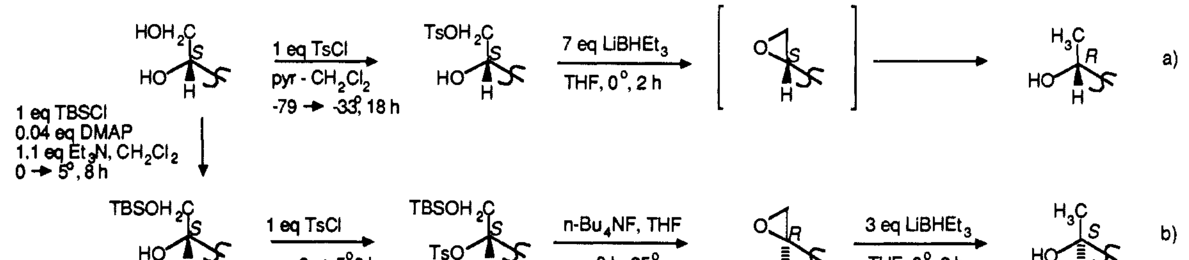
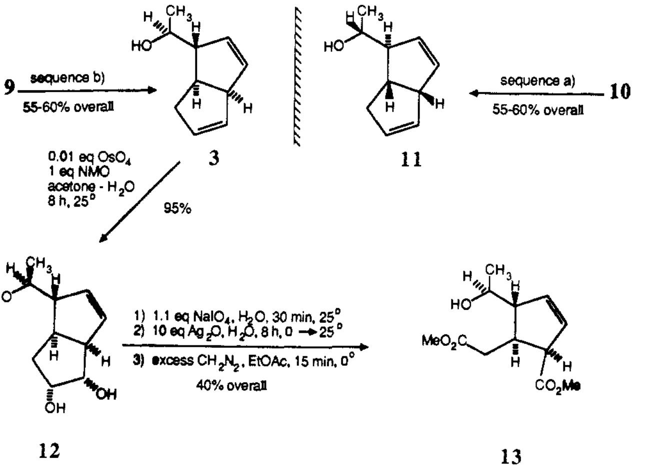
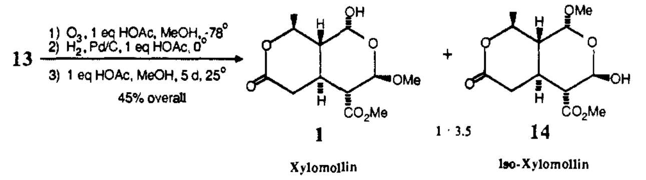
Scheme III



Scheme IV



Scheme V



between **6** and **7** to be as shown.

Reaction of **3** with catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide afforded the triol **12** in high yield with excellent stereo- and regiochemical control (Scheme IV). Cleavage with periodate and further oxidation with nonbasic silver oxide[10] followed by esterification with excess diazomethane afforded diester **13**.[11] Oxidation of **13** with ozone followed by catalytic reduction exposed all of the functionality represented in **2**. The unique lactone, acetal–hemiacetal system present in the natural product was then formed upon extended treatment with mild acetic acid in methanol (Scheme V).[13,14] A regioisomer, isoxylomollin (**14**), was also produced with the same stereochemistry at carbons 1, 3, and 4[15] as in **1** but where the methoxy and hydroxy groups at C-1 and C-3 have been interchanged. The preferential formation of **14** is reasonable[16] and indeed, prolonged treatment with mild acid only further enriched the mixture in **14** at the expense of **1**.

We have accomplished a total synthesis of this highly unusual and biologically active iridoid terpene in optically active form by a unique combination of stereochemical methods. In particular, two new stereochemical centers were formed with high levels of absolute as well as relative asymmetric induction at the same time that a third was controlled by kinetic resolution. In addition, the development of divergent schemes for further elaboration of the adduct with either net inversion or retention at the secondary carbinol center expands the scope of applications for our asymmetric ene reaction.

Acknowledgment. We are grateful for support of this research by the National Institutes of Health (GM-31750) and by the Robert A. Welch Foundation (F-626).

Supplementary Material Available: Experimental details for the preparation of and spectral data for all intermediates (16 pages). Ordering information is given on any current masthead page.

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(10) The use of nonbasic silver oxide is critical here. Standard procedures for the preparation of this reagent invariably employ excess base and use of such material for the oxidation of the intermediate dialdehyde derived from **12** afforded very low yields of diacid.

(11) Repeated attempts to effect lactonization of **13** by using a variety of reaction conditions were unsuccessful, with migration of the double bond into conjugation with the ester functionality occurring more rapidly than ring closure. Apparently the strain induced by the presence of the double bond in the bicyclic, trans-fused hydrindane lactone is substantial. A simpler model, lacking the unsaturation, closed spontaneously.[12]

(12) Baldwin, S. W.; Crimmins, M. T. *Tetrahedron Lett.* **1978**, 4197.

(13) It is not clear at this time whether xylomollin is an artifact of the isolation procedure (that involved extraction with methanol) or is present in the fruit.

(14) Both carbon-13 and proton NMR spectra of synthetic xylomollin were identical with those obtained on a sample of natural material kindly provided by Professor Nakanishi. The melting points were also essentially identical (137–139 °C (MeOH), synthetic; 138–139 °C (EtOH, authentic), while the optical rotation was slightly low ($[\alpha]_D$ −40.0° (c 0.42, MeOH) vs. −44.3° (concentration not specified, MeOH)). However, the synthetic sample slowly converted to isoxylomollin in neutral methanol over time and the rotation of the latter is lower ($[\alpha]_D$ −25.2 (c 0.5, MeOH). The sample recovered after the rotation measurement was in fact contaminated with isoxylomollin.

(15) The axial orientation of the C1 hydroxyl group is presumably dictated by the anomeric effect and avoidance of a peri interaction with the C-10 methyl group. Equatorial orientations for the remaining groups would then be expected.

(16) Assuming fixed stereochemistry,[15] it might be anticipated that the methoxy group would be preferred in an axial and the hydroxy group in an equatorial orientation based on the preference for β- over α-glucose and α- over β-methyl glucoside.

Use of Pulsed Time-Resolved Photoacoustic Calorimetry To Determine the Strain Energy of *trans*-1-Phenylcyclohexene and the Energy of the Relaxed 1-Phenylcyclohexene Triplet

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The energetics of nonspectroscopic species on excited-state surfaces, as well as the energies of highly strained, short-lived transients on ground-state surfaces, have generally been accessible only through indirect arguments.[3,4] Such information, however,

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Scheme I

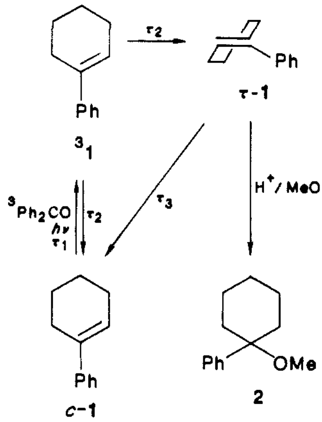

Table I. Deconvolution Fitting Parameters for the Photosensitized Isomerization of *cis*-1-Phenylcyclohexene[a,b]

	methanol	cyclohexane
ϕ_1[c]	0.34 ± 0.04[d]	0.36 ± 0.04
ϕ_2	0.47 ± 0.03	0.44 ± 0.04
τ_2, ns	64 ± 7	66 ± 8
ϕ_3	0.19 ± 0.02	0.20 ± 0.02
τ_3, μs	9.7 ± 2.0	9.4 ± 2.5

[a] ϕ_n values are defined as the fraction of the photon energy (84.8 kcal/mol for 337-nm excitation) released as heat for the relaxation process n. [b] 337 nm, <20 μJ, 300 K, 10^{-3} M benzophenone, 0.1 M *c*-**1**. [c] τ_1 is defined as 1 ns which is the limit of the transducer resolution. [d] Errors are 1σ; values are from at least four separate experiments, where each experiment is carried out at five different photolysis energies.

is clearly critical to defining the potential energy surfaces and is a necessary prelude to understanding reaction dynamics. We now report the application of time-resolved photoacoustic calorimetry[5-9] to the triplet sensitization of *cis*-1-phenylcyclohexene to determine the relaxed triplet energy and the enthalpy of isomerization to the highly strained *trans*-1-phenylcyclohexene.

The photochemistry of *cis*-1-phenylcyclohexene has been well studied.[10-13] The triplet photosensitization of *cis*-1-phenylcyclohexene (*c*-**1**) generates the triplet state of **1**, ^{3}**1**. The triplet state decays, τ_2 = 65 ns,[14-17] to give a mixture of *cis*- and *trans*-**1**. The unstable *t*-**1** then isomerizes to *c*-**1**, τ_3 = 9 μs,[11,12] Scheme I.

Pulsed time-resolved photoacoustic calorimetry[5-8] affords reaction enthalpies for photoinitiated reactions. Deconvolution of the experimental waveforms allows the simultaneous determination of the dynamics and energetics of photoinitiated reactions by measuring the time evolution of heat deposition. The details of the methodology are presented in ref 9. The experimental waveform obtained from *c*-**1** (0.1 M) sensitized by benzophenone (10^{-3} M, 337 mm, 5 ns, <20 μJ, 300 K) in argon-outgassed methanol or cyclohexane is shown in Figure 1. The kinetic, τ, and enthalpic, ϕ, fitting parameters are obtained from the deconvolution of the experimental acoustic wave,[9] Table I. Three transients were employed in the deconvolution analysis in order to obtain an acceptable fit to the experimental wave, as shown in Figure 1. In assessing the accuracy of the five fitting parameters, which were each independently varied, there are three experimental observables to serve as a check. The first two observables are the olefin triplet and trans olefin lifetimes. The third observation is that since there is no net chemistry, the sum of the three enthalpic amplitudes should be 1.0.

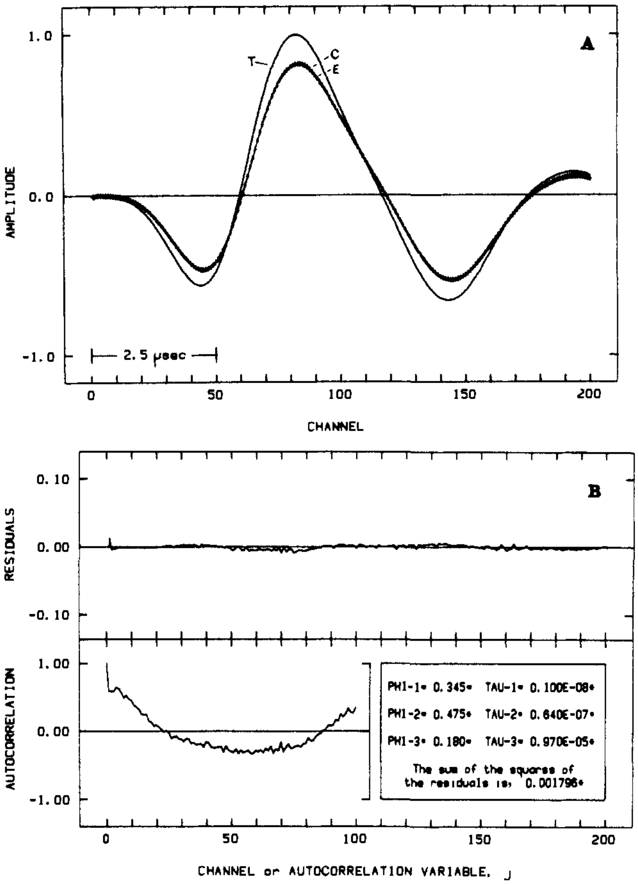

Figure 1. Deconvolution of the waveform from the 337-nm irradiation of 10^{-3} M benzophenone in the presence of 0.1 M *cis*-1-phenylcyclohexene in methanol. (A) T wave-transducer reponse, ferrocene; E wave-experimental (solid line); C wave-convoluted (dotted line). (B) Diagnostics of the convolution.

The first rate, $\tau \simeq$ 1 ns,[18] corresponds to the triplet energy transfer to form ^{3}**1** and its rapid thermalization. The energy of ^{3}**1** can be obtained from the relationship $E_T = E_{h\nu}\,(1 - \phi_1)$ where E_T is the energy of ^{3}**1**, and $E_{h\nu}$ is the photon energy (84.8 kcal/mol at 337 nm). The average value of ϕ_1 = 0.34 ± 0.04 gives a triplet energy of 56.0 ± 3.4 kcal/mol in methanol. The second rate, τ_2 = 64 ± 7 ns, associated with the decay of the olefin triplet, is in agreement with the triplet lifetime[14-17] of 65 ns determined by flash photolysis.

The parameter τ_3, 9.7 ± 2.5 μs, is in agreement with flash spectroscopic determinations of the *t*-**1** lifetime.[11,12] The heat of isomerization of *c*-**1** to *t*-**1**, E_{c-t}, can be obtained from the relationship $E_{c-t} = \phi_3 \times E_{h\nu}/\phi_{\text{form}}$, where ϕ_{form} is the quantum yield of benzophenone-sensitized isomerization of *c*-**1** to *t*-**1**. We have measured ϕ_{form} by scavenging *t*-**1** with H_2SO_4 (0.004–0.25 M)

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(16) We have measured the lifetimes of ^{3}**1** to be 63 ± 2 ns in methanol and 67 ± 1 ns in heptane by transient absorption spectroscopy.

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(18) The measured triplet-triplet energy transfer rate is ~7 × 10^9 M^{-1} s^{-1}, and thus ^{3}**1** should be populated in ca. 1.4 ns, using 0.1 M *c*-**1**.

in methanol to afford 1-phenyl-1-methoxycyclohexane (**2**), via the 1-phenylcyclohexyl carbocation.[10,11] Extrapolation of the double-reciprocal plot of the quantum yield of formation of **2** vs. [H_2SO_4], after correction for $^3Ph_2CO$ quenching by H_2SO_4 and for the small (2.2%) inefficiency of conversion of the carbocation to ether,[19] affords $\phi_{form} = 0.36 \pm 0.01$ (2σ)[20] and thus a value of 44.7 ± 5 kcal/mol for $E_{c\text{-}t}$. The sum of the amplitude factors, $\phi_1 + \phi_2 + \phi_3$, equals unity, indicating all the photon energy is recovered as heat within experimental error. Results in cyclohexane are almost identical. However, the inability to measure ϕ_{form} in aprotic solvent prevents a computation of $E_{c\text{-}t}$ in cyclohexane.

The values of E_T and $E_{c\text{-}t}$ are the first experimental measurements of the relaxed energy of a short-lived twisted alkene triplet[21] and of the heat of geometric isomerization to the most strained cycloalkene known, respectively. The E_T value of 56 ± 3.4 kcal/mol is but slightly lower than the expected[22] spectroscopic triplet energy of 60 kcal/mol. We believe that this corresponds to partial relaxation (i.e., <90° rotation) of the triplet.[19] Therefore, the triplet surface is nearly flat, similar to the trans to perpendicular region for stilbene triplet.[23]

The energy $E_{c\text{-}t}$ of 44.7 kcal/mol is remarkably close to the prediction of molecular mechanics (MM) for *trans*-cyclohexene ($E_{c\text{-}t}$ = 42.4 kcal/mol).[24] Given the $\Delta H_f(c\text{-}\mathbf{1}) = -4.0 \pm 1.6$ kcal/mol[25] and the strain energy $E_s(c\text{-}\mathbf{1})$ = 1.2 kcal/mol,[26] then $\Delta H_f(t\text{-}\mathbf{1}) = 41 \pm 5$ kcal/mol and $E_s(t\text{-}\mathbf{1}) = 46 \pm 5$ kcal/mol. We note the structural prediction by MM of substantially pyramidalized vinyl carbons in these and related compounds.[4,24] The implications of this for the chemistry of *trans*-cyclohexenes and for dynamics on the ground-state surface will be discussed in a future report.

In conclusion, we have demonstrated the applicability of time-resolved photoacoustic calorimetry to the study of alkene ground and triplet surfaces. Further studies should allow a wealth of thermochemical information on relaxed olefin triplets and strained ground-state isomers.

Acknowledgment. This work was supported by the donors of Petroleum Research Fund, Administered by the American Chemical Society, and NSF (CHE 8213637). K.S.P. acknowledge support from the Alfred P. Sloan Foundation and the Henry and Camille Dreyfus Foundation for a teacher-scholar grant. J.L.G. acknowledges generous support from an NIH postdoctoral fellowship. Transient absorption studies were performed at the Center for Fast Kinetics Research at the University of Texas at Austin, supported by NIH Grant RR-00668 from the Biotechnology Branch of the Division of Research Resources and by The University of Texas at Austin.

Registry No. 1-Phenylcyclohexene, 771-98-2.

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(19) To be elaborated in a full paper.

(20) Bonneau and Herran[17] report 0.34 ± 0.07 by a less extensive series of measurements by the same technique. We gratefully acknowledge helpful discussions with Dr. Bonneau.

(21) Gorman's elegant equilibration studies of triplet olefin thermochemistry necessarily involve somewhat to longer lived and thus usually more constrained triplets; see: (a) Gorman, A. A.; Hamblett, I.; Irvine, M.; Raby, P.; Standen, M. C.; Yeates, S. *J. Am. Chem. Soc.* **1985**, *107*, 4404. (b) Gorman, A. A.; Hamblett, I.; Jensen, N.-H. *Chem. Phys. Lett.* **1984**, *111*, 293. (c) Gorman, A. A.; Hamblett, I. *Ibid.* **1983**, *97*, 422. (d) Gorman, A. A.; Gould, I. R.; Hamblett, I. *J. Am. Chem. Soc.* **1981**, *103*, 4553. Reference 21d in particular describes the difficulty of applying the technique to triplets with a substantial degree of twist.

(22) Crosby, P. M.; Dyke, J. M.; Metcalfe, J.; Rest, A. J.; Salisbury, K.; Sodeau, J. R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 182. The energies of planar substituted styrenes triplets are ca. 60 kcal/mol; 1-phenylcyclopentene, the closest model, is 59.6 kcal/mol.

(23) See: Saltiel, J.; Marchand, G. R.; Kirkor-Kaminska, E.; Smothers, W. K.; Mueller, W. B.; Charlton, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 3144 and references therein.

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Intramolecular vs. Intermolecular Alkyl C-H Bond Activation. Complete Thermodynamic and Kinetic Parameters for a Reversible Cyclometalation

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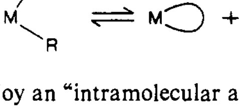
Despite the widespread occurrence of intramolecular C-H activating[1,2] cyclometalation processes[3] (eq 1) and the possibility



(1)

that they may enjoy an "intramolecular advantage"[4,5] over competing intermolecular processes, relevant comparative thermodynamic (ΔH, ΔS) and kinetic ($\Delta H^‡$, $\Delta S^‡$) information is surprisingly sparse. For one rhodium system, Jones and Feher[6] showed that an intramolecular process enjoyed a slight thermodynamic (only $\Delta G°$ could be measured) advantage but also a slight kinetic disadvantage (only in $\Delta H^‡$). We recently reported kinetic/mechanistic studies of intermolecular alkane activation[7] and closely related intramolecular cyclometalation[8] at thorium centers (eq 2-4). C-H scission was found to be rate-limiting, and

$$\underset{\mathbf{1}}{Cp'_2\overline{ThCH_2CMe_2C}H_2} + RH \rightarrow \underset{\mathbf{2}}{Cp'_2Th(R)CH_2CMe_3} \qquad (2)$$

$$\underset{\mathbf{3}}{Cp'_2Th(CH_2CMe_3)_2} \rightarrow \underset{\mathbf{1}}{Cp'_2\overline{ThCH_2CMe_2C}H_2} + CMe_4 \qquad (3)$$

$$\underset{\mathbf{4}}{Cp'_2Th(CH_2SiMe_3)_2} \rightleftharpoons \underset{\mathbf{5}}{Cp'_2\overline{ThCH_2SiMe_2C}H_2} + SiMe_4 \qquad (4)$$

$$Cp' = \eta^5\text{-}Me_5C_5$$

thermochemical data (ΔH)[9] suggest that eq 3 and 4 are entropically driven. We now report that the reversibility of eq 4 can be rendered observable, presenting a unique opportunity to quantify, in toto, thermodymamic and kinetic aspects of the in-

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