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Registry No. 1, 50-81-7; 2, 137-66-6; SDS, 151-21-3; DBHN, 14976-54-6; linoleic acid, 60-33-3.

William A. Pryor,* Michael J. Kaufman
Daniel F. Church

Departments of Chemistry and Biochemistry
Louisiana State University
Baton Rouge, Louisiana 70803

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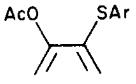
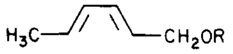
Regioselective Diels-Alder Reactions. A Synthesis of the Left-Hand Portion of CC-1065

Summary: Diene **2b** reacted regioselectively with dienophiles. Adduct **6** was converted into the left-hand portion of CC-1065 in 10% overall yield.

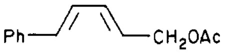
Sir: In the Diels-Alder reaction, the effect of a functional group attached directly to the diene unit has been extensively studied. The regiochemical control conferred by certain substituents coupled with the stereochemical control inherent in a concerted cycloaddition have made the Diels-Alder reaction a powerful synthetic tool.[1] The observation that the regiochemical outcome with dienes such as **1** can be reversed by Lewis acid catalysis has increased the versatility of this reaction.[2] However, there are still many instances (e.g., with unsymmetrical 1,4-dialkyl dienes) wherein regiocontrol cannot be achieved. In the process of devising solutions to this longstanding problem, we studied the effects exerted by substituents *not directly attached* to the diene unit, an idea which has only once been tested.[3] We report herein that dienes **2b** and **3** exhibit synthetically useful regioselectivity with a variety of dienes.



1

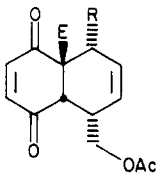


2a, R = CH_3
2b, R = $COCH_3$
2c, R = $COC(CH_3)_3$
2d, R = $COCF_3$
2e, R = $COCH_2Cl$

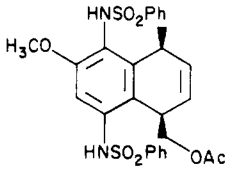


3

While diene **2a** reacted with carbomethoxybenzoquinone[4] in benzene at 25 °C to produce a 60:40 ratio of isomers, **2b** afforded a 20:1 ratio of isomers. The major isomer was assigned structure **4** on the basis of NMR decoupling experiments at 300 MHz. In particular, the methine proton adjacent to the methyl group was coupled only to the vinyl proton and the methyl group, while the proton adjacent to the acetoxymethyl group was coupled to four different protons. Additionally, diene **3** reacted with carbomethoxybenzoquinone to produce a 1.5:1 ratio wherein **5** predominated. In experiments designed to better understand the rationale for the selectivity observed with **2b**, pivalate ester **2c** was treated with carbomethoxybenzoquinone to afford approximately equal amounts of two isomers. Additionally, dienes **2d** and **2e** afforded mostly products derived from the decomposition of the diene when treated with either ethyl propiolate or carbomethoxybenzoquinone. Decomposition also resulted when sorbyl chloride was used.

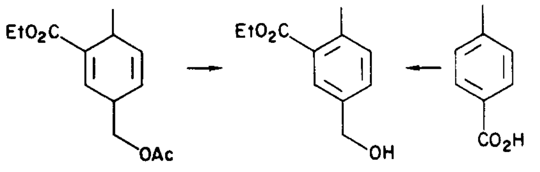


4, R = CH_3
E = CO_2Me
5, R = Ph

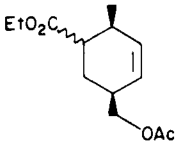


6

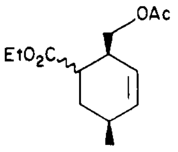
Diene **2b** reacted with methoxybenzoquinone bis(benzenesulfonimide)[5] at 25 °C to give, after aromatization with potassium acetate-acetic acid, adduct **6** in 55% yield[6] with a selectivity of greater than 25:1. The structure of **6** was determined by X-ray crystallography. Interestingly, **2b** reacted with ethyl propiolate to produce only one isomer. Its structure was shown to be **7** on the basis of conversion to **8** using DDQ[7] followed by acetate hydrolysis. Ester **8** was independently synthesized from *p*-toluic acid in three steps.[8] The reaction of **2b** with ethyl acrylate (135 °C) afforded exo/endo mixtures of both **9** and **10**. Ultimately, the regioselectivity was determined by conversion to **8**.[9] Diesters **9** were favored over **10** by a ratio of 9:1. The origin of the selectivity may arise from secondary orbital overlap involving the acetate carbonyl carbon and the orbital at C-3 of diene **2b**.[10] This analysis would explain the lack of regioselectivity with diene **2c**. Alternatively, if the Diels-Alder transition state involves concerted but not completely synchronous bond formation,[11] the acetoxymethyl group would be expected to destabilize the transition state leading to **10**, while the methyl group would be expected to stabilize the transition state leading to **9**.[12]



7 8



9



10

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(1) Desimoni, G. "Natural Products Synthesis"; Washington, D.C., 1983; ACS Monograph 180.

(2) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554 and references cited therein. Cohen, T.; Kosarych, Z. *Tetrahedron Lett.* **1980**, *21*, 3955.

(3) One group that has been tested is the CH_2SiMe_3 group.

(4) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1174.

(5) Kraus, G. A.; Yue, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1198.

(6) The predominant byproduct is (diaminomethoxy)benzene bis(benzenesulfonamide).

(7) Carretto, J.; Sib, S.; Simalty, M. *Bull. Soc. Chim. Fr.* **1972**, 2312.

(8) The steps involved bromination (excess Br_2, 0 °C), reduction (BH_3, THF, $-78 \rightarrow 25$ °C), and ester formation (2 equiv of *n*-BuLi; $ClCO_2Et$).

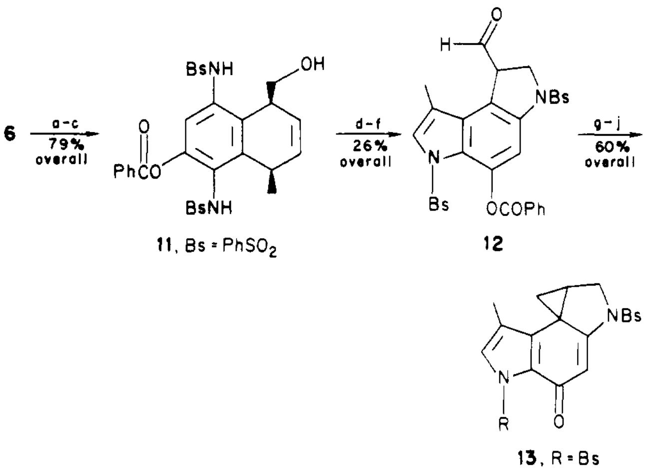
(9) The steps involved acetate hydrolysis (HCl, EtOH) and a three-step aromatization scheme (2.2 equiv of LDA, Br_2; DBN, 50 °C; DDQ, benzene).

(10) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976; pp 106-109.

(11) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650. For a synthetic application, see: Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.

(12) This would be true whether ionic or diradical intermediates were postulated.

Scheme I[a]



11, Bs = PhSO$_2$

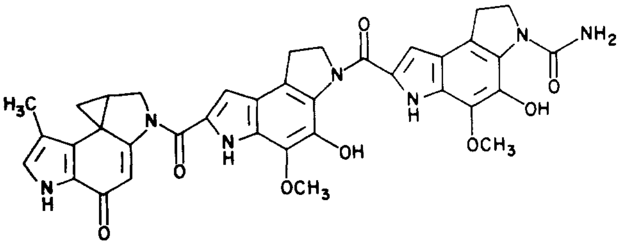
12

13, R = Bs

14, R = H

[a] Reaction conditions: (a) BBr$_3$ in hexane/CH$_2$Cl$_2$, −78 °C → 30 °C, 20 min. (b) (PhCO)$_2$O, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 24 h. (c) Dioxane, 4 M H$_2$SO$_4$, MeOH (4:1:1). (d) PhSO$_2$Cl, 2 equiv of Et$_3$N, 0 °C, CH$_2$Cl$_2$. (e) O$_3$, 1:1 CH$_2$Cl$_2$:MeOH, −78 °C; excess Me$_2$S, catalytic H$_2$SO$_4$, 0 °C. (f) HCl, dioxane. (g) Dibal, THF, 0 °C. (h) CH$_3$SO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$; room temperature. (i) LiAlH$_4$, THF, 0 °C. (j) DBU, PhCH$_3$, 50 °C.

Whatever governs the selectivity, the results will be useful in synthetic design. We have found that the selective production of 6 forms the basis for an expedient synthesis of 14, the left-hand portion of CC-1065, a natural product which exhibits inhibitory activity against L1210 and P388 leukemias in mice.[13] This portion was initially synthesized by Wierenga in 15 steps.[14] Recently, Magnus has reported an elegant synthesis of this portion by way of a dipolar cycloaddition strategy.[15] Our approach begins with the cleavage of the arylmethyl ether of 6 with BBr$_3$ in methylene chloride.[16] Benzoylation of the resulting phenol ((PhCO)$_2$O, Et$_3$N) and selective hydrolysis of the acetate provided alcohol 11 (Scheme I). Aldehyde was synthesized by phenylsulfonylation of the alcohol followed in situ by ring formation. Ozonolysis with reductive workup under acidic conditions[17] furnished a 2-methoxy-2,3-dihydroindole unit which was readily aromatized (HCl, dioxane) to indole 12. Dibal reduction of aldehyde 12 followed by mesylation of the resulting alcohol and debenzoylation afforded a hydroxymesylate which was converted into 13[18] with DBU in toluene at 50 °C. Removal of the phenylsulfonyl group attached to the indole nitrogen atom could be selectively achieved by using NaOCH$_3$.[15] Overall the synthesis proceeds in 11 steps from 6 with an overall yield of 10%.



CC-1065

Acknowledgment. We thank the National Institutes of Health and the A. P. Sloan Foundation for support of this work. We thank Dr. Ray Firestone for helpful suggestions.

Registry No. (*E,E*)-**2a**, 93923-35-4; (*E,E*)-**2b**, 57006-69-6; (*E,E*)-**2c**, 93923-36-5; (*E,E*)-**2d**, 93923-37-6; (*E,E*)-**2e**, 93923-38-7; (*E,E*)-**3**, 93923-39-8; **4**, 93923-40-1; **5**, 93923-43-4; **6**, 93923-44-5; **7**, 93923-45-6; **8**, 93923-46-7; **9** (isomer 1), 93923-47-8; **9** (isomer 2), 93923-48-9; **10** (isomer 1), 93923-49-0; **10** (isomer 2), 93923-50-3; **22**, 93942-85-9; **12**, 93923-51-4; **13**, 93923-52-5; **14**, 93923-53-6; CC-1065, 69866-21-3; ethyl propiolate, 623-47-2; ethyl acrylate, 140-88-5; *p*-toluic acid, 99-94-5; methyl (1α,4α,4aβ,8aβ)-1-(methoxymethyl)-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4-carboxylate, 93923-41-2; methyl (1α,4α,4aα,8aα)-1-(methoxymethyl)-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate, 93984-17-9; methyl (1α,4α,4aβ,8aβ)-1-[(1-oxo-2,2-dimethylpropoxy)methyl]-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate, 93923-42-3; methyl (1α,4α,4aα,8aα)-1-[(1-oxo-2,2-dimethylpropoxy)methyl]-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate, 93984-18-0; carbomethoxybenzoquinone, 3958-79-0; (*E,E*)-sorbyl chloride, 17100-75-3; methoxybenzoquinone bis(benzenesulfonimide), 83202-21-5.

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(13) Martin, D. G.; Hanka, L. J.; Neil, G. L. *Proc. Am. Assoc. Cancer Res.* **1978**, *19*, 99.

(14) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621.

(15) Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389. Magnus, P.; Or, Y.-S. *J. Chem. Soc., Chem. Commun.* **1983**, 26. Halazy, S.; Magnus, P. *Tetrahedron Lett.* **1984**, *25*, 421.

(16) McOmie, J. F. W.; West, D. E. *Org. Synth.* **1969**, 50.

(17) After Me$_2$S is added, catalytic H$_2$SO$_4$ is necessary to ensure a clean reaction. Presumably, it increases the rate of methoxydihydroindole formation.

(18) Cyclopropane 13: 300-MHz NMR (CDCl$_3$) δ 0.91 (t, J = 5 Hz, 1 H), 1.76 (dd, 1 H), 1.93 (s, 3 H), 2.84–2.89 (m, 1 H), 3.94 (dd, 1 H), 4.10 (d, J = 10 Hz, 1 H), 6.38 (s, 1 H), 7.47–8.07 (m, 10 H); 75-MHz ^{13}C NMR δ 9.81, 21.29 (2 C), 32.31, 54.76, 108.44, 115.50, 126.99, 127.16, 128.48, 128.60, 129.50, 133.68, 134.04, 134.39, 136.82, 138.66, 157.05, 174.87.

George A. Kraus,* Stephen Yue, James Sy
Department of Chemistry
Iowa State University
Ames, Iowa 50011

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Suvanine, a Novel Sesterterpene from an *Ircinia* Marine Sponge

Summary: Reported is a novel sesterterpene, suvanine (1), which contains both guanidinium bisulfate and furan functionality and the same tricarbocyclic skeleton as cheilanthatriol (3) but with different stereochemical features.

Sir: A growing list of sponges in the order Dictyoceratida are sources of sesterterpenes, and the family Thorectidae has the largest representation.[1] Within this latter group is the genus *Ircinia* which stands out because nine described species and two undescribed species are sources of a variety of acyclic sesterterpenes, acyclic sesterterpenes with mixed biogenesis, or novel polyoxygenated carbocyclic lactones.[2] During recent field work we collected an un-

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(1) Crews, P.; Naylor, S. *Prog. Chem. Org. Nat. Prod.*, submitted for publication.

(2) (a) Cimino, G.; De Stefano, S.; Minale, L.; Fattorusso, E. *Tetrahedron* **1972**, *28*, 333. (b) Cimino, G.; De Stefano, S.; Minale, L. *Tetrahedron* **1972**, *28*, 1315. (c) Cafieri, F.; Fattorusso, E.; Santacroce, C.; Minale, L. *Tetrahedron* **1972**, *28*, 1579. (d) Faulkner, D. J. *Tetrahedron Lett.* **1973**, 3821. (e) Rothberg, I.; Shubiak, P. *Tetrahedron Lett.* **1975**, 769. (f) Baker, J. T. *Pure Appl. Chem.* **1976**, *48*, 35. (g) Hofheinz, W.; Schonholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367. (h) Alfano, G.; Cimino, G.; De Stefano, S. *Experimentia* **1979**, *35*, 1136. (i) Gregson, R. P.; Ouvrier, D. *J. Nat. Prod.* **1982**, *45*, 412. (j) Gonzalez, A. G.; Rodriguez, M. L.; Barrientos, S. M. *J. Nat. Prod.* **1983**, *46*, 256.