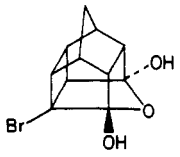
($CDCl_3$) δ 1.9 (m, 2 H), 2.6 (m, 2 H), 2.9 (s, 3 H), 3.3 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.5 (d), 40.5 (t), 43.7 (d), 44.2 (d), 50.5 (d), 50.8 (d), 54.3 (d), 54.9 (d), 55.8 (s), 203.5 (s), 207.4 (s); IR (CCl_4) 1750 (s), 1450 (m), 1250 (m), 1220 (m), 1010 (m), 980 cm^{-1} (m); mass spectrum (70 eV), *m/e* (relative intensity) 253.8 (M^+, 64.1), 251.9 (54.2), 172.9 (50.8), 144.9 (78.1), 116.9 (67.8), 114.9 (81.4), 93.9 (39.0), 90.9 (49.2), 65.8 (100.0), 64.9 (49.0), 59.7 (44.1), 54.8 (49.2), 50.9 (49.2), 50.1 (42.4).

Upon exposure to air, the distillate solidified; the resulting solid could be recrystallized from ethyl acetate–hexane mixed solvent to afford a colorless microcrystalline solid (232 mg, 18%), mp 94–95 °C. Elemental microanalysis of this solid suggested that it is a monohydrate of 4; the probable structure[1] of this material is shown below:



Elemental microanalysis was performed on hydrated 4.

Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.55; H, 4.12.

Pentacyclo[5.3.0.0^{2,6}.0^{3,10}.0^{4,8}]decan-5-one-2-carboxylic Acid (5). To a solution of dibromide **2** (1.67 g, 5.0 mmol) in tetrahydrofuran (25 mL) was added crushed sodium hydroxide pellets (1.0 g, 25 mmol), and the resulting mixture was heated at 80 °C for 4 h. The reaction mixture was then poured into cold, aqueous sodium bicarbonate solution and extracted with ether. The aqueous layer was then acidified and extracted with ethyl acetate. The organic layer was washed with water, dried (anhydrous magnesium sulfate), and filtered, and the filtrate was concentrated in vacuo. A viscous oil was thereby obtained; this material solidified on standing. The crude solid (238 mg, 26%) was recrystallized from ethyl acetate–hexane mixed solvent to afford **5** (200 mg, 21%) as a colorless microstalline solid: mp 74–75 °C; ^1H NMR ($CDCl_3$) δ 1.6 (m, 2 H), 2.0–3.5 (m, 7 H), 9.0 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 35.7 (d), 38.5 (s), 41.2 (t), 41.8 (d); 42.6 (d), 42.8 (d), 43.9 (d), 45.5 (d), 50.0 (d), 177.0 (s), 214.3 (s); IR (KBr) 3200 (s, br), 2930 (m), 1760 (s), 1680 (s), 1560 (s), 1420 (m), 1320 (m), 1010 cm^{-1} (m); mass spectrum (70 eV), *m/e* (relative intensity) 190.1 (M^+, 5.0) 162.0 (15.0), 161.0 (15.6), 145.0 (20.0), 144.0 (17.2), 118.0 (10.6), 117.0 (100.0), 116.0 (42.8), 115.0 (43.9), 104.0 (13.3), 103.0 (12.2), 91.1 (17.8), 89.0 (17.2), 79.0 (17.8), 78.0 (17.2), 66.0 (26.7), 65.0 (11.7), 63.0 (27.2), 62.0 (13.9), 57.6 (13.3), 53.0 (21.7), 52.0 (14.4), 51.0 (14.4), 45.0 (17.8), 41.1 (16.1).

Anal. Calcd for $C_{11}H_{10}O_3$: M_r 190.0630. Found: (high-resolution mass spectrometry): M_r 190.0629.

Base-Promoted Rearrangement of 4 to 5. To a solution of **4** (253 mg, 1.0 mmol) in tetrahydrofuran (15 mL) was added crushed sodium hydroxide pellets (200 mg, 5.0 mmol), and the resulting mixture was heated at 80 °C for 4 h. Workup of the reaction mixture in the manner described above for the rearrangement of **2** to **5** afforded a viscuos oil which solidified upon standing. Recrystallization of the crude product from ethyl acetate–hexane mixed solvent afforded pure **5** (37 mg, 19%), which was identical in all respects with the material prepared via base-promoted rearrangement of **2**.

Decarboxylation of 5. A solution of keto carboxylic acid **5** (190 mg, 1.0 mmol) in dimethylformamide (10 mL) was refluxed under a nitrogen atmosphere for 48 h. The progress of the reaction was monitored approximately every 6 h by thin layer chromatography. The reaction mixture was then adsorbed onto a silica gel chromatography column and eluted with petroleum ether. Ketone **6** was isolated from the eluate (55 mg, 38%) as a colorless microcrystalline solid, mp 124–125 °C (lit.[13] mp 124–126 °C). The ^1H NMR and IR spectra of **6** were in accord with literature values:[13,14] ^{13}C NMR ($CDCl_3$) δ 32.0 (d), 38.5 (d), 39.8 (d), 40.5 (d), 41.4 (t), 43.0 (d), 43.1 (d), 43.3 (d), 49.6 (d), 217.1 (s); mass spectrum (70 eV), *m/e* (relative intensity) 147.0 (2.9), 146.0 (M^+, 17.6), 145.0 (7.2), 131.0 (5.3), 119.0 (3.2), 118.0 (31.2), 117.0 (100.0), 116.1 (9.9), 115.0 (24.8), 104.0 (14.2).

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Registry No. 1, 25282-60-4; 2, 80661-89-8; 4, 94669-94-0; 4 (monohydrate deriv), 94645-35-9; 5, 94645-36-0; 6, 15584-52-8; NaOH, 1310-73-2.

Communications

Application of Pericyclic Reactions to the Synthesis of Strained Molecules. Intramolecular Diels–Alder Cycloadditions. The Synthesis of a (*Z*,*Z*)-Bicyclo[4.3.1]deca-1,6-diene

Summary: The intramolecular Diels–Alder reaction has been employed for the synthesis of derivatives of (*Z*,*Z*)-bicyclo[4.3.1]deca-1,6-diene, a highly strained class of bridgehead dienes (the spectroscopic and chemical properties of these compounds are also reported).

Sir: Bridgehead dienes are representatives of a class of strained organic molecules that contain two torsionally distorted carbon–carbon double bonds.[1] The potential interplay between the two double bonds makes them particularly interesting candidates for evaluating the chemical and spectroscopic consequences of through-space interactions of neighboring π systems.[2]

The high reactivity of the individual double bonds often precludes their *sequential* introduction; synthetic strategies that generate the double bonds simultaneously offer a particular advantage in this respect.

(*Z*,*Z*-Bicyclo[4.3.1]deca-1,6-diene (1) is one of the more highly strained representatives of this family of molecules, with a calculated strain energy in excess of 34 kcal/mol.[3] Conceptionally, the most direct entry is suggested by a type-II intramolecular Diels–Alder cycloaddition, eq 1.

(1)

This approach has been employed in the successful synthesis of the prototypical bridgehead olefin bicyclo-

(1) For a review of these compounds, see: Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. Possible involvement of a (*Z*,*Z*)-bicyclo[4.3.1]deca-1,6-diene has been reported by several groups, see: Warner, P.; Boulanger, W. *Tetrahedron Lett.* **1980**, *21*, 123, Turkenburg, L. A. M.; van Straten, J. W.; deWolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1980**, *102*, 3256. Warner, P.; Chu, I.-S.; Boulanger, W. *Tetrahedron Lett.* **1983**, *24*, 4165.

(2) (a) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1, (b) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 696, (c) Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245, (d) Martin, H.-D.; Mayer, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 283. (e) Wiberg K. B.; Matturro, M. G.; Okarna, P. J., Jason, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 2194.

(3) (a) Warner, P.; Peacock, S. *Tetrahedron Lett.* **1983**, *24*, 4169, (b) Shea, K. J., unpublished results.

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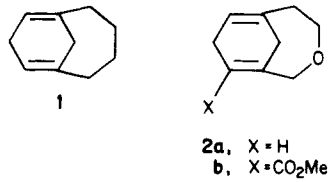
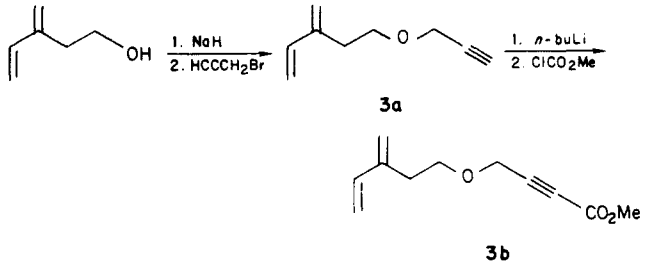


[3.3.1]non-1-ene.[4] The application of this approach to the formation of more highly strained bridgehead dienes, i.e., **1**, is the subject of the present communication.

A systematic survey of reactions represented by eq 1 has revealed that Diels–Alder cycloadditions can provide an efficient entry into the bicyclo[*n*.3.1] bridgehead diene ring system.[5] We now report the synthesis and isolation of highly strained bridgehead dienes **2a,b**.

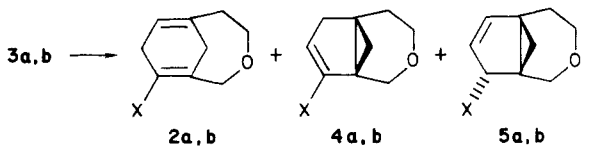
The dienyne precursors **3a,b** were prepared by condensation of the sodium salt of 3-methylene-1-penten-5-ol[6] (NaH, DME, 45–50 °C, 1 h) with propargyl bromide (1.1 equiv., –10 °C, 3 h, 72%). Following purification by flash



chromatography (SiO_2, pentanes/ether 15:1), the dienyne either **3a** was treated with *n*-BuLi (THF, –78 °C, 1.03 equiv) and then methyl chloroformate (1.2 equiv, –78 °C, 1 h), to give, after chromatographic workup, methyl ester **3b** (90%).[7]

The thermal behavior of dieneynes **3a,b** were surveyed by using both gas-phase and solution-phase techniques. Our initial investigations were conducted in the gas phase by employing an atmospheric pressure flow pyrolysis apparatus.[8] The onset of chemistry occurred at temperatures in excess of 270 °C (hot zone contact time 20 s). Three major reaction products were observed. Their relative amounts were found to be sensitive to both contact time and temperature. At constant contact time a plot of product distribution vs. temperature indicates formation of a single primary reaction product. Subsequently, two new products are observed which are formed at the expense of the primary product (Figure 1).

The two "secondary" reaction products **4b** and **5b** were isolated from the thermolysis of **3b**.[9] Examination of their



proton spectra revealed two high-field AB quartets; **4b** (1.11, d, J = 4 Hz; 0.30, d, J = 4 Hz) and **5b** (1.0, d, J = 4 Hz; 0.83, d, J = 4 Hz), characteristic of cyclopropyl methylenes. A complete spectral analysis of the isomeric esters proved to be compatible with the isomeric [4.3.1]-propellanes **4b** and **5b**. Interestingly, a single isomer of **5b** is obtained; the stereochemistry of the carbomethoxy

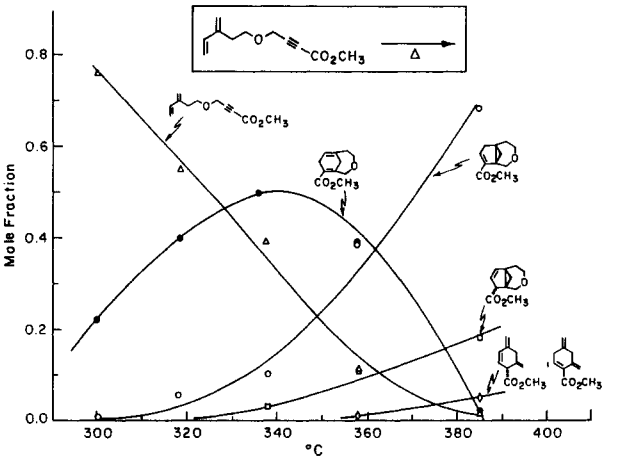


Figure 1. Plot of product distribution vs. temperature for the thermolysis of dienyne ester **3b**. Reactions were run at atmospheric pressure (N_2 carrier gas).

group is tentatively assigned endo (vide infra).[10]

Under optimum conditions, the primary reaction product comprises 50% of the thermolysate (340 °C). These conditions permit synthesis of sufficient quantities of **2b** for isolation by preparative VPC. The ^1H NMR spectrum reveals a single vinyl absorption at 6.12 ppm ($CDCl_3$, m). The remaining proton and ^{13}C NMR evidence is entirely consistent with the assigned bridgehead diene structure. Bridgehead diene **2b** is an extremely reactive compound that polymerizes in solution at room temperature. Similar reactivity is also noted for **2a**.

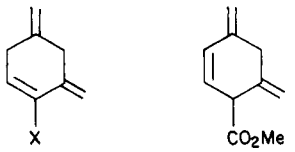
The juxtaposition of a donor and acceptor double bond in **2b** manifests itself in the UV spectrum. A very weak broad absorption centered at 297 nm is found in addition to the principal absorption at 209 nm. For comparison, a monocyclic model compound, 2,4-dimethyl-1-carbomethoxy-1,4-cyclohexadiene exhibits λ_{max} (hexanes) 236 nm.

Propellanes **4** and **5** are structurally related to bridgehead diene **2**. A mechanistic relationship was established by an independent thermolysis experiment. When **2a** was subjected to the reaction conditions (400 °C, 20 s), propellanes **4a** and **5a** are formed (56%) together with bis(methylene)cyclohexene **6a** (32%) and unreacted starting material (12%). The thermal rearrangement that converts **2a** to a mixture of **4a** and **5a** is viewed as a homo 1,5-hydrogen shift.[10] For comparison, the rearrangement of 1-methyl-2-vinylcyclopropane to 1,4-hexadiene is strongly exothermic. Thus, the normal tendency of this reaction to favor acyclic diene is reversed as in the case of **2a** as a result of the bridgehead diene strain energy.[11]

At temperatures in excess of 350 °C the onset of a new reaction manifold is noted (Figure 1). The two new products isolated from thermolysis of **3b** are isomeric methyl esters with a molecular formula of $C_{10}H_{12}O_2$ (loss of CH_2O).

(4) Shea, K. J.; Wise, S. *J. Am. Chem. Soc.* **1978**, *100*, 6519.
(5) Shea, K. J.; Burke, L. D., unpublished results.
(6) Prepared by reaction of ethylene oxide with 2-(1,3-butadienyl)-magnesium chloride: Kondo, K.; Dobashi, S.; Matsumoto, M. *Chem. Lett.* **1976**, 1007.
(7) All new compounds gave satisfactory spectroscopic properties (^1H, ^{13}C, IR, MS).
(8) Shea, K. J.; Wise, S.; Burke, L. D.; Davis, P. D.; Gilman, J. W.; Greeley, A. C. *J. Am. Chem. Soc.* **1982**, *104*, 5708.
(9) Subsequent studies of thermolysis conditions revealed that passage of benzene solutions of **3b** through a vertically mounted packed quartz thermolysis tube (N_2 flow) produced comparable results to the gas-phase flow pyrolysis apparatus. As a result of the faster throughput of this latter technique, it was employed extensively for product isolation studies. A description of this apparatus will appear in the full report of this work. The cycloaddition of **3b** is also achieved in 0.1 M solutions of benzene at 210 °C (30 min, 30%).
(10) For reviews of homo 1,5-hydrogen shifts, see: Gajewski, J. J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1984. Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. A similar rearrangement was proposed to account for the distribution of deuterium in the pyrolysis of the bridgehead diacetate of 1,6-dihydroxybicyclo[4.3.1]decane. The stereoelectronic requirements for the homo 1,5-hydrogen shift would be expected to produce the *endo*-carbomethoxypropellane **5b**.

Spectral properties of the two reaction products[7] permit assignment to isomeric bis(methylene)cyclohexenes **6b** and **7**, products that result from extrusion of formaldehyde



6a, b **7**

from either bridgehead diene **2b** or propellanes **4b** and **5b**. Quite surprisingly, under the reaction conditions, bridgehead diene **2b** is found to be the principle precursor of **6b** and **7** and *not* propellanes **4b** and **5b**.

The isolation of highly strained bridgehead dienes from these reactions affirms the remarkable utility of the Diels–Alder cycloaddition for the synthesis of novel, highly strained bridgehead alkenes. Chemical and spectroscopic investigations of these compounds is continuing.

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Supplementary Material Available: Spectral data for **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5b**, **6a**, **6b**, and **7** (5 pages). Ordering information is given on any current masthead page.

(11) Isomerization of bicyclo[3.1.0]hex-2-ene to 1,4-cyclohexadiene is exothermic by 11 kcal/mol (Ellis, R. J.; Frey, H. M. *J. Chem. Soc. A* **1966**, 553). The equilibrium **2a** ⇄ **4a** + **5a** lies exclusively to the right (350 °C), $\Delta H > 4$ kcal/mol. The bridgehead diene system **2a** represents a shift of at least 15 kcal/mol in the thermodynamics of the isomerization. Other examples of "wrong-way" homo 1,5-hydrogen shifts have also been noted: (a) Kirsch, R.; Priebe, H.; Hopf, H. *Tetrahedron Lett.* **1984**, *25*, 53, (b) Klarmer, F.; Rungeler, W.; Malfeld, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 595.

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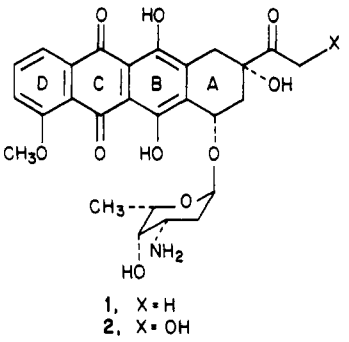
Anthracyclinones by Oxidative Dearomatization: Total Synthesis of SM-173B and Aranciamycinone

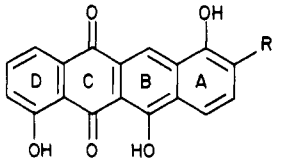
Summary: The aromatic naphthacenequinone **11** was converted by selective oxidative dearomatization of the A ring to enone **12** which was transformed into the aglycons SM-173B (**4**) and aranciamycinone (**5**).

Sir: The clinically important antineoplastic activities of certain anthracycline antibiotics, notably daunorubicin (**1**) and doxorubicin (adriamycin, **2**), have led to the development of a formidable array of strategies for the total synthesis of anthracyclinones.[1] None of these strategies, however, generate natural aglycons from fully aromatic tetracyclic precursors. We now demonstrate the first synthetic conversion of a naphthacenequinone (**3**) to a natural anthracyclinone.

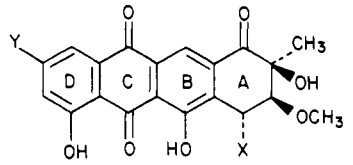
Our synthetic targets were the aglycons SM-173B (**4**)[2]



1, X = H
2, X = OH



3, R = H
11, R = CH_3



4, X = Y = H
5, X = OH; Y = H
6, X = OH; Y = OCH_3

and aranciamycinone (**5**),[3] which, like the related steffimycinone (**6**),[4] have not yet been synthesized.[5] The appropriate naphthacene precursor to these targets was the dark red trihydroxyquinone **3**, most conveniently prepared by regiospecific condensation[6] of ester **7** with the naphthalene **8** followed by methylation, phthalide reduction, cyclization in CF_3COOH–$(CF_3CO)_2O$, and Jones oxidation. The resulting trimethoxyquinone **9**[7] was demethylated ($NaSC_2H_5$, DMF, reflux, 18 h) to **3** in 35% overall yield from **8**. Introduction of the methyl group at C-9 (anthracyclinone numbering) was achieved by the selective Mannich reaction of quinone **3** using a slight excess of HCHO and pyrrolidine (THF, 40 °C, 80% yield) to yield amine **10** and then reductive elimination (1.1 equiv of $Na_2S_2O_4$, aqueous DMF, room temperature to 160 °C, 20 min, 90% yield) to the methyl quinone **11** [^{1}H NMR (Me_2SO-d_6) δ 2.43, CH_3]. This unusual sequence probably proceeds through the hydroquinone by the intramolecular redox chemistry suggested in Scheme I.

With quinone **11** in hand, we proceeded to test our hypothesis that in such systems only the A ring is a true phenol, whereas rings B and D are deactivated toward oxidation. Reaction of **11** with 1.05 equiv of $Pb(OAc)_4$[8] (THF–HOAc, 4 °C, 2 h) proceeded cleanly to give 50–55% of the acetoxy enone **12** [mp 226–230 °C; IR ($CHCl_3$) 1730, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (H-7, d, J = 10.2 Hz), 6.29 (H-8, d, J = 10.2 Hz). Reactions at the A-ring double bond of **12** proved unexpectedly frustrating. Both catalytic (H_2, Pd–C) and hydride reduction ($NaBH_4$) of **12** regenerated quinone **11**. Treatment of **12** with Br_2/CCl_4, *m*-CPBA, CF_3CO_3H or *t*-BuOOH/$VO(AcAc)_2$[9] gave back

(1) A comprehensive review is provided by Arcamone (Arcamone, F. In "Doxorubicin"; Academic Press: New York, 1981), and by the earlier review of Kelly (Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288).

(2) Fujiwara, A.; Tozoe, M.; Hoshino, T.; Sekine, Y.; Fujiwara, M. *Tennen Yuko Kagobutsu Toronkai Koen'Yoshishu*, 22nd, **1979**, 448, cited in *Chem. Abstr.* **1980**, *93*, 130479*u*.

(3) Keller-Schierlein, W.; Sauerbier, J.; Vogler, U.; Zähner, H. *Helv. Chim. Acta* **1970**, *53*, 779.

(4) Kelly, R. C.; Schletter, I.; Koert, J. M.; MacKellar, F. A.; Wiley, P. F. *J. Org. Chem.* **1977**, *42*, 3591.

(5) Synthesis of 8-demethoxyaranciamycinone by way of intramolecular Wittig cyclization has been described by Krohn and Broser (Krohn, K. and Broser, E. *Liebigs Ann. Chem.* **1982**, 1907. See also: Krohn, K.; Broser, E. *J. Org. Chem.* **1984**, *49*, 3766. The absolute configuration depicted in **5** is based on the latter paper. For an approach to the steffimycinone series, see: Gesson, J. P.; Jacquesy, J. C.; Renoux, B. *Tetrahedron Lett.* **1983**, *24*, 2761.

(6) Broadhurst, M. J.; Hassall, C. H. *J. Chem. soc., Perkin Trans. 1* **1982**, 2227.

(7) Trimethoxyquinone **9** had mp 235–236 °C. All intermediates gave correct C, H analyses or mass spectra, as well as 400-MHz ^{1}H NMR spectra consistent with the proposed structures.

(8) Metlesics, W.; Schinzel, E.; Vilesek, H.; Wessely, F. *Monatsh. Chem.* **1957**, *88*, 1069. Cavill, G. W. K.; Cole, E. R.; Gilham, P. T.; McHugh, D. J. *J. Chem. Soc.* **1954**, 2785.

0022-3263/85/1950-0727$01.50/0