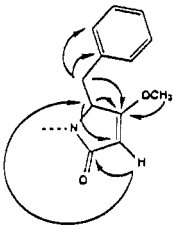
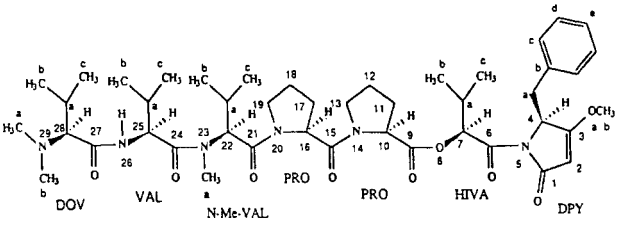


Figure 1. Selected HMBC correlations for the dolapyrrolidone unit.

and the blue-green algae constituents of the malyngamide[13] and pukeleimide[14] types.

Assignment of the ^1H and ^{13}C NMR chemical shifts for dolastatin 15 has been entered in ref 15. Sequence determination of dolastatin 15 (1) was achieved using ^1H-[^1H] NOE and long-range proton carbonyl coupling information from the HMBC experiment (Figure 1 and Table I). The assigned structure (1) was further supported by collision-activated decomposition (MS/MS)[3b] of the SP-SIMS ions combined with HREI mass spectral results



1

(see Scheme I). The absolute configuration was established by a combination of X-ray crystal analysis and synthetic procedures that will be summarized in a future report.[16]

Appearance of the pyrrolidone methyl vinyl ether group in dolastatin 15 and in constituents of the *Lyngbya* genus of blue-green algae provides further circumstantial evidence[3a] that *Dolabella auricularia* may be obtaining and/or structurally modifying constituents of such cyanobacteria. Should this exogenous procurement of potent cell growth inhibitory and/or antineoplastic substances eventually be proven correct, the ability of *D. auricularia* to store and/or produce potent cell growth inhibitory and antineoplastic substances of unusual structure is extraordinary.[2a,3] Indeed if these biosynthetic products are eventually shown to be obtained by exogenous procurement, the sensing and selection mechanisms of this sea hare must be magnificent. Further studies concerned with biological evaluations and structural modifications of dolastatin 15 are in progress.

Acknowledgment. With pleasure we thank for financial support Grants CA-16049-05-12 awarded by the NCI, DHHS, the Fannie E. Rippel Foundation, the Robert B. Dalton Endowment, Eleanor W. Libby, The Waddell Foundation (Donald Ware), the Arizona Disease Control Research Commission, Herbert K. and Dianne Cummings (The Nathan Cummings Foundation, Inc.), Polly J. Trautman, and Lotte Flugel. For other assistance we thank Drs. F. E. Boettner, R. A. Nieman, Messrs. P. L. Daschner and L. Williams, NSF Grant CHE-8409644, and the NSF Regional Instrumentation Facility in Nebraska (Grant CHE-8620177).

(12) Capon, R. J.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 4771.
(13) Cardellina, J. H. II; Franz, J.; Moore, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 240.
(14) Cardellina, J. H. II; Moore, R. E. *Tetrahedron Lett.* **1979**, *22*, 2007.
(15) Dolastatin 15 (1) 400-MHz ^1H and ^{13}C NMR (deuteriomethylene chloride, in ppm with respect to TMS). Dolapyrrolidone unit: ^1H 4.71 (s, H-2), 3.74 (s, 3 H, H-3b), 4.77 (dd, 4.8, 2.9, H-4), 3.52 (dd, 14.0, 4.5, H-4a), 3.04 (dd, 13.8, 3.5, H-4a'), 7.14 (m, H-4c), 7.20 (m, H-4d), 7.18 (m, H-4e); ^{13}C 169.26 (C-1), 94.73 (C-2), 178.16 (C-3), 59.86 (C-4), 58.29 (C-3b), 34.87 (C-4a), 134.16 (C-4b), 129.97 (C-4c), 128.11 (C-4d), 126.97 (C-4e). 2-Hydroxyisovaleric acid unit: ^1H 5.89 (d, 2.7, H-7), 2.19 (dsept, 2.7, 6.6, H-7a), 0.91 (d, 6.6, 3 H, H-7b), 1.07 (d, 6.6, 3 H, H-7c); ^{13}C 169.47 (C-6), 77.83 (C-7), 28.86 (C-7a), 15.78 (C-7b), 19.82 (C-7c). Proline-1 unit: ^1H 4.83 (dd, 8.9, 2.7, H-10), 2.38 (m, H-11), 2.22 (m, H-11'), 2.25 (m, H-12), 2.03 (m, H-12'), 3.75 (dd, 14.8, 8.9, H-13), 3.60 (dd, 14.7, 6.9, H-13'); ^{13}C 171.44 (C-9), 58.25 (C-10), 28.53 (C-11), 24.61 (C-12), 46.37 (C-13). Proline-2 unit: ^1H 4.63 (dd, 8.1, 4.8, H-16), 2.13 (m, H-17), 2.11 (m, H-17'), 2.15 (m, H-18), 1.85 (m, H-18'), 3.90 (dd, 16.7, 7.1, H-19), 3.78 (dd, 16.5, 7.0, H-19'); ^{13}C 170.79 (C-15), 58.04 (C-16), 28.36 (C-17), 24.68 (C-18), 47.80 (C-19). *N*-Methylvaline unit: ^1H 5.13 (d, 11.1, H-22), 2.27 (dsept, 11.2, 6.6, H-22a), 0.77 (d, 6.6, 3 H, H-22b), 1.03 (d, 6.6, 3 H, H-22c), 3.17 (s, 3 H, H-23a); ^{13}C 169.12 (C-21), 59.18 (C-22), 27.29 (C-22a), 18.52 (C-22b), 19.10 (C-22c), 30.68 (C-23a). Valine unit: ^1H 4.79 (dd, 9.3, 6.8, H-25), 1.98 (oct, 6.7, H-25a), 0.93 (d, 6.6, 6 H, H-25b and H-25c), 6.87 (d, 9.2, H-26); ^{13}C 172.97 (C-24), 53.61 (C-25), 31.10 (C-25a), 18.04 (C-25b), 19.59 (C-25c). *N,N*-Dimethylvaline unit: ^1H 2.44 (d, 6.4, H-28), 2.07 (oct, 6.4, H-28a), 0.92 (d, 6.6, 3 H, H-28b), 0.99 (d, 6.6, 3 H, H-28c), 2.24 (s, 6 H, H-29a and H-29b); ^{13}C 171.80 (C-27), 76.54 (C-28), 27.66 (C-28a), 17.64 (C-28b), 20.17 (C-28c), 42.95 (C-29a and C-29b).
(16) Experiments by Pettit, G. R.; Singh, S. B.; Herald, D. L.

Theoretical Predictions of Torquoselectivity in Pentadienyl Cation Electrocyclizations

E. Adam Kallel and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90024-1569

Received October 26, 1989

Summary: The electrocyclization of the pentadienyl cation was investigated with ab initio theory. Computations were performed at the RHF/3-21G and MP2/6-31G* levels of theory. The activation energy was predicted to be 1–10 kcal/mol. The heat of reaction was predicted to be −27 to −34 kcal/mol. Hydroxy, formyl, boryl, fluoro, and amino substituent effects were examined at the 3-21G level. The resonance donors (OH, F, NH_2) were found to stabilize the cyclization transition state when substituted on the outside, while the resonance acceptors (BH_2, CHO) were found to prefer cyclization when placed inside, as found earlier for cyclobutenes.

Sir: Since the first report of electronic factors controlling the outward or inward rotation of substituents in the conrotatory electrocyclizations of substituted cyclobutenes,[1] many examples have been observed experimen-

(1) Kirmse, W.; Rondan, N.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.

0022-3263/89/1954-6006$01.50/0

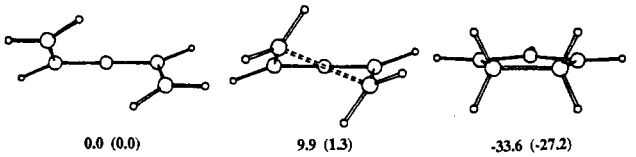


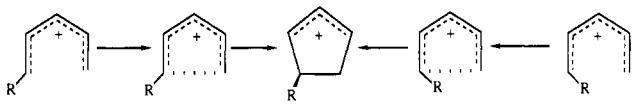
Figure 1. E_{rel} (kcal/mol) by RHF/3-21G (MP2/6-31G*) calculations.

tally and predicted computationally.[2] This phenomenon has been called torquoselectivity.[3] Houk and Rondan[1] showed that electron-donating substituents rotate outward, while strongly electron-withdrawing substituents prefer to rotate inward. This effect should not be unique to cyclobutene, since it arises from the interactions of substituent orbitals with those of breaking σ bonds. We have now studied the effect in another conrotatory electrocyclization, that of substituted pentadienyl cations. The system presents a considerable challenge to simple theory, as the cation might be expected to interact differently with substituents than neutral molecules.

The pentadienyl cation cyclization has been studied by Sorensen and others,[4] who first reported the generation of the pentadienyl cation[5] and elucidated the conrotatory nature of the cyclization by studying the cyclization of methyl-substituted pentadienyl cations.[6] The protonated ketone analogue of this system (Nazarov cyclization) has been studied in more detail experimentally.[7]

The pentadienyl cation cyclization was investigated using the GAUSSIAN programs of Pople and co-workers.[8] The calculations were carried out using the 3-21G and 6-31G* basis sets. Geometries were optimized at the RHF/3-21G level, and the nature of each stationary point was confirmed by frequency calculations. The resulting geometry was used as a starting point for the MP2/6-31G* optimizations or the single point calculations.

The calculated energetics of the reaction and geometries of the stationary points on the surface are shown in Figure 1. The reactant is the C_2 s-cis structure which has the termini separated by 2.95 Å. The planar C_{2v} structure was found to contain one imaginary frequency which corresponded to distortion to the C_2 structure. The reaction exothermicity is in accord with the estimates of Sorensen and Rauk for these cyclizations of 15-35 kcal/mol.[4] The small activation barrier at the 3-21G level decreases to 1.3 kcal/mol with inclusion of correlation. The transition state is quite early, with the forming C–C bond length equal to 2.45 Å in the transition state and 2.95 Å in the cis conformer of the reactant. Spellmeyer and Houk[9] have shown that MP2/6-31G* calculations slightly overestimate the activation energy of the conrotatory opening of cyclobutene. Schleyer has also reported the disappearance of



R-	1-E-pentadienyl cation	outward T.S.	cyclopentenyl cation	inward T.S.	1-Z-pentadienyl cation
H	33.6	43.5	0.0	43.5	33.6
NH_2	-19.3	8.9	0.0	23.6	-13.9
BH_2	20.3	30.7	0.0	25.1	19.5

Figure 2. Substituted pentadienyl cation conrotatory cyclization energetics (RHF/3-21G energies (kcal/mol) (relative to substituted cyclopentenyl cation).

the barrier in the cyclopropyl cation ring opening upon inclusion of electron correlation.[10] As a consequence we cannot predict with certainty whether there is an activation barrier for the pentadienyl cation cyclization in the gas phase. Schleyer reported 3-21G calculations which indicate that the all-trans conformer of pentadienyl cation is 8.3 kcal/mol more stable than the all-cis conformer.[11] Activation barriers for cyclizations have been observed experimentally by Bladek and Sorensen for 1,1-dimethyl-, 1,1,5-trimethyl-, and 1,1,5,5-tetramethylpentadienyl cation cyclizations. They range from 17 to 20 kcal/mol.[12] Parts of these barriers likely arise from rotation of the trans reactant to the less stable cis reactant.

Substitutent effects were examined for amino and boryl groups substituted at C-1. All calculations were carried out at the 3-21G level. The energies of the stationary points are shown in Figure 2. Of particular note are the relative energies for the transition states involving a substituent on an outward or an inward position. A substituent on the outward position is favored by 14.7 kcal/mol for amino substitution. This preference is predicted for electron donors by the theory described earlier. The filled orbital of an inwardly rotating electron donor has an unfavorable cyclic four-electron interaction with the breaking σ bond. The theory also predicts that inward rotation can be the lower energy process for strongly electron-withdrawing substituents, since there can be a stabilizing two-electron interaction upon inward rotation. For the cyclization of the 1-borylpentadienyl cation, the BH_2 inward substituted transition state is preferred by 5.6 kcal/mol. These effects are not as large as calculated or observed for the electrocyclic openings of cyclobutenes. This effect may be due to the earliness of the transition states for the pentadienyl cation reactions and to the greater flexibility of the pentadienyl cation system, which allows greater distortion to limit unfavorable overlap. For cyclobutene, an amino group favors outward rotation by 17 kcal/mol and boryl favors inward by 18 kcal/mol.[13]

For most cases, the cyclization reaction is exothermic. However, the ring opening is predicted to be the favorable direction of reaction for the 4-aminocyclopentenyl cation. This cation is 27 kcal/mol less stable than the 1-aminopentadienyl cation, resulting from outward conrotation, as a result of the conjugative stabilization of the pentadienyl cation by the amino group.

Partial optimizations were carried out on hydroxyl, fluoro, formyl, methyl, and (for comparison to the full optimizations) boryl-substituted transition states. The

(2) Houk, K. N.; Rondan, N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (c) Rudolf, K.; Spellmeyer, D. C.; Houk K. N. *J. Org. Chem.* **1988**, *52*, 3708.
(3) (a) Houk, K. N. In *Strain and Its Implications In Organic Chemistry*; de Meijere, A., Blechert, S. Ed.; Kluwer Academic Publishers Boston, 1989; pp 25–37. (b) Buda, A. B.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 2264.
(4) Sorensen, T. S.; Rauk, A. carbocations. In *Pericyclic Reactions*, Marchand, A. P., Lehr, R. E., Eds.; New York, 1977; Vol. II, p 21.
(5) Deno, N. C.; Pittman, C. U. *J. Am. Chem. Soc.* **1966**, *86*, 1871.
(6) Campbell, P. H.; Chiu, N. W. K.; Deugau, K.; Miller, I. J.; Sorensen, T. S. *J. Am. Chem. Soc.* **1971**, *91*, 6404.
(7) (a) Nazarov, I. N.; Koltyarevsky, I. L. *J. Gen. Chem. USSR (Engl. Trans.)* **1950**, *20*, 1441. (b) Sorensen, T. S. *J. Am. Chem. Soc.* **1967**, *89*, 3782. (c) Paquette, L. A.; Firstad, W. E.; Dime, D. S.; Bailey, T. S. *J. Org. Chem.* **1980**, *45*, 3017.
(8) GAUSSIAN 86, Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fluder, E. M.; Pople, J. A.; Carnegie-Mellon Quantum Chemistry Publishing Unit: Pittsburgh, PA, 1986.
(9) Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *110*, 3412.
(10) Schleyer, P. v. R.; Bremer, M. *J. Org. Chem.* **1988**, *53*, 2362.
(11) Schleyer, P. v. R.; Bentley, T. W.; Koch, W.; Kos, A. J.; Schwarz, H. *J. Am. Chem. Soc.* **1987**, *109*, 6953.
(12) Bladek, R.; Sorensen, T. S. *Can. J. Chem.* **1972**, *50*, 2806.
(13) Kallel, E. A.; Houk, K. N. Unpublished results.

substituent was placed on the parent transition structure obtained by the 3-21G optimization. The substituent geometry was then optimized, and the relative energies for inward and outward conrotation were calculated. In the case of boryl substitution, the partial optimization agreed quite well with the full optimization. Inward conrotation was preferred by 5.9 kcal/mol in the constrained case and by 5.5 kcal/mol in the fully optimized case. Strongly electron-donating groups (OH, F) prefer to rotate outward. The preference for outward rotation is 14 kcal/mol for OH and 14 kcal/mol for F. Strongly electron-withdrawing substituents (BH_2, CHO) prefer to rotate inward, with formyl substitution giving a preference for inward rotation of 2 kcal/mol. Thus the stereoelectronic effect found for cyclobutenes is predicted to operate in the conrotatory interconversion of pentadienyl cations and cyclopentenyl cations as well.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and the UCLA Office of Academic Computing for computer time used for these calculations.

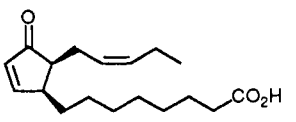
Cycloalkenone Synthesis via Lewis Acid Catalyzed Retro Diels–Alder Reactions of Norbornene Derivatives: Synthesis of 12-Oxophytodienoic Acid

Paul A. Grieco* and Norman Abood

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

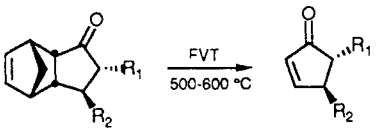
Received September 14, 1989

Summary: Norbornene derivatives of type 1 undergo retro Diels–Alder reactions at or below ambient temperature in the presence of methylaluminum dichloride and a reactive dienophile. Application of the [4 + 2] cycloreversion methodology to the synthesis of 12-oxophytodienoic acid **3** is described.



3

Sir: Retro Diels–Alder reactions have received considerable attention in natural products synthesis in part because the methodology allows for the stereospecific formation or regeneration of an olefin.[1] In particular, the retro Diels–Alder reaction permits the preparation of the thermodynamically less stable 4,5-dialkylcyclopent-2-enones of type **2** (cf. eq 1).[2,3] The use of flash vacuum

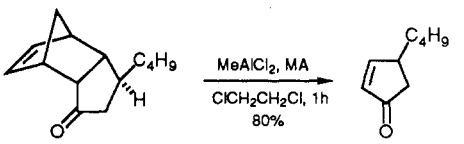


(1)

1 2

pyrolysis to effect such cycloreversions has become the standard procedure ever since the introduction of the method by Stork[2] in the early 1970s. We report that substrates such as **1** undergo Lewis acid catalyzed retro Diels–Alder reaction at or below room temperature in the presence of a reactive dienophile. In addition we describe the total synthesis of 12-oxophytodienoic acid (**3**) (12-oxoPDA),[4] an extremely sensitive cyclopentenone widely distributed in plants.

In a preliminary study, a 0.15 M solution of norbornene derivative **4** in 1,2-dichloroethane was treated at ambient temperature with 1.1 equiv of methylaluminum dichloride[5] in the presence of maleic anhydride (MA). After 1 h, an 80% yield of cyclopentenone **5** was obtained. The rearranged cyclopentenone **6** could not be detected. In the absence of added external dienophile to drive the reaction to completion, one gets complex mixtures with only negligible quantities of **5** being produced. For example, after



4 5

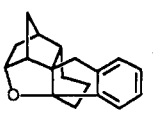
(1) For reviews, see: (a) Ripoll, J.-L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19. (b) Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121. (c) Ichihara, A. *Ibid.* **1987**, 207.

(2) Stork, G.; Nelson, J. G.; Rouessac, F.; Gringore, O. *J. Am. Chem. Soc.* **1971**, *93*, 3091.

(3) For a recent application of flash vacuum thermolysis to the construction of optically active cyclopentenones, see: Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357.

(4) Zimmerman, D. C.; Feng, P. *Lipids* **1978**, *13*, 313. Vick, B. A.; Zimmerman, D. C.; Weisleder, D. *Lipids* **1979**, *14*, 734. Baertschi, S. W.; Ingram, C. D.; Harris, T. M.; Brash, A. R. *Biochemistry* **1988**, *27*, 18.

(5) Triflic acid in the presence of a reactive dienophile will catalyze the retro Diels–Alder reaction. For example, treatment (1 h) of a 0.25 M solution of norbornene derivative **4** in methylene chloride cooled to 0 °C with 6.0 equiv of triflic acid in the presence of 5.0 equiv of *N*-methylmaleimide (NMM) gave rise to a 79% yield of cyclopentenone **5**. In the absence of NMM one gets complex mixtures and extensive decomposition. There are, however, serious limitations to employing triflic acid. In the case of norbornene derivative **14**, exposure of **14** to triflic acid and NMM at 0 °C, as detailed above, leads not to the formation of 2-benzylcyclohexenone, but instead affords the polycyclic ether i, mp 114–115 °C, in 60% yield.



i

0022-3263/89/1954-6008$01.50/0