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A NOVEL SYNTHESIS OF β-LACTONE PRECURSORS OF PYRAMIDALIZED ALKENES

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Abstract—β-Lactone precursors **11** and **12** of pyramidalized alkenes **3**, $n = 1$ and 2, have been synthesized by a two-step route involving transannular Paterno–Buchi reaction of methyleneketones **7** and **8**, followed by RuO_4 oxidation of the resulting oxetanes **9** and **10**. Evidence for the formation of alkene **3**, $n = 2$, by pyrolysis of **12** is presented.

The study of alkenes in which the carbons forming the double bonds are pyramidalized has developed into an area of active experimental and theoretical research. It has been found that in asymmetric environments double bonds tend to pyramidalize slightly, in order to minimize eclipsing interactions; and this effect has been shown to have important effects on reactivity and stereoselectivity in addition reactions to double bonds.[1]

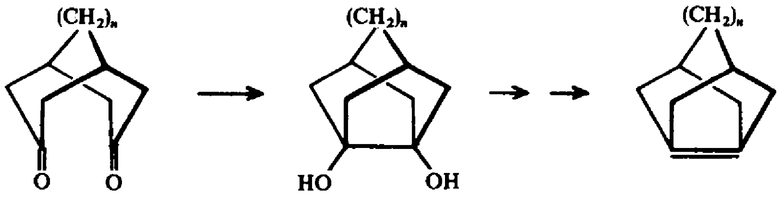
Substantial pyramidalization at doubly bonded carbons is predicted to be favorable when the bond angles about these carbons at planar geometries are constrained to be far from 120°.[2] For example, bicyclo[n.1.0]alk-1(n+2)-enes have been computed to prefer pyramidalized geometries for small values of n. Recently, a derivative of bicyclo[4.1.0]hept-1(6)-ene has been prepared whose X-ray structure shows the double bond to be distinctly nonplanar.[3]

Further evidence for the correctness of the theoretical prediction comes from the work of Szeimies.[4] His group has succeeded in generating and chemically trapping polycyclic molecules containing bicyclo[2.1.0]pent-1(4)-ene and bicyclo[1.1.0]but-1(3)-ene moieties, in which the additional bridges preclude planarity of the double bonds. The mildness of the reaction conditions required for olefin formation is in accord with the computational finding that these two bicyclic olefins actually prefer non-planar geometries.[2]

Research in this laboratory on pyramidalized olefins has focused on the generation of a homologous series of tricyclic alkenes (**3**). Members of this series may be viewed as derivatives of bicyclo[3.3.0]oct-1(5)-ene, in which the additional bridge from C-3 to C-7 causes pyramidalization of the double bond when the number of methylene groups is sufficiently small. Since the double bond in bicyclo[3.3.0]oct-1(5)-ene strongly resists pyramidalization, the lower members of this series are computed to have large olefin strain energies.[5,6]

Our initial synthetic approach envisioned transannular reductive ring closure of the diketones (**1**) to the diols (**2**), thus allowing olefin formation by a bifunctional elimination and so averting the possibility of the formation of isomers of **3**. The viability of this approach was demonstrated by the Zn/HCl reduction of cyclooctane-1,5-dione to bicyclo[3.3.0]octane-1,5-diol,[7] which could be transformed to bicyclo[3.3.0]oct-1(5)-ene by a variety of known methods for formation of olefins from diols.[8]

Transannular reductive ring closure was also



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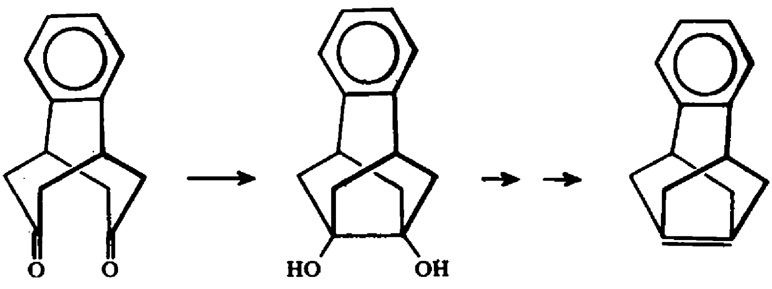


4 5 6

successful in preparing the bridged diol (2) with $n = 1$[7] and a derivative (5) of diol 2 with $n = 2$.[9] However, all of the methods that allowed the preparation of the unbridged olefin from bicyclo[3.3.0]octane-1,5-diol were uniformly unsuccessful in the formation of either of the bridged olefins, 3, $n = 1$, or 6.

Preparation of 6 was ultimately achieved by heating the N,N-dimethylaminodioxolane derived from 5 in refluxing tetraglyme in the presence of Lewis acids.[9] Although 6 was not isolated under these rather brutal reaction conditions, evidence for its formation was obtained by chemical trapping with diphenylisobenzofuran (DPIBF). In the absence of the trapping reagent, the $_\pi 2_s + _\pi 2_a$ dimer of 6 was obtained.

Despite the success of this route in generating 6, the last step was less than satisfactory in that the reaction conditions precluded the isolation of the olefin. Attempts to decompose salts of the N,N-dimethylaminodioxolane by gas phase pyrolysis, so that 6 could be isolated at low temperatures for spectroscopic study, failed.[8] Moreover, efforts to form the more highly strained $n = 1$ alkene (3) by treatment of the N,N-dimethylaminodioxolane derived from 2, $n = 1$, with Lewis acids in refluxing tetraglyme also met with failure.[8] Therefore, research was initiated on the preparation of alternative precursors for the lower members of this series of pyramidalized alkenes.

β-Lactones seemed attractive as potential precursors of strained olefins, since β-lactones undergo loss of CO_2 at moderate temperatures.[10] Moreover, β-lactones would be expected to undergo facile hydrolysis to β-hydroxyacids. Following hydroxyl group activation, salts of these latter compounds might undergo decarboxylative fragmentation,[11] providing an alternative method for introduction of the pyramidalized double bonds.

One approach to the required β-lactones would involve dehydration of the corresponding hydroxyacids. We have, in fact, synthesized 7-carboxytricyclo[3.3.1.0^{3,7}]nonan-3-ol, as a potential precursor of 3, $n = 1$.[12] However, we have not yet found a satisfactory method for the dehydration of this β-hydroxyacid to the β-lactone (11).

In this paper we report a different method for the synthesis of β-lactones, which has allowed the preparation of 11 and 12. Our route involves a transannular Paterno–Buchi reaction[13] of methyleneketones 7 and 8 to afford, respectively, oxetanes 9 and 10. RuO_4 oxidation[14] of the oxetanes yields the β-lactones. We also present evidence that olefin 3, $n = 2$ is, indeed, formed by pyrolysis of the $n = 2$ β-lactone (12).

The photolysis of 7 in cyclohexane has previously been reported to yield a mixture of 9 and 7-methylnoradamantan-3-ol.[15] The latter product is formed by hydrogen abstraction from the solvent. By performing the irradiation in benzene, hydrogen abstraction was suppressed, and 9 was the only product isolated. Presumably because of the unfavorable geometry for ring closure in the $n \rightarrow \pi^*$ state of 7, the quantum yield for this process is quite low (0.004),[16] and long irradiation times were required to effect conversion of 7 to 9.

The RuO_4 oxidation of 9 to 11 also proved to be quite slow, requiring several days for completion. Under the same reaction conditions—two phases, using catalytic RuO_4 in CCl_4, with reoxidation of RuO_2 by excess $NaIO_4$ in the aqueous phase[17]—compounds containing tetrahydrofuran rings were oxidized to δ-lactones in a matter of hours. Nevertheless, despite the sluggishness of the oxidation of 9, 11 was isolated in 50% yield.

β-Lactone 12 was obtained from 8[18] by the same two-step sequence. Irradiation of 8 in benzene afforded oxetane 10 in 62% yield. Oxidation of 10 with catalytic RuO_4 gave a 48% yield of 12.

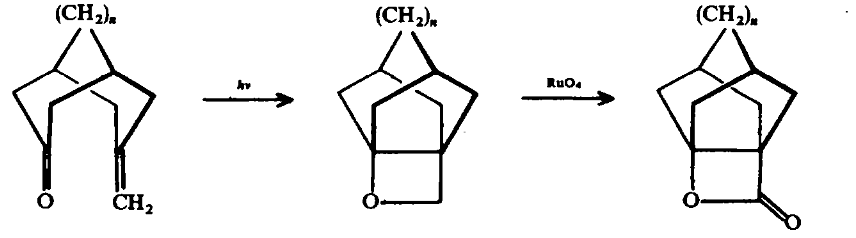
β-Lactone 12 proved unusually stable toward decarboxylation, presumably because of the strained nature of the double bond in the pyrolysis product (3, $n = 2$). Thus, whereas β-lactones ordinarily undergo loss of CO_2 at temperatures around 150°,[10] 12 melted at 194.0–195.5° without decomposition. Evolution of CO_2 from the melt was observed only when temperatures near 250° were reached.

Decarboxylation of 12, both in the gas phase and in solution, gave strong evidence for the formation of olefin 3, $n = 2$. Thus, passage of 12 through a tube heated to 450°—either as a pentane solution with a nitrogen flow or by sublimation under high vacuum, followed by warming the material that was trapped—led to isolation of a dimer of 3, $n = 2$. The observation of only four resonances in the ^{13}C-NMR spectra of the dimer was wholly consistent with the anticipated[9] $_\pi 2_s + _\pi 2_a$ mode of dimerization.

When the pyrolysis of 12 was conducted in refluxing tetraglyme in the presence of DPIBF, a crystalline adduct was isolated in 50% yield. The NMR spectra of the adduct identified it as the product of the expected Diels–Alder reaction between DPIBF and olefin 3, $n = 2$.

The fact that 3, $n = 2$, can be generated in the gas phase by pyrolysis of 12 has allowed the physical trapping of the olefin in matrix isolation. Spectroscopic studies of the $n = 2$ olefin are being pursued actively, and preparation of the more highly strained $n = 1$ member of the series (3) by pyrolysis of β-lactone 11 is being investigated.

We are also pursuing the possibility that the



7 $n = 1$
8 $n = 2$

9 $n = 1$
10 $n = 2$

11 $n = 1$
12 $n = 2$

methodology described here can be developed as an alternative to the Wittig reaction for ketones whose rapid enolization results in the failure of methods that involve the presence of strong bases. Carbon–carbon bond formation in such ketones by Paterno–Buchi reaction with terminal olefins, followed by RuO_4 oxidation of the oxetanes formed and subsequent pyrolysis of the resulting β-lactones, might prove a useful synthetic method.

EXPERIMENTAL

General procedures. ^{1}H-NMR spectra were obtained using either a Varian EM-360L (60 MHz), CFT-20 (80 MHz), or a Bruker WM-500 (500 MHz) spectrometer; ^{13}C-NMR spectra were obtained using a Bruker CXP-200 (50 MHz) spectrometer. The NMR spectra were recorded as $CHCl_3$-d_1 solns with chemical shifts reported in ppm downfield from internal reference TMS. The IR absorption spectra were obtained using a Beckman Acculab 4 and were recorded as CH_2Cl_2 solns vs a solvent reference cell. The UV/vis absorption spectra were obtained using a Hewlett–Packard 8450A UV/VIS spectrophotometer. The mass spectra were obtained using a Hewlett–Packard 5985A GC/MS system equipped with a fused silica capillary column and operating in the electron impact mode with ionizing energy of 70 eV. Exact masses were determined using a VG 7070 GC/MS and associated VG 2035 F/B Data System operating in either electron impact (70 eV) or chemical ionization (CH_4) mode.

2-*Oxatetracyclo*[4.3.1.1^{4,8}.0^{1,4}]*undecane* (**9**). A soln of 1.0 g (6.7 mmol) **7**[19] in 75 ml dry, degassed benzene was irradiated under N_2 with an unfiltered 450 W medium pressure, mercury vapor, Hanovia lamp. A film of white material slowly coated the quartz condenser inside the immersion well during the photoreaction. The efficiency of the reaction improved when the film was removed by rinsing with alcoholic KOH. Photolysis for 16 hr effected 50% conversion of **7** to **9**. The two compounds were separated by flash column chromatography on 10 g of Merck silica gel 60, 230–400 mesh, using hexane–EtOAc (2 : 1) as eluent. Oxetane **9** eluted first, followed by 480 mg of **7**, which could be resubmitted to photolysis. Isolated as a crystalline solid was 450 mg (45%) of **9**, m.p. 192–194° (lit.[15] 192–194°). ^{1}H-NMR (500 MHz): δ 1.36 (d of t, 1H, J = 13.2, 2.2 Hz), 1.46 (d of t, 1H, J = 13.2, 2.2 Hz), 1.79 (d of d, 2H, J = 10.3, 2.5 Hz), 1.96 (d of d, 2H, J = 9.6, 2.5 Hz), 2.10 (d, 2H, J = 10.3 Hz), 2.18 (d, 2H, J = 9.6 Hz), 2.45 (broad s, 2H), 4.36 (s, 2H). IR: 2980, 2890, 1300, 980 cm^{-1}. MS: *m/e* 106 (15.0), 92 (100.0).

2-*Oxatetracyclo*[4.3.1.1^{4,8}.0^{1,4}]*undecan*-3-*one* (**11**). To a stirred soln of 200 mg sodium metaperiodate and 2 mg RuO_2 in 10 ml water was added 2 ml CCl_4. When the solids had dissolved and the yellow color of the RuO_4 appeared, a soln of 280 mg (1.87 mmol) **9** in 5 ml CCl_4 was added dropwise. Vigorous stirring of the two-phase soln for 4 days resulted in the complete oxidation of **9**, as indicated by gas chromatographic analysis. The organic phase was separated from the aqueous, and the RuO_4 in the organic phase was quenched by the addition of a few drops of isopropanol. The soln was filtered to remove the precipitated RuO_2, dried, and the solvent evaporated. The crude product was purified by flash chromatography on 2 g silica using hexane–EtOAc (1 : 1) as eluent. Isolated as a crystalline solid was 153 mg (50%) of **11**, m.p. 189.0–190.0°. ^{1}H-NMR (500 MHz): δ 1.61 (d of t, 1H, J = 13.5, 2.5 Hz), 1.69 (d, 1H, J = 13.5 Hz), 1.86 (d of d, 2H, J = 11.4, 2.5 Hz), 2.15 (m, 4H), 2.35 (d, 2H, J = 10.3 Hz), 2.74 (broad s, 2H). ^{13}C-NMR: δ 172.42, 89.80, 68.75, 45.84, 45.58, 42.14, 35.10. IR: 2960, 1820 cm^{-1}. UV (pentane): $\lambda_{max} = 218$ nm ($\varepsilon = 98$). MS: 164 (M$^+$, 6.4), 136 (100.0), 121 (13.7). Exact mass: calc for $C_{10}H_{12}O_2$, 164.0837; found, 164.0881.

2-*Oxatetracyclo*[4.4.1.1^{4,9}.0^{1,4}]*dodecane* (**10**). A soln of 1.00 g (6.09 mmol) of **8**[18] in 150 ml dry, degassed benzene was irradiated under N_2 through a Pyrex filter with a 550 W high pressure, mercury vapor, Hanovia lamp for 70 hr. The solvent was evaporated *in vacuo*, and the residue was dissolved in EtOAc and filtered through a short column of silica gel. Removal of the solvent *in vacuo* gave a white crystalline solid (0.62 g, 62%), m.p. 171–173°. ^{1}H-NMR (60 MHz): δ 1.50–2.48 (complex m, 14H), 4.32 (s, 2H). ^{13}C-NMR: δ 103.31, 79.11, 52.16, 47.07, 44.94, 38.64, and 30.15. IR (CCl_4): 2938, 2870, 1463, 970, and 942 cm^{-1}. MS: *m/e* 164 (M$^+$, 6), 149 (13), 135 (11), 121 (18), 106 (98), 91 (85), and 79 (100). Exact mass: calc for $C_{11}H_{16}O$, 164.1200; found, 164.1218.

2-*Oxatetracyclo*[4.4.1^{4,9}.0^{1,4}]*dodecan*-3-*one* (**12**). To a stirred soln of 2.0 g sodium periodate and 20 mg RuO_2 in 100 ml water was added 5 ml CCl_4. When the yellow color of the RuO_4 appeared, a soln of 0.50 g (3.04 mmol) of **10** in 10 ml CCl_4 was added dropwise. The mixture was kept yellow by adding portions of a soln of 3.0 g sodium periodate in 50 ml of water. After 6 days of vigorous stirring at room temp, a few ml of isopropyl alcohol was added to terminate the reaction. The mixture was extracted with 3 × 50 ml CH_2Cl_2, washed with water, dried over $MgSO_4$, and filtered. Removal of solvent gave the crude product, which was purified by flash chromatography on silica gel with hexane–EtOAc (2 : 1) as eluent to yield 0.26 g (48%) of white crystals of **12**, m.p. 194–195.5°. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.60 (d, 2H, J = 12.0 Hz), 1.78 (s, 4H), 1.98 (d, 2H, J = 12.1 Hz), 2.19 (d of d, 2H, J = 12.1 and 5.2 Hz), 2.35 (d of d, 2H, J = 12.0 and 5.2 Hz), 2.64 (broad s, 2H). ^{13}C-NMR ($CDCl_3$): δ 174.28, 94.94, 72.26, 43.44, 42.66, 38.91, and 30.02. IR (KBr disc): 2940, 1818, 1461, 1133, and 900 cm^{-1}. UV (pentane): $\lambda_{max} = 217$ nm ($\varepsilon = 48$). MS: *m/e* 178 (M$^+$, 1), 150 (17), 134 (53), 119 (60), 106 (62), and 91 (100). Exact mass: calc for $C_{11}H_{14}O_2$, 178.0993; found, 178.0997.

Flow system pyrolysis of **12**. β-Lactone **12**, 30 mg, in 30 ml pentane was passed through a flow system pyrolysis apparatus[20] (N_2 flow rate 40 ml min^{-1}) three times at 450°. After removal of solvent, the residue was filtered through a pad of silica gel using hexane as eluting solvent. Evaporation of solvent gave 10.2 mg (45.2%) of a solid, which was pure by NMR. The dimer did not melt below 200° but began to darken around 125°. ^{1}H-NMR (500 MHz): δ 1.28 (d, 8H, J = 12.2 Hz), 1.64 (m, 8H), 1.97 (d of d, 8H, J = 12.2, 5.2 Hz) and 2.41 (m, 4H). ^{13}C-NMR: δ 30.87, 39.33, 42.45, and 55.97. Exact mass: calc for $C_{20}H_{28}$, 268.2190; found, 268.2197.

Pyrolysis of **12** *in tetraglyme containing diphenylisobenzofuran.* β-Lactone **12**, 60 mg (0.34 mmol), and diphenylisobenzofuran (130 mg, 0.51 mmol) were dissolved in 2 ml of freshly distilled tetraglyme. The mixture was degassed three times under vacuum at room temp, and then argon was admitted to the system. The mixture was then heated to reflux for 3 hr under argon atmosphere. After cooling the soln to room temp, ether was added, and the soln was washed with water and dried. Evaporation gave a residue, which was dissolved in CH_2Cl_2. Maleic anhydride dissolved in CH_2Cl_2 was added to this soln until the fluorescent yellow color of DPIBF was discharged. The solvent was removed under vacuum, and the residue was dissolved in benzene. The soln was passed through a short pad of florosil, and the benzene was evaporated. The residue was recrystallized from CH_2Cl_2–MeOH to give 68 mg (50%) of white crystals of the Diels–Alder adduct, m.p. 175–176°. ^{1}H-NMR (500 MHz): δ 1.36 (d, 2H, J = 12.2 Hz), 1.51 (d, 2H, J = 12.3 Hz), 1.57 (d of d, 2H, J = 12.3, 5.2 Hz), 1.73 (m, 4H), 1.90 (d of d, 2H, J = 12.2, 5.2 Hz), 2.33 (m, 2H), 6.98–7.10 (m, 4H), and 7.33–7.60 (m, 10H). ^{13}C-NMR: δ 30.84, 31.10, 40.23, 43.64, 44.19, 46.33, 71.02, 93.32, 121.34, 125.96, 126.11, 127.06, 128.16, 138.84, and 147.79. Exact mass: calc for $C_{30}H_{28}O$, 404.2139; found, 404.2137.

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