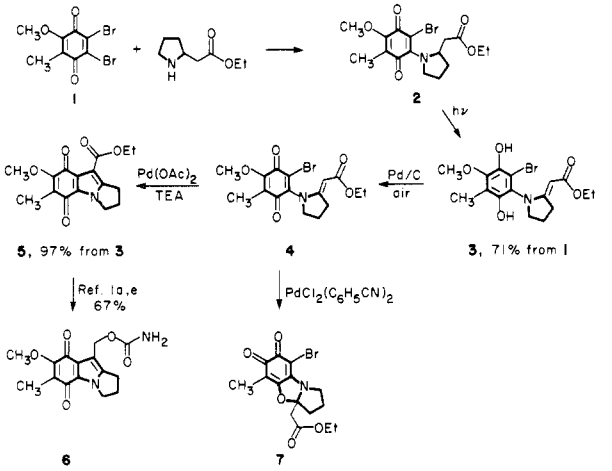
from **3**. We briefly studied the reaction of another soluble palladium(II) species, $PdCl_2(PhCN)_2$.[3] Treatment of **4** with this catalyst formed *o*-quinone **7**, as did treatment with acid.[1a]

The extension of this ring-closure methodology to the chirospecific synthesis of 1,2-substituted mitomycin analogues is under way.



(3) Kharasch, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882.

Experimental Section

Materials. Acetonitrile was distilled from calcium hydride, and triethylamine was refluxed with, and distilled from, tosyl chloride. Palladium acetate was obtained from Aldrich Chemical Company. The use of a sample of palladium acetate obtained from Engelhard Industries caused considerable side-product formation during ring closure. Although the elemental analysis of this catalyst was acceptable (Calcd. C, 21.4; H, 2.7. Found. C, 21.2; H, 2.8), the Engelhard material proved to be insoluble in hot acetone, chloroform, acetonitrile, and benzene. Subsequent reactions were carried out only with Aldrich palladium acetate, which displayed the reported solubility properties.[2a]

Palladium Oxidation of Hydroquinone 3 to Quinone 4 and Palladium-Catalyzed Ring Closure of 4 to 5. To a stirred suspension of **3** (25.0 mg, 65 μmol) in ethyl acetate (1.0 mL) at room temperature in an air atmosphere was added 10% Pd/C (12 mg). After 75 min the catalyst was filtered off, and the solution was evaporated to give a residue, **4** (24.9 mg, 100%), identical with material prepared previously.[1a] This residue was dissolved in acetonitrile (1.0 mL), and the solution was added to $Pd(OAc)_2$ (1.0 mg, 4.4 μmol) in acetonitrile (100 μL) with stirring. Triethylamine (6.6 mg, 65 μmol) was then added, and the mixture was stirred for an additional 2 h at which time it was partitioned between water (3 mL) and dichloromethane (7 mL). The organic layer was washed with water (2 mL), dried ($MgSO_4$), filtered, and evaporated to a yellow solid (21 mg). Filtration of a solution of this solid in dichloromethane through a plug of SiO_2 (100 mg) and evaporation of the filtrate provided pure **5** (19.2 mg, 97%), identical with material prepared by the previous route.[1a]

Communications

A Regiocontrolled Annulation Approach to Highly Substituted Aromatic Compounds[1]

Summary: The thermal combination of cyclobutenone derivatives with heterosubstituted acetylenes provides a regiocontrolled route to highly substituted aromatic compounds.

Sir: Hexasubstituted aromatic rings are common features incorporated in the structures of a variety of biologically active natural products.[3] The conventional synthetic approach to highly substituted arenes of this type involves the elaboration of simple aromatic precursors via electrophilic substitution and metalation–alkylation reactions. Unfortunately, these strategies lack convergence and frequently are not applicable to the synthesis of the more highly substituted aromatic compounds. As the number of substituents about an aromatic ring increases, so also does the difficulty in controlling the regiochemical course of the introduction of additional substituents. For the synthesis of such systems we consequently favor *annulation strategies* in which the aromatic ring is assembled in a single step, with all (or most) substituents already in place.[4]

In connection with our interest in the synthesis of certain antitumor antibiotics,[3] we have developed an efficient regiocontrolled annulation approach to highly substituted aromatic systems. As formulated in Scheme I, this annulation involves the *one-step* thermal combination of a heterosubstituted alkyne with a cyclobutenone derivative and proceeds via a cascade of four pericyclic reactions.[5] Heating a cyclobutenone derivative above 80 °C results in a reversible four-electron electrocyclic cleavage to generate a vinylketene,[6a] which combines with a ketenophilic acetylene derivative (X = OR, SR, NR_2) in a regiospecific [2 + 2] cycloaddition.[7] Reversible electrocyclic cleavage[6a] of the resulting 2-vinylcyclobutenone then furnishes a

(1) This work was presented (in part) at the 183rd National Meeting of the American Chemical Society, March 30, 1982.

(2) Alfred P. Sloan Research Fellow, 1981–1985.

(3) Mycophenolic acid: Birkinshaw, J. H.; Raistrick, H.; Ross, D. J. *Biochem. J.* **1952**, *50*, 630. Mitomycins: Franck, R. W. *Progr. Chem. Org. Nat. Prod.* **1979**, *38*, 1. Ascochlorin: Ellestad, G. A.; Evans, R. H.; Kunstmann, M. P. *Tetrahedron* **1969**, *25*, 1323. Ascofuranone: Sasaki, H.; Hosokawa, T.; Sawada, M.; Ando, K. *J. Antibiotics* **1973**, *26*, 676.

(4) For examples of previous (generally multistep) annulation approaches to benzene derivatives, see footnote 6 in Boger and Mullican (Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002) and also: Barton, D. H. R.; Dressaire, G.; Willis, B. J.; Barrett, A. G. M.; Pfeffer, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 665. Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1983**, *24*, 4939. Chan, T. H.; Brownbridge, P. *Tetrahedron* **1981**, *37* (Suppl. 1), 387. Jaxa-Chamiec, A. A.; Sammes, P. G.; Kennewell, P. D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 170. Schultz, A. G.; Shen, M. *Tetrahedron Lett.* **1981**, *22*, 1775. Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200. Tius, M. A.; Thurkauf, A. *Ibid.* **1983**, *48*, 3839. Dötz, K. H.; Pruskil, I.; Muhlemeier, J. *Chem. Ber.* **1982**, *115*, 1278 and references cited therein.

(5) For the application of a related "pericyclic cascade" in an annulation approach to eight-membered rings, see: Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

(6) For reviews, see: (a) Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; pp 124–190. (b) Reference 6a, pp 260–375.

(7) For previous examples of vinylketene [2 + 2] cycloadditions, see: Reference 5. Jackson, D. A.; Rey, M.; Dreiding, A. S. *Tetrahedron Lett.* **1983**, *24*, 4817. Trahanovsky, W. S.; Surber, B. W.; Wilkes, M. C.; Preckel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779 and references cited therein.

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Scheme I

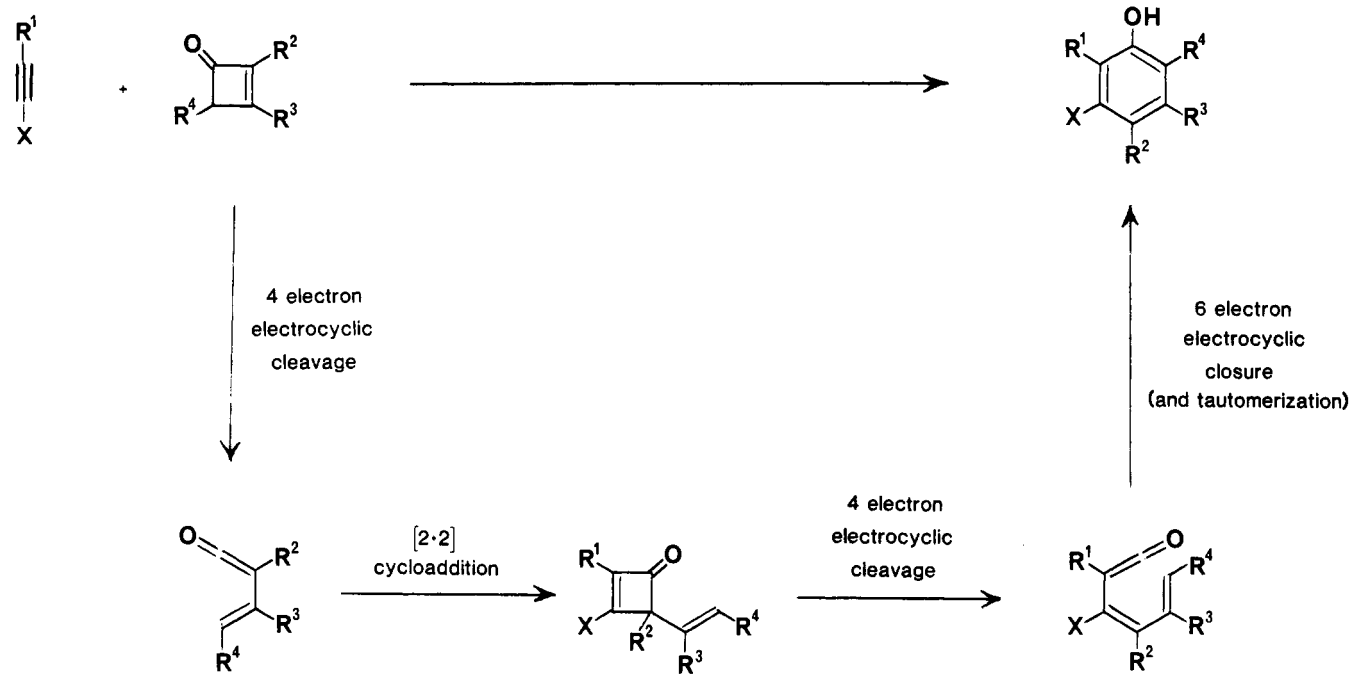
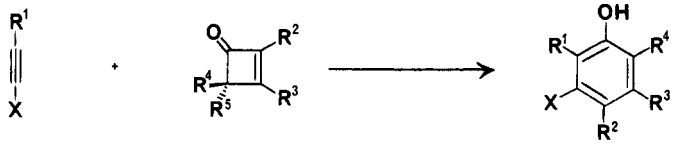


Table I. Regiocontrolled Aromatic Annulations



entry	acetylene R¹	acetylene X	cyclobutenone R²	cyclobutenone R³	cyclobutenone R⁴	cyclobutenone R⁵	reaction conditions,[a] °C, h	% yield[b]
1	1 H	OCH_3	7[c] H	CH_3	H	H	80, 26[g,h]	14,[k] 71
2	2 CH_3	OCH_3	7				80, 21	15,[l] 92
3	2		8[c] CH_3	CH_3	H	H	120, 71	16,[m] 61
4	3 *n*-Hex	OCH_3	9[d] H	*n*-Pr	H	H	80, 22	17, 69-82
5	3		10[e] CH_3	Et	CH_3	H	160, 48	18, 33
6	3		11[c] CH_3	OEt	H	H	125, 96[h]	19, 71
7	4 farnesyl	OCH_3	7				80, 4[i]	20, 65-68
8	5 CH_3	SCH_3	8				135, 73[h]	21,[n] 86
9	5		12[c] H	*n*-Bu	H	H	80, 24[j]	22, 82
10	6 *n*-Hex	NMe	7				150, 2	23, 74
11	6		10				160, 2	24, 83
12	2		13[f] H	CH_3	Cl	Cl	135, 2.5[g]	25,[o] 65

[a] Reactions were carried out in benzene (entries 1, 2, 4-7, 10, and 11), chloroform (entries 3, 8, and 9), or toluene (entry 12) by using 1.0-1.2 equiv of alkyne unless otherwise indicated. [b] Isolated yields of products purified by recrystallization or chromatography. [c] For preparation, see ref 5. [d] Prepared in 51% yield by the reaction of *n*-PrMgBr with 3-ethoxycyclobutenone; see ref 5. [e] Ficini, J.; Bessyre, J.; Claeys, M. *Bull. Soc. Chim. Fr.* **1975**, 1809. [f] Prepared in 75% yield by the addition of dichloroketene (see ref 24) to propyne. [g] 1.1 equiv of 2,4,6-tri-*tert*-butylphenol was added. [h] 2.5 equiv of cyclobutenone component was employed. Crude product was treated with 10-20% KOH in methanol (65 °C, 4-28 h). [i] 1.5 equiv of 7 was employed. [j] 2 equiv of 5 was employed. [k] mp 61-62 °C: Henrich, F.; Roters, P. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4210. [l] mp 65.5-66.5 °C: St. Pfau, A. *Helv. Chim. Acta* **1928**, *11*, 864. [m] mp 83.5-84.5 °C: Bruun, T. *Acta Chem. Scand.* **1971**, *25*, 2837. [n] mp 73.5-74.5 °C. [o] mp 97-98 °C.

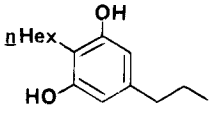
dienylketene, which is subject to six-electron electrocyclization[6b] to afford a cyclohexadienone. Tautomerization finally yields the highly substituted phenol.[8]

Table I delineates the scope of this regiocontrolled phenol annulation. In a typical reaction, a 0.4–2.0 M solution of the cyclobutenone component (in benzene, chloroform, or toluene) is heated at 80–160 °C in the presence of a slight excess of the heterosubstituted acetylene in a sealed Pyrex tube. Optimal conditions vary from case to case, with some annulations proceeding most efficiently by employing an excess of the cyclobutenone component. In these reactions the crude annulation product is treated with 10% KOH in methanol prior to purification, in order to saponify the small amount of ester formed by the reaction of the phenolic product with excess vinylketene.

Application of the annulation to the alkynyl ethers

(8) Our general annulation method finds precedent in the α-napthol synthesis discovered by Smith and Hoehn and related reactions: Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1941**, *63*, 1181. Nieuwenhuis, J.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1958**, *77*, 1153. Druey, J.; Jenny, E. F.; Schenker, K.; Woodward, R. B. *Helv. Chim. Acta* **1962**, *71*, 600. Wittmann, H.; Illi, V.; Sterk, H.; Ziegler, E. *Monatsh. Chem.* **1968**, *99*, 1982. England, D. C.; Krespan, C. G. *J. Org. Chem.* **1970**, *35*, 3308. Kipping, C.; Schiefer, H.; Schönfelder, K. *J. Prakt. Chem.* **1973**, *315*, 887. Neuse, E. W.; Green, B. R. *Liebigs Ann. Chem.* **1974**, 1534. Mayr, H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 500. Huisgen, R.; Mayr, H. *J. Chem. Soc., Chem. Commun.* **1976**, 55. Ficini, J.; Falou, S.; d'Angelo, J. *Tetrahedron Lett.* **1977**, 1931.

1-4[9-11] provides efficient regiocontrolled routes to a variety of differentially protected resorcinol and phloroglucinol derivatives. The synthesis of the antifungal antibiotics DB-2073 (**26**)[15] and grifolin (**27**)[16] demonstrates the utility



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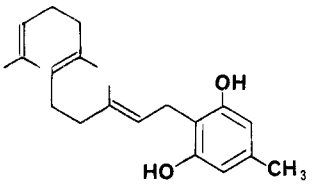

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of this approach. Thus, exposure of **17** to 4 equiv of trimethylsilyl iodide[17] in acetonitrile (reflux, 24 h) produced DB-2073 in 89% yield, while cleavage of the methyl ether in annulation product **20** was achieved by treatment with excess methylmagnesium iodide[18] at 165 °C for 15 min (49-83% yield). Pure grifolin was obtained in 21-43% overall yield (from (*E,E*)-farnesol) in this manner.[19]

Both alkynyl thioethers[20] and ynamines[21] participate as reactive ketenophiles in the regiocontrolled phenol annulation. The thioethers function in these reactions as ketenophilic equivalents for unactivated acetylenes, since the resulting annulation products readily undergo desulfurization to yield *monooxygenated* benzene derivatives. Thus, treatment of aryl sulfide **21** with excess Raney nickel[22] in methanol (reflux, 2 h) furnished 2,4,5-trimethylphenol[23] in 99% yield after chromatographic purification.

Finally, annulations employing 4,4-dichlorocyclobutenone derivatives[24] generate highly substituted 2-chlorophenols, presumably via intermediate 6,6-dichlorocyclohexadienones which undergo radical-mediated dechlorination at the elevated reaction temperature.

Further studies are underway in our laboratory to demonstrate the utility of this methodology in the total synthesis of antitumor antibiotics.[3]

Acknowledgment. Annulation experiments involving dichlorocyclobutenones were carried out by Katherine S. Takaki. We thank the National Institutes of Health and Eli Lilly and Co. for generous financial support.

Supplementary Material Available: Full characterization (250-MHz ^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data and/or elemental analyses) for all new compounds (7 pages). Ordering information is given on any current masthead page.

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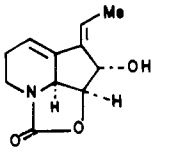
Cambridge, Massachusetts 02139
Received February 29, 1984

(9) Preparation of 1: Jones, E. R. H.; Eglington, G.; Whiting, M. C.; Shaw, B. L. In "Organic Syntheses"; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 404.
(10) Acetylenes **2** and **3** were prepared by using the general method of Newman: (Newman, M. S.; Geib, J. R.; Stalick, W. M. *Org. Prep. Proc. Int.* **1972**, *4*, 89). For earlier syntheses, see: Nooi, J. R.; Arens, R. F. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 284.
(11) Alkynyl ether **4** was prepared in one step in 67-76% yield from (*E,E*)-farnesol[12] by sequential treatment in THF with 1.1 equiv of CH_3Li (-78 °C, 35 min), 1.1 equiv of MsCl (-78 °C, 1 h), and 1.4 equiv of MeOC≡CMgBr in the presence of 0.05 equiv of Li_2CuCl_4[13] (-78 → 25 °C).
(12) Pure (*E,E*)-farnesol was prepared from (*E*)-geranylacetone by reaction with (a) $(i\text{-PrO})_2POCH_2CO_2Et$-KO-*t*-Bu[14] (THF, 0 → 50 °C; 87% yield as a 93:7 mixture of *E* and *Z* isomers) and (b) DIBAL in CH_2Cl_2-hexane at -78 °C (50% yield, isomers separated on a Waters Prep LC-500).
(13) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(14) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(15) Kitahara, T.; Kanda, H. *J. Anbibiotics* **1975**, *28*, 943. For an earlier synthesis, see: Achenbach, H.; Kohl, W.; Kunze, B. *Chem. Ber.* **1979**, *112*, 1841.
(16) Goto, T.; Kakisawa, H.; Hirata, Y. *Tetrahedron* **1963**, *19*, 2079.
(17) Olah, G. A.; Narang, S. C.; Gupta, B. G.; Malhorta, R. *J. Org. Chem.* **1979**, *44*, 1247.
(18) Mechoalam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6159 and references cited therein.
(19) This constitutes the first total synthesis of grifolin that is both regio- and stereoselective. For previous approaches, see: Marquet, J.; Moreno-Manas, M. *Chem. Lett.* **1981**, 173 and references cited therein.
(20) Preparation of **5**: Brandsma, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes, and Cumulenes"; Elsevier: Amsterdam, 1981; pp 106-107.
(21) Ynamine **6** was prepared in 56% yield by the method of Montijn et al. (Montijn, P. P.; Harryvan, E.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1211).
(22) Pettit, G. R.; van Tamelen, E. E. *Org. React. (N.Y.)* **1962**, *12*, 356.
(23) Mp 63.5-64 °C (lit. mp 62 °C: Morgan, G. T.; Pettit, A. E. J. *J. Chem. Soc.* **1934**, 418).
(24) Readily available via the addition of dichloroketene to alkynes: Hassner, A.; Dillon, J. L. *J. Org. Chem.* **1983**, *48*, 3382. See also: Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23.

Synthesis of 2-Substituted Δ^3-Piperidines: The Nitrogen Analogue of the Ferrier Rearrangement. An Approach to Streptazolin

Summary: The Lewis acid induced reaction of *N*-carbethoxy-4-hydroxy-1,2,3,4-tetrahydropyridine (**6**) with various carbon nucleophiles has been studied as a route to 2-substituted Δ^3-piperidines.

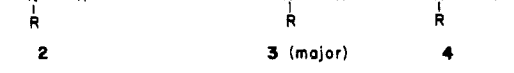
Sir: In our efforts to synthesize the structurally unique antimicrobial agent streptazolin, [2a*S*-(2aα,3α,4*Z*,7bα)]-4-ethylidene-2a,3,4,6,7,7b-hexahydro-3-hydroxy-1*H*-2-oxa-7a-azacyclopent[*cd*]inden-1-one (**1**),[1] we needed to have



Streptazolin (1)

access to a 2-substituted-1,2,5,6-tetrahydropyridine. While the metal hydride reduction of substituted pyridinium salts represents a well-known technique for the production of tetrahydropyridines, it has generally been observed that the presence of a substituent at the 2-position leads to generation of the 2-substituted-1,2,3,6-tetrahydropyridine **3** as the major product.[2]

It thus became of interest to ascertain whether one could obtain access to compounds like **4** through an S_N2' (or S_N1') like reaction on the tetrahydropyridinol **6**. Such a



2 3 (major) 4

reaction does, of course, bear close resemblance to the well-known Ferrier rearrangement process of glycals.[3] The known 4-oxo-1,2,3,4-tetrahydropyridine **5**[4] was reduced to the alcohol **6** by using $NaBH_4/CeCl_3$.[5] On exposure of this alcohol in turn to allyltrimethylsilane in the presence of

(1) Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.
(2) (a) Ferles, M.; Pliml, J. *Adv. Heterocycl. Chem.* **1970**, *12*, 43. (b) Lyle, R. E.; Anderson, P. S. *Ibid.* **1966**, *6*, 45.
(3) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180.
(4) Haider, A.; Cornuz, G.; Wyler, H. *Helv. Chim. Acta* **1975**, *58*, 1287.
(5) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

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