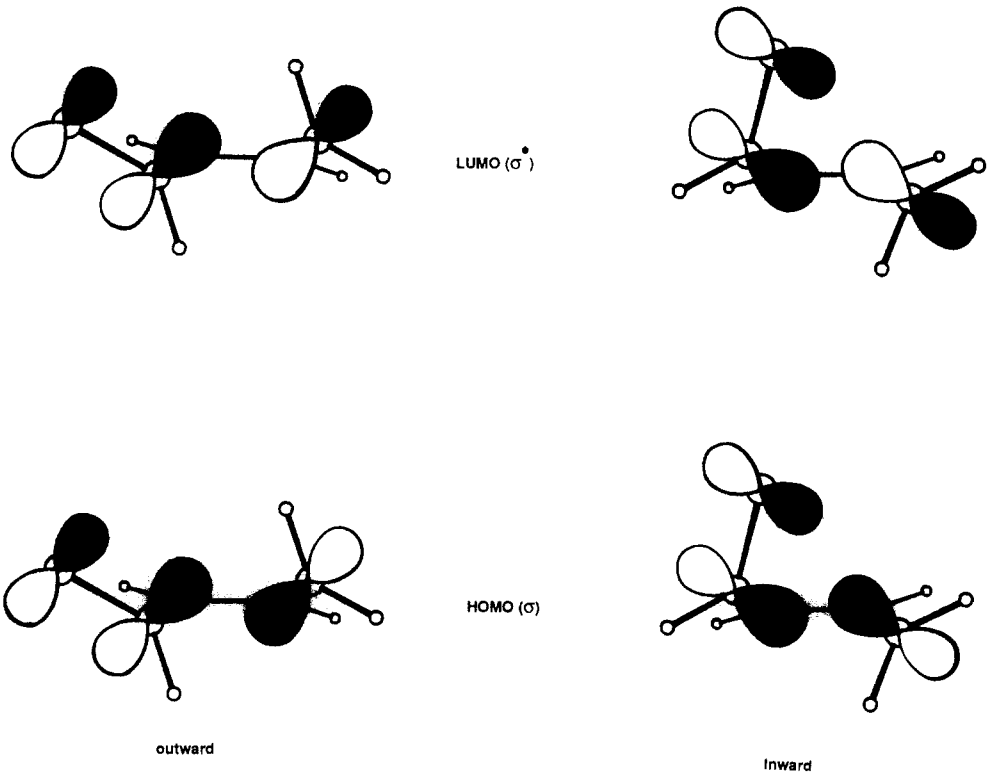
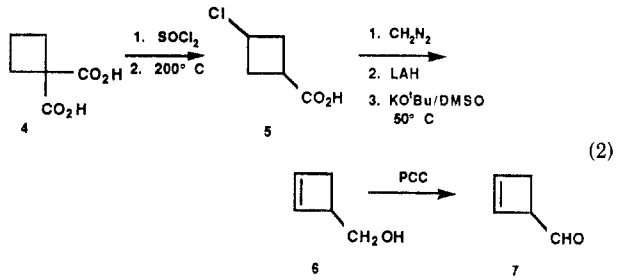


Figure 2. Frontier molecular orbitals of the cyclobutene conrotatory transition structure.

The calculations indicate that the cyano group should rotate outward even though it is a good acceptor. The interaction of the filled π_{CN} orbitals of the cyano group with the σ and σ^* orbitals of the breaking bond overwhelms the interaction of the relatively high-lying π^*_{CN} orbital. The formyl group has a lower lying π^*_{CHO} acceptor orbital, and the interaction of this orbital with the σ orbital causes inward rotation to be favored. This difference between CN and CHO is consistent with the greater conjugative electron-withdrawing ability of the latter.[7]

An experimental test of this prediction was undertaken with 3-formylcyclobutene prepared according to eq 2.



(2)

Commercially available cyclobutane-1,1-dicarboxylic acid (**4**) was selectively chlorinated at the 3-position and decarboxylated to afford 3-chlorocyclobutanecarboxylic acid (**5**) in 42% yield.[8] Conversion of the acid to the corresponding methyl ester (68% yield), reduction to the known alcohol[9] (54% yield), and dehydrochlorination gave 3-(hydroxymethyl)cyclobutene (**6**) in 27% yield.[9]

Oxidation of this alcohol with PCC at 25 °C according to the Corey-Suggs procedure[10] gives 3-formylcyclobutene (**7**), which was purified by filtration through a short Florisil column. Upon standing in solution at 25 °C, **7** undergoes ring-opening to pentadienal with a half-life of approximately 50 h. (*Z*)- and (*E*)-2,4-pentadienal are known compounds which are readily distinguished by NMR.[11] The reaction was conveniently followed by 500-MHz NMR spectroscopy at 50–70 °C. Only the (*Z*)-pentadienal is observed! Since 2% of the *E* isomer could have been detected, the predicted inward rotation is favored by at least 2.7 kcal/mol. An Arrhenius plot of the rate data gives $\log A = 14.2 \pm 1.2$ and $E_a = 27.2 \pm 1.8$ kcal/mol, in good agreement with prediction. In the presence of acids or bases, (*Z*)-pentadienal rapidly and completely isomerizes to the more stable *E* isomer.

In conclusion, the formyl group has been predicted to rotate inward, and this nonintuitive course of events was verified experimentally.

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(7) Wells, P. R. *Linear Free Energy Relationships*; Academic: New York, 1968.
(8) (a) Lampman, G. M.; Aumiller, J. C. *Org. Synth.* **1957**, 73. (b) Nevill, W. A.; Frank, D. S.; Trepka, R. J. *J. Org. Chem.* **1962**, *27*, 422.
(9) (a) Hanack, M.; Riedlinger, K.; *Chem. Ber.* **1967**, *200*, 2107. (b) Davies, A. G.; Griller, D.; Ingold, K. U.; Lindsay, D. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 633.
(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(11) Fang, K.; Ph.D. Dissertation, West Virginia University, Morgantown, WV, 1984; *Diss. Abstr. Int. B* **1985**, *46* (3), 840.

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