to overproduce the enzyme,[25] we reinvestigated the stereochemistry of reaction for the normal substrates and have determined the complete time course of hydrogen exchange for IPP and DMAPP with yeast isomerase.

Exchange of hydrogens in IPP and DMAPP with water was detected by following the loss of signal in ^{1}H NMR spectra upon incubation of IPP with isomerase in D_2O. For the experiment summarized in Figure 1, IPP (10 mM) was incubated with 0.1 mg (sp act. 19 μmol min^{-1} mg^{-1}) of recombinant *Saccharomyces cerevisiae* IPP isomerase. Upon addition of enzyme, a rapid conversion of IPP to DMAPP was seen as evidenced by the appearance of resonances for DMAPP[26] at δ 5.44 (C(2)), 4.45 (C(1)), 1.75 ((*E*)-methyl), and 1.71 ((*Z*)-methyl) ppm and a concomitant decrease in the intensity of resonances for IPP[27] at δ 4.86 (C(4)), 4.06 (C(1)), 2.40 (C(2)), and 1.77 (methyl) ppm.

Figure 1A shows the time course of the reaction for the C(1) methylene protons. A rapid change in the concentrations of IPP and DMAPP was observed upon addition of enzyme. Equilibrium was reached within 10 min, and the intensities of the peaks remained constant thereafter. The C(1) hydrogens did not exchange with D_2O during the course of the experiment, and $K_{eq}^{24°} = 2.2$ was calculated from the relative intensities of the C(1) resonances. The time course for signals in the methyl region is shown in Figure 1B. During the first few minutes, the intensity of the resonance for the methyl group in IPP decreased rapidly as signals for the (*E*)-methyl and (*Z*)-methyl groups in DMAPP increased. However, rapid exchange of the (*E*)-methyl protons in DMAPP with D_2O quickly reduced the intensity of that signal until, after 20 min, it was no longer detected. The intensity of the resonance for the (*Z*)-methyl group of DMAPP reached a maximal value after 10 min. However, in contrast to the C(1) methylene protons, signals for the methyl group in IPP and the (*Z*)-methyl in DMAPP slowly decreased after equilibrium was reached, indicating exchange of these protons with D_2O. Addition of more enzyme after 70 min increased the rate of the slow exchange reaction by approximately 4-fold. Similar behavior was observed for the protons attached to C(2) of IPP and DMAPP, as shown in Figure 1C. In this case, the C(2) signal in IPP decreased rapidly, with a concomitant increase for C(2) in DMAPP, as equilibrium was obtained. Between 20 and 70 min, the intensities remained essentially constant. However, upon addition of more IPP isomerase at 70 min, the C(2) signals in both compounds decreased as well! After continued incubation for 19 h, only the two resonances at δ 4.06 and 4.45 ppm for the C(1) methylene protons of IPP and DMAPP, respectively, remained in the ^{1}H NMR spectrum. Both signals were simple doublets with a 6.9-Hz coupling to phosphorus. A ^{2}H spectrum of IPP and DMAPP from this sample gave resonances for all positions, except for C(1), with intensities consistent with a 1:2.2 mixture of isomers.

Rates for the three exchange processes seen in Figure 1 were estimated from initial slopes. The first exchange resulted in the rapid loss of intensity[28] for the *pro-R* C(2) and C(4) hydrogens of IPP and the rapid rise and fall of the (*Z*)-methyl signal in DMAPP. These exchanges are coincident with establishment of the equilibrium. The second exchange resulted in loss of intensity for the methyl group in IPP and the (*E*)-methyl in DMAPP at a rate of approximately 2% that of the first process. The slowest exchange (0.5% of the fast process) resulted in loss of the *pro-S* and olefinic signals at C(2) in IPP and DMAPP, respectively.

For an enzyme, yeast IPP isomerase catalyzes interconversion of IPP and DMAPP with a rather low degree of stereochemical fidelity. At least three kinetically distinguishable exchange processes were detected. The most facile was consistent with the accepted stereochemistry for isomerization, an antarafacial protonation of the *re* face of the double bond in IPP and elimination of the H_R proton at C(2). If one assumes that the catalytic residues are optimally positioned for addition/elimination by the preferred stereochemistry, the slower exchanges most likely arise from other conformers of the enzyme–substrate complex. It is interesting to note that elimination of *either* C(2) proton will give DMAPP or of *any* methyl proton will give IPP from the tertiary carbocationic species. Thus, there is no stereochemical imperative for the reaction catalyzed by IPP isomerase and there are no consequences in vivo for low stereoselectivity beyond adding to the consternation of chemists by scrambling isotope in artificially labeled precursors.

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(26) ^{1}H NMR spectrum (D_2O): δ 1.71 (s, 3 H, (*E*)-methyl), 1.75 (s, 3 H, (*Z*)-methyl), 4.45 (dd, $J_{H,H}$ = 6.9 Hz, $J_{H,P}$ = 6.9 Hz, 2 H, H at C(1)), and 5.44 ppm (t, $J_{H,H}$ = 6.9 Hz, 1 H, H at C(2)).

(27) ^{1}H NMR spectrum (D_2O): δ 1.77 (s, 3 H, methyl), 2.40 (t, $J_{H,H}$ = 6.6 Hz, 2 H, H at C(2)), 4.06 (td, $J_{H,H}$ = 6.6 Hz, $J_{H,P}$ = 3.3 Hz, 2 H, H at C(1)), and 4.86 ppm (s, 2 H, H at C(4)).

(28) k_{cat} = 9 s^{-1} for yeast IPP isomerase.[25]

1,2,3-Cyclohexatriene and Cyclohexen-3-yne: Two New Highly Strained C_6H_6 Isomers

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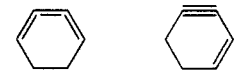
Enormous effort has been devoted toward the exploration of structural limitations in organic compounds.[1] Cyclic butatrienes[2] and cyclic enynes[3] are two fundamental classes of strained hydrocarbons for which limiting ring sizes are as yet unknown. We describe here evidence for the synthesis and trapping of 1,2,3-cyclohexatriene (**1**) and cyclohexen-3-yne (**2**). These highly strained and reactive substances redefine known limitations for their respective homologous series. Additionally, **1** and **2** are of interest as new benzene isomers.



1 2

Less strained, larger ring homologues of **1** and **2** are known. Szeimies and co-workers have reported the successful trapping of 1,2,3-cycloheptatriene; however, attempts to prepare **1** were unsuccessful.[4] We have described the preparation and isolation of 1,2,3-cyclononatriene.[5] Strained cyclic enynes have been generated by a variety of methods; the smallest previously reported homologue is cyclohepten-3-yne.[3]

A new and presumably general route to cyclic butatrienes is exemplified by the present synthesis of **1** (Scheme I). Kinetic deprotonation of enone **4**[6] with lithium diisopropylamide (LDA), followed by addition of *N*-phenyltrifluoromethanesulfonimide,[7] gave 1,3-diene **5** in 50% yield.[8] Reaction of **5** with CsF in DMSO

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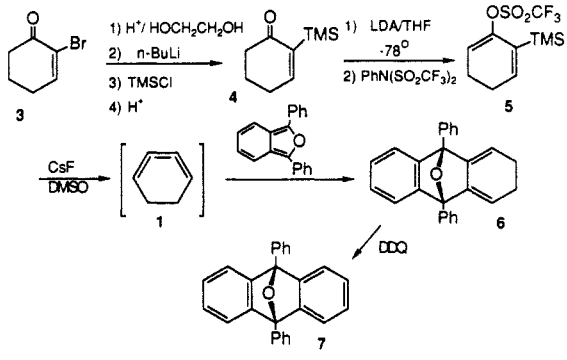
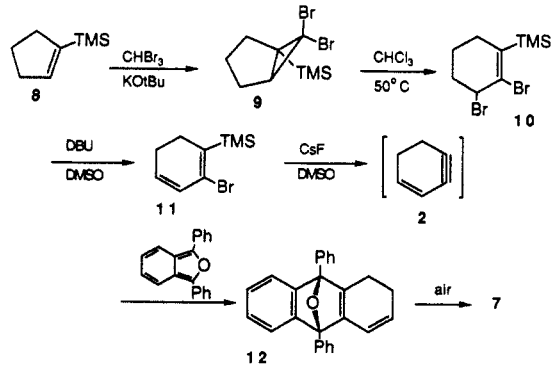
Scheme I



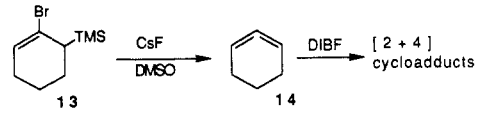
Scheme II



at 25 °C in the presence of diphenylisobenzofuran (DIBF) afforded crystalline adduct **6** in 24% yield after chromatography. The structure of **6** (C_s symmetry) was confidently assigned from spectral data and DDQ oxidation to **7**.[9] Ample literature precedent supports the conclusion that **6** is formed from [2 + 4] cycloaddition of cumulene **1** at its most strained π bond.[1,2,4]

Synthesis of conjugated enyne **2** (Scheme II) follows a similar strategy in the final step. Dibromocarbene addition to **8**, thermal rearrangement to **10**, and treatment of **10** with DBU afforded diene **11** (30% yield from **8**). Treatment with CsF, as above, led to **12** in 30% isolated yield. Air oxidation of **12** gave **7**. Control experiments showed that **11** did not react with DIBF under the reaction conditions. We attribute the formation of **12** to cycloaddition of DIBF with strained enyne **2**.

The fluoride-induced elimination of β-substituted organosilanes has been applied to the preparation of benzyne and strained alkenes,[10] but not to strained cumulenes and enynes. In principal, a similar approach should yield strained allenes; indeed, we find that **13**[11] readily leads to 1,2-cyclohexadiene (**14**), which is trapped by DIBF to yield two stereoisomeric cycloadducts in a ratio identical with that previously reported.[2,12]



We believe that these synthetic approaches should be generally applicable to other ring sizes. Routes to cyclic butatrienes are sparse; this method should make them readily accessible from cyclic enones. Experiments to prepare both smaller and larger homologues are in progress.

Acknowledgment. We are grateful to the National Science Foundation for support of this research through Grant CHE-8722079 and an equipment grant for a 360-MHz NMR spectrometer.

(8) Data for new compounds include the following. **5**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.28–6.30 (1 H, t, J = 4.34 Hz), 5.73–5.76 (1 H, t, J = 4.51 Hz), 2.14–2.31 (4 H, symmetrical mult), 0.17 (9 H, s); ^{13}C NMR δ 150.50, 141.23, 133.55, 111.79, 22.58, 21.73, -1.09; UV (hexane) λ_{max} 260 nm (ϵ 2050), 203 (2200). **6**: ^{1}H NMR δ 7.81–7.83 (4 H, d, J = 7.16 Hz), 7.52–7.56 (4 H, t, J = 7.29 Hz), 7.42–7.46 (2 H, t, J = 7.29 Hz), 7.31–7.33 (2 H, dd, J = 3.07, 5.34 Hz), 7.16–7.18 (2 H, dd, J = 3.07, 5.34 Hz), 5.69 (2 H, br s), 2.22–2.24 (4 H, m); ^{13}C NMR δ 146.52, 138.76, 135.27, 128.49, 127.92, 126.80, 126.30, 119.43, 114.28, 88.34, 22.31. Anal. C, H. **10**: ^{1}H NMR δ 4.83 (1 H, br s), 2.37–2.44 (1 H, dd, J = 5.27, 18.38 Hz), 2.18–2.29 (2 H, m), 2.05–2.15 (1 H, dt, J = 3.14, 13.96 Hz), 1.92–2.05 (1 H, m), 1.73–1.77 (1 H, m), 0.23 (9 H, s); ^{13}C NMR δ 143.28, 130.90, 57.14, 33.78, 32.21, 17.32, -0.94. Anal. C, H. **11**: ^{1}H NMR δ 5.83–6.02 (1 H, dt, J = 1.79, 9.72 Hz), 5.83–5.88 (1 H, dt, J = 4.36, 9.72 Hz), 2.22–2.27 (2 H, m), 2.05–2.13 (2 H, m), 0.25 (9 H, s); ^{13}C NMR δ 135.26, 130.92, 129.93, 126.57, 28.53, 21.50, -0.68; UV (hexane) λ_{max} 275 nm (ϵ 4400), 205 (3960). **12**: ^{1}H NMR δ 7.76–7.80 (2 H, d, J = 7.1 Hz), 7.68–7.70 (2 H, d, J = 7.1 Hz), 7.38–7.53 (6 H, m), 7.19–7.26 (2 H, t, J = 7.0 Hz), 6.92–7.01 (2 H, quint, J = 7.5 Hz), 6.17–6.20 (1 H, br d, J = 9.66 Hz), 5.66–5.71 (1 H, dt, J = 4.2, 9.6 Hz), 2.62–2.70 (1 H, ddd, J = 4.82, 7.52, 17.0 Hz), 2.28–2.35 (2 H, m), 2.04–2.16 (1 H, m); ^{13}C NMR δ 151.68, 151.48, 150.56, 147.65, 135.20, 134.69, 128.69, 128.53, 128.20, 127.94, 126.56, 126.06, 125.15, 124.73, 120.14, 120.13, 119.60, 92.46, 92.16, 23.19, 22.66. This compound easily air-oxidizes to **7**.

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Discovery of a New Fragmentation Reaction[1]

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Fragmentation reactions form one of the major classes of organic transformations, providing the foundation for a variety of strategies for complex molecule synthesis.[2] Decades of research have firmly established that these reactions proceed stereospecifically, in accord with expectations based on molecular orbital analysis.[2] We describe herein a remarkable fragmentation process that provides the basis for a new fragmentation mechanism and for a new mechanistic probe for substitution reactions.

As part of our interest in developing a metathetical approach to medium-ring synthesis (Scheme I: **1** + **2** → **4**), we previously reported[3] that kinetically controlled fragmentation of lactone **3** gives predominantly the (*Z*,*Z*)-cyclodecadiene **4** and lesser amounts of its thermodynamically favored Cope isomers **5**, in accord with a concerted cycloreversion or a stepwise path proceeding through a conformationally relaxed diyl.[4] In an effort

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