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Stereoisomers of Bicyclo[8.8.2]icos-19-ene: Synthesis, Novel Properties, and Molecular Mechanics Calculations[1]

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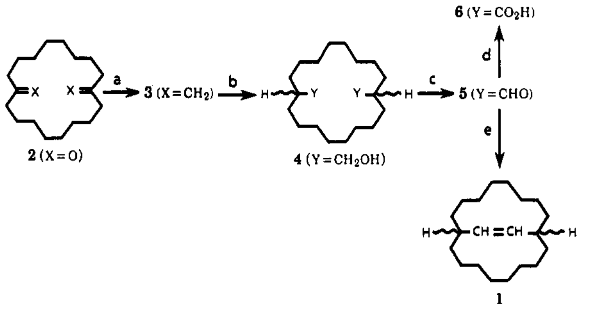
Summary: A mixture comprising four of the five possible stereoisomers of title compound **1**, novel bicyclic alkenes with properties resembling those of betweenanenes,[2] has been synthesized in four steps from 1,10-cyclooctadecadione (**2**).[3] Molecular mechanics calculations have been performed on all five stereoisomers of **1**.

In our quest to synthesize molecules with sterically hidden functional groups[4-8] we encountered diketone **2**, which exhibited unusual behavior during attempts to prepare monoadducts at just one of the two carbonyls.[7-9] Instead of the 1:2:1 (**2**–monoadduct–diadduct) product mixture predicted[10] for the reaction of **2** with 1 equiv of reagent, *di*adducts and unreacted **2** were the only isolable components of the product mixture. The apparent interaction between the carbonyl groups, which retards nucleophilic addition to the first carbonyl,[8] suggests that the 18-membered ring has accessible conformations which bring the C_1 and C_{10} substituents into close proximity.[11] This behavior of **2** has now been exploited to generate a novel family of bicyclic alkenes.

Scheme I outlines the synthetic approach to a stereoisomeric mixture of the title compound. Diketone **2** underwent a Wittig reaction to give diene **3**,[12] and subsequent hydroboration/oxidation afforded a mixture of cis and trans diol **4**.[13] PCC oxidation of **4** led to a mixture of cis and trans dialdehyde **5**,[14] an unstable oil which underwent rapid oxidation to dicarboxylic acid **6**[15] when exposed to air.

Scheme I[a]



[a] Key: (a) $Ph_3P{=}CH_2$ (4.9 equiv), THF, 25 °C, 50 h, 93% (chromatographed); (b) 9-BBN (3.9 equiv), THF, 25 °C, 20 h; aq NaOH (7.5 equiv); 30% H_2O_2 (6.3 equiv); 64% (recrystallized); (c) PCC (4.2 equiv), $CDCl_3$, reflux, 90 min 100% (crude); (d) air; (e) $TiCl_3$ $(DME)_{1.5}$ (15 equiv), Zn/Cu (42 equiv), DME, reflux, addn 24 h, reflux 3.5 h, 19.5% (chromatographed).

Under high dilution conditions, freshly prepared dialdehyde **5** underwent intramolecular McMurry (low-valent titanium) carbonyl coupling[16] to give a product mixture comprising, in the order of GC elution,[17] two major and two minor components.[18] All four components exhibited virtually superimposable LR mass spectra, each with a strong molecular ion at m/z 276, while HRMS measurements confirmed molecular formula $C_{20}H_{36}$. Unfortunately, exhaustive attempts to separate the mixture on a preparative scale, including chromatography on silver-impregnated silica gel, have not succeeded. Nevertheless, evidence for the alkene bridge was obvious from NMR spectra of the mixture.[18] The ^{13}C spectrum exhibited two olefinic carbon signals at δ 135.27 and 133.58 (intensity ratio 3:1), values typical for 1,2-disubstituted alkenes. Similarly, the 250-MHz ^1H spectrum showed three complex vinyl hydrogen multiplets centered at δ 5.60, 5.30, and 5.00 (~2:1:7).

The molecular topology of **1** has subtle stereochemical consequences. The two bridgehead hydrogens in **1**, like those in precursors **4** and **5**, can be cis or trans, as can be the configuration about the double bond. This suggests that there should be four stereoisomers of **1**. Less obvious

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(12) Semisolid, mp 25 °C; ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.07, 109.28, 35.15, 28.06, 27.91, 26.79; ^1H NMR (250 MHz, $CDCl_3$) δ 4.69 (s, 4 H), 2.03 (t, J = 7 Hz, 8 H), 1.43 (m, 8 H), 1.32 (br s, 16 H); HRMS m/z 276.2813 (calcd 276.2817).

(13) Mp 119–120 °C; ^{13}C NMR (signals with asterisks are assigned to the minor diastereomer, about 40% of the total) δ 66.62, 39.45, 36.33*, 28.94, 28.86*, 28.47, 27.93, 25.11, 24.94*; ^1H NMR δ 3.51 (d, J = 6.3 Hz, 4 H), 1.55 (m, 2 H), 1.32 (br s, 32 H); CIMS (isobutane) m/z 313 (M + H); HRMS m/z 294.2946 (calcd for M – H_2O, 294.2923), 276.2865 (calcd for M – $2H_2O$ 276.2817). Anal. Calcd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90. Found: C, 76.48; H, 12.64. Though GC–MS indicates only one component, diol **4** is believed to be a ca. 3:1 mixture of cis/trans diastereomers. While there is only one hydroxymethylene signal in both the ^1H and ^{13}C NMR spectra, there are *two* methine carbon signals (δ 39.45 and 36.33, 3:1) and two extra methylene carbon signals (δ 28.86 and 24.94).

(14) Oil; ^{13}C NMR (asterisks indicate signals from minor diastereomer, ca. 45% of total) δ 205.38, 50.21, 50.13*, 27.94*, 27.89, 27.64, 26.12, 25.11, 24.98*; ^1H NMR δ 9.63 and 9.60 (E/Z doublets, J = 1.0 and 1.3 Hz, 2 H), 2.32 (sym m, 2 H), 1.52 (br m) and 1.33 (s) totaling 32 H; HRMS m/z 308.2696 (73, calcd for $C_{20}H_{36}O_2$ 308.2715), 290.2587 (52, M – H_2O, calcd for $C_{20}H_{34}O$ 290.2610). As with **4**, dialdehyde **5** appears to be a 55/45 mixture of cis/trans diastereomers. Though it is homogeneous by GC–MS, and there is only one formyl group resonance in both ^1H and ^{13}C spectra, there are *two* methine carbon signals (δ 50.21 and 50.13, 55:45) and two extra methylene carbon signals (δ 27.94 and 24.98).

(15) Solid, mp 170–173 °C; ^1H NMR (CD_3COCD_3) δ 2.43 (m, 2 H), 1.59 (br s, ~8 H), 1.35 (br s, ~24 H) (the two acidic hydrogens exchanged with solvent); HRMS m/z 324 (2, M – O), 322 (2, M – H_2O), 306.2539 (30, calcd for $C_{20}H_{34}O_2$ (M – H_2O – O) 306.2559). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.53; H, 11.01. Diacid **20** is also presumed to be a mixture of cis/trans diastereomers.[13,14]

(16) (a) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.

(17) Column: 15 m × 0.25 mm (o.d.) 25 μm SPB1: T 80 °C + 10°/m. Retention times: I, 10.5 m; II, 11.2 m; III, 11.3 m; IV, 11.4 m. The third and fourth components were only partially resolved from the second one.

(18) An oil comprising four diastereomers:[17] ^{13}C NMR δ 135.27, 133.58, 44.85, 41.56, 34.43, 34.35, 33.84, 31.90, 29.74, 28.48, 26.28, 25.67, 25.34, 24.94, 24.59, 24.22, 24.14, 22.87; ^1H NMR δ 5.60 (m, ca. 0.3 H), 5.30 (m, 0.15 H), 5.00 (m, 1.1 H), 1.95 (br m, ca. 2.3 H), 1.19 (br m, ca. 30 H), 0.80 (m, ca. 1.7 H); HRMS (I) m/z 276.2832 (30, calcd 276.2817), 163 (26), 149 (19), 135 (36), 121 (36), 109 (47), 108 (43), 95 (88), 94 (87), 81 (100), 80 (88); (II) m/z 276.2798 (13), 163 (19), 149 (19), 135 (37), 121 (40), 108 (52), 95 (94), 94 (92), 81 (100), 80 (85).

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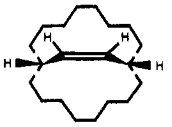
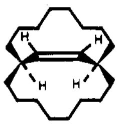
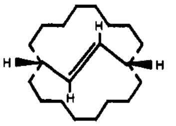
is the fact that when the bridgehead hydrogens are cis, there is the possibility of both *inside* and *outside* homeomorphic isomers.[19,20] Drawings of these five structures are shown below.



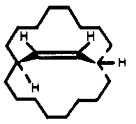
1a [*cis*, *cis* (outside)]



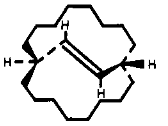
1b [*cis*, *cis* (inside)]



1c (*trans*, *cis*)



1d (*cis*, *trans*)



1e (*trans*, *trans*)

Unfortunately, such drawings provide an imperfect representation of these structures. Dreiding models suggest that *inside* isomer **1b** suffers considerably *less* transannular steric crowding than does *outside* isomer **1a**, a prediction consistent with experimental and theoretical results by others on large-ring bicyclic systems.[19,20] By contrast, in trans,cis isomer **1c** the bridgehead hydrogens are neither inside nor outside the 18-membered ring, but more or less perpendicular to it and roughly parallel to each other. For this reason **1c** does not exist in homeomorphic forms. In **1d**, as in **1a** and **1b**, the cis double bond bridge occupies a relatively accessible "basket handle" orientation. By contrast, in both **1c** and trans,trans isomer **1e** the double-bond bridge lies completely within the 18-membered ring, with the π-bond parallel to its mean plane.

To gain further insight into their conformational differences, we have carried out molecular mechanics calculations on each of the five structures.[21] Their relative minimized energies (in kcal/mol) follow the order **1a** (59.77) > **1d** (52.41) > **1c** (51.58) > **1e** (47.94) > **1b** (45.19).[22] In all five of these structures, the eight nuclei of the HCCH=CHCH linkage define a plane perpendicular to the mean plane of the 18-membered ring (see supplementary material). In **1c** and **1e**, such a conformation should effectively shield the π bond from attack by any reagent. The activation barrier for rotating the trans HC=CH plane of **1e** or **1c** *into* the mean ring plane (rendering the π bond perpendicular to it, and therefore more accessible) is calculated to be *ca.* 20 kcal/mol. Finally, calculated attempts to bring about homeomorphic isomerization of **1a** into **1b** (or vice versa) did not lead to interconversion, but rather to double-bond isomerization.[23]

In order to measure the chemical accessibility of the double bonds in the stereoisomers of 1, the mixture was allowed to react with bromine in deuteriochloroform while the reaction mixture was monitored by ^{1}H NMR. When 0.25 equiv of bromine had been added, the red color completely discharged and the ^{1}H spectrum indicated nearly complete loss of the δ 5.30 signal, a decrease and simplification of the δ 5.60 multiplet to a dd (J = 4.7, 2.5 Hz), but little change in the major signal at δ 5.00. After 0.5 equiv had been added, a pale yellow color persisted; the δ 5.30 signal was absent, the δ 5.60 signal was less than half its original intensity, while the δ 5.00 signal was still intact. Also at this point, new signals near δ 4.5, attributable to bromomethine hydrogens, began to appear. Finally, after 1 equiv of bromine had been added (and the red solution was warmed to 60 °C for 30 min), ^{1}H NMR indicated only a trace of the δ 5.60 signal, an intact δ 5.00 signal, and two bromomethine signals at δ 4.60 (s) and 4.42 (dd, J = 13, 4 Hz) in the ratio 1:3.

A consistent picture emerges from these data. It appears that the major isomers of 1 (I and II[17,18]) correlate with the ^{1}H NMR signal at δ 5.00 and the ^{13}C signal at 135.27, and that these isomers survive bromination. The facts that (a) the trans double bond isomers **1c** and **1e** have the most sterically *inaccessible* π bonds, (b) they are two of the three most stable structures by MM calculations, and (c) intramolecular McMurry coupling of dialdehydes leads to trans double bonds in large rings,[16] together suggest that I and II are, in fact, **1c** and **1e**. Minor isomers III and IV, which *do* undergo bromination, are most probably **1b** and **1d**, whose cis double bonds are the most exposed of the five structures.

Thus, structures **1c** and **1e** represent novel analogues of betweenanenes, whose sterically inaccessible double bonds are also inert toward reagents that normally attack carbon–carbon multiple bonds.[2] Further work is under way to study the properties of these unique molecules.

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Supplementary Material Available: A figure showing two orthogonal views of the lowest calculated energy conformations of **1a–e** and a description of the methods used in the molecular mechanics calculations (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[20] Sanders, M.; Krause, N. *J. Am. Chem. Soc.* **1990**, *112*, 1791.

[21] Biosyn's Insight II and Discover software was used in these calculations. See supplementary material.

[22] The conformational entropy of each structure can be gauged by the number of conformational energy minima within ca. 2 kcal/mol of the lowest energy structure. The number of such minima are: **1a**, 1; **1b**, 3; **1c**, 2; **1d**, 2; **1e**, 6.

[23] Drieding models *do* permit this isomerization, but only with difficulty.