The First Example of (2,5) Ene Cyclization: Solid Acid-Catalyzed Oxonium-Ene Reaction†

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Among the six different types of intramolecular ene reactions (ene cyclizations), the (2,5) ene cyclization has never been reported. The first example of the (2,5) intramolecular ene reaction is exploited involving oxonium ion as an intermediate. The cyclization is efficiently catalyzed by solid acids such as montmorillonite K10 to organize the (2,5) oxonium-ene reaction in preference to (2,4) (Oppolzer's type II) in the mesopore of the solid acids. This regiochemical fidelity is consistent with the direct conversion of oxonium ion to the (2,5) ene product via an intramolecular ene pathway involving the hydrogen shift of the methyl protons with close proximity in the mesopore of K10.

Introduction

Conceptually, intramolecular ene reactions[1] (ene cyclizations) are classified into six different types of cyclization,[2,3] since ene and enophile moieties can be connected at three and two different positions, respectively. Therefore, the positions, wherein the shortest tether connects the [1,5] hydrogen shift system, are exemplified in a (*m*,*n*) (*m* = 1, 2, or 3; *n* = 4 or 5) fashion (Scheme 1). The ring size may be designated by numerical prefix *l*-. Among these types, only the (2,5) ene cyclization has never been reported.[4]

When an enophile is composed of a carbonyl (Y = O) or an olefin (Y = C) moiety, the well-known (2,4) ene cyclization (Oppolzer's type II)[1b] proceeds (Scheme 2). Therefore, we must construct the (2,5) ene system in which the enophile consists of an imine (X = N), the iminium ion ($X = N^+$), or the oxonium ($X = O^+$) counterpart. Herein, we wish to report the first example of the (2,5) ene cyclization that involves the oxonium ion[5,6] as the enophile component; the (2,5) oxonium-ene reaction in the mesopore of solid acids such as montmorillonite K10.

Result and Discussion

In our first attempt on the (2,5) ene cyclization (Scheme 3), several homogeneous Lewis acids[7] such as Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$, Me_2AlOTf, and $BF_3{\cdot}OEt_2$ were examined in order to generate the oxonium ions from lactols and their benzyl ethers. However, only a trace amount of the (2,5) ene product was obtained. Eventually, heterogeneous solid acids such as montmorillonite K10[8,9] were found to be an effective catalyst for this reaction (Table 1).

In terms of (2,5) ene selectivity, montmorillonite K10 was the best heterogeneous catalyst among the solid acids employed such as HY, LaY, and ZSM-5 zeolites, as shown in Table 1. The reaction using montmorillonite K10 proceeded smoothly at room temperature to afford the desired (2,5) ene product **3** selectively (Table 1, entry 1). Amberlyst 15E was also effective even in better combined yield, but with the lower (2,5) selectivity (Table 1, entry 2). Amberlite IR-120B, Nafion or *p*-TsOH was not useful for this cyclization (Table 1, entries 3−5).

The representative results with K10 are listed in Table 2. The typical experimental procedure is as follows. The reaction of lactol **1** with K10 in toluene at room temperature in the presence of molecular sieves 4A (MS4A)[10] afforded the (2,5) ene product **3**, along with the (1,5) ene-type product **4** and the isomerized product **5** just after filtration of K10. Inspection of Table 2 reveals the characteristic features of the present oxonium-ene cyclization. Selectivity for the (2,5) ene cyclization critically depended on the solvent employed (Table 2, entries 1−4). When dichloromethane or toluene was used as a solvent, high selectivity was observed for the (2,5) ene cyclization (Table 2, entries 1 and 4). In 1,4-dioxane, the (2,5) selectivity was decreased to give mainly the (1,5) ene product **4** (Table 2, entry 2).[11] In acetonitrile, by contrast, no ene cyclization product was obtained (vide infra) (Table 2, entry 3).[12] Interestingly, the reaction conducted

† Dedicated to the memory of Professor W. Oppolzer.

(1) For excellent and comprehensive reviews of intramolecular ene reactions (ene cyclizations), see: (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (c) Taber, D. F. *Intramolecular Diels−Alder and Alder Ene Reactions*; Springer−Verlag: Berlin, 1984.

(2) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(3) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403.

(4) For the attempt on the (2,5) ene cyclization, see: Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1984**, *49*, 183. They used methyl 6-methyl-2-methylene-6-heptenoate as a substrate for the (2,5) ene cyclization. However, the reaction could not be accomplished with homogeneous Lewis acid catalyst such as $EtAlCl_2$.

(5) For (1,5) oxonium-ene cyclizations (Oppolzer's type III), see: (a) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248. (b) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (c) Blumenlopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.

(6) For intermolecular oxonium-ene reactions, see: Mikami, K.; Kishino, H. *Tetrahedron Lett.* **1996**, *37*, 3705, and references listed therein.

(7) For reviews on Lewis acid promoted ene reactions, see: Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. Snider, B. B. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: London, 1989; pp 147−167. Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vols. 2 and 5.

(8) For carbonyl-ene reactions using montmorillonite K10, see: Roudier, J. F.; Foucaud, A. *Tetrahedron Lett.* **1984**, *25*, 4375.

(9) Aldrich: Lot. No. 07812AN

(10) Aldrich: powder, <5 μm, activated, Lot. No. 02910CR

(11) In THF, the formation of endo product **6** was observed (**3**:**4**:**5**:**6** = 23:63:0:13 (66% combined yield)).

(12) Dimerized ether of the substrate **1** was obtained (49%).

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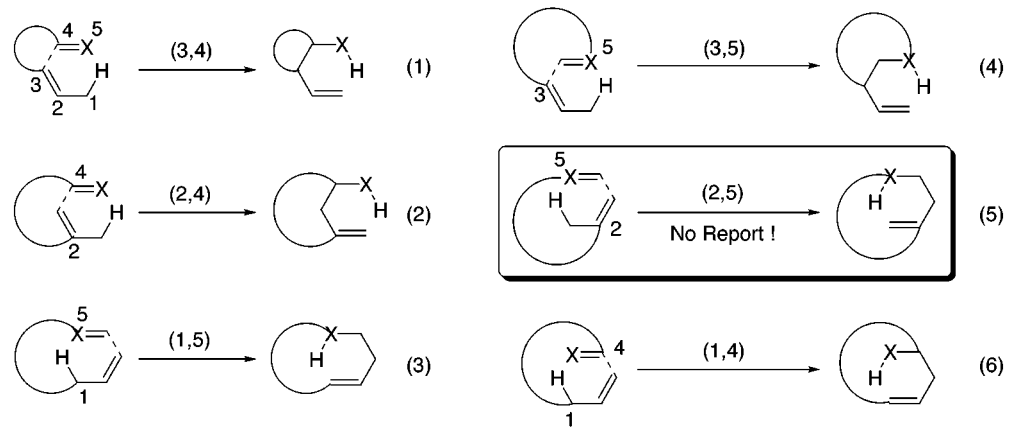
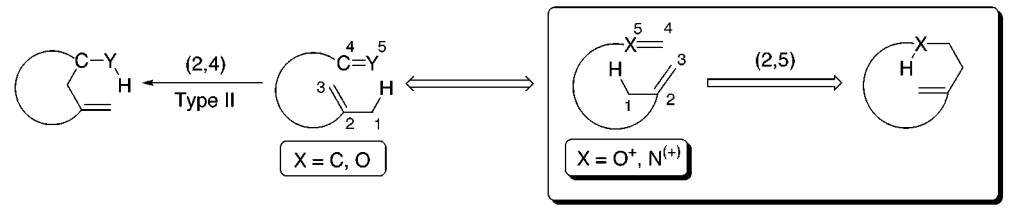
Scheme 1



Scheme 2



Scheme 3

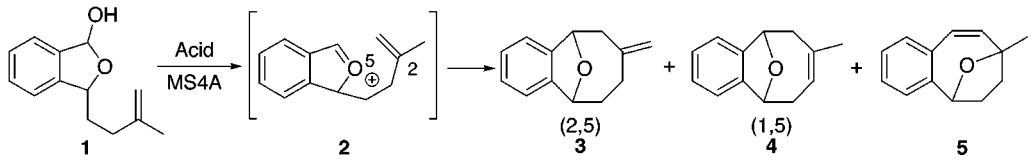


Table 1. Oxonium-ene Reactions Using Various Solid Acids[a]

entry	acids	yield (%)[b]	(2,5) selectivity (%)[c]
1	Montmorillonite K10	47	79
2	Amberlyst 15E	68	37
3	Amberlite IR-120B	0[d]	
4	Nafion	trace[e]	
5	*p*-TsOH	trace[f]	

[a] The reactions were carried out in dichloromethane at room temperature for 10 min unless otherwise noted. [b] Combined yield of **3**, **4**, and **5**. [c] Percent ratio of **3** with respect to the total amount of **3**, **4**, and **5**, determined by capillary GC. [d] The reaction mixture was stirred for 23 h. [e] For 0.5 h. [f] For 0.5 h.

Table 2. Solid Acid-Catalyzed Oxonium-ene Reaction of Lactol 1[a]

entry	acid (g/mmol of **1**)	solvent (M of **1**)	time (min)	yield (%)[b]	**3**:**4**:**5**[c]
1	K10 (0.8)	CH_2Cl_2 (0.1)	10	47	79:13:8
2	K10 (0.8)	1,4-dioxane (0.1)	20	58	26:51:23
3	K10 (0.8)	MeCN (0.1)	16 h	0	
4	K10 (0.8)	toluene (0.1)	10	40	86:10:4
5	K10 (0.8)	toluene (0.01)	10	68	86:9:5
6	K10 (2)	toluene (0.01)	10	67	55:25:20
7	K10 (2)	toluene (0.01)	0.5	66	73:14:13
8	K10 (0.4)	toluene (0.01)	0.5	44	88:8:4

[a] In the presence of MS4A (1 g/mmol of **1**). [b] Combined yield of **3**, **4**, and **5** after silica gel chromatography. [c] Determined by capillary GC.

in dilute (0.01 M of **1**) toluene solution gave a better combined yield (Table 2, entry 5). The reaction with a larger amount of K10 (2 g/mmol of **1**) gave the lower (2,5) selectivity (Table 2, entry 6). By shortening the reaction time (30 s), the (2,5) selectivity was improved up to 88% in the presence of a smaller amount of K10 (0.4 g/mmol of **1**) (Table 2, entry 8). At a lower reaction temperature (0 °C) in dichloromethane, almost the same level of the (2,5) selectivity was obtained along with a slightly decreased yield.

Significantly, the catalytic activity of K10 was found to be sensitive to its water content. The K10 used in these reactions was "activated" through dehydration by heating in vacuo. However, when the weight percent of the water content[13] in K10 was low (<2%), the only low combined yield (about 20%) was obtained after a long reaction time. These results are consistent with the nature of this solid acid; K10 functions as a Brønsted acid whose acid sites are derived from the water molecules coordinated to the cations on the framework of the clay.[14−16] Indeed, when using acetonitrile as a solvent, no ene product was obtained (vide supra), because most of the cation sites were coordinated by acetonitrile instead of water. How-

(13) The control of water content in K10 is attained as follows. First, K10 was dried completely by heating (500 °C) in vacuo (0.05 Torr) for 10 h. Then, the desired amount of water was introduced.

(14) Ballantine, J. A. In *Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood: London, 1992; Part 2, Chapter 4, pp 101−102. Laszlo, P. *Preparative Chemistry Using Supported Reagents*; Academic Press: New York, 1987.

(15) (a) Tateiwa, J.; Hashimoto, K.; Yamauchi, T. Uemura, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2361. (b) Tateiwa, J.; Kimura, A.; Takasuka,; M. Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2169.

(16) (a) In porphyrin synthesis, the cyclization is efficiently catalyzed in the clay nanospaces; Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Chem. Lett.* **1993**, 117. (b) Shinoda, T.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1995**, 493; 495.

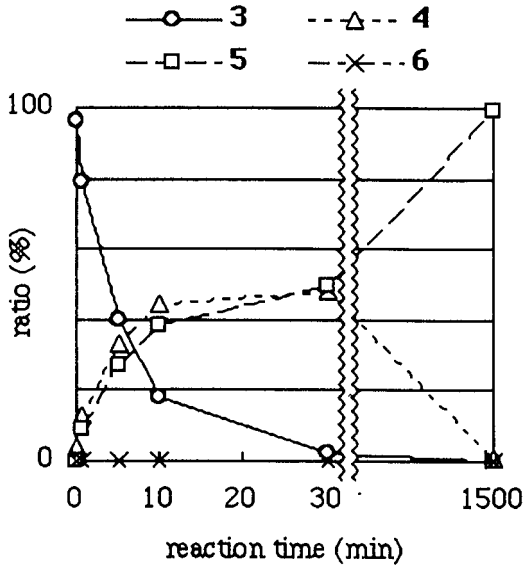
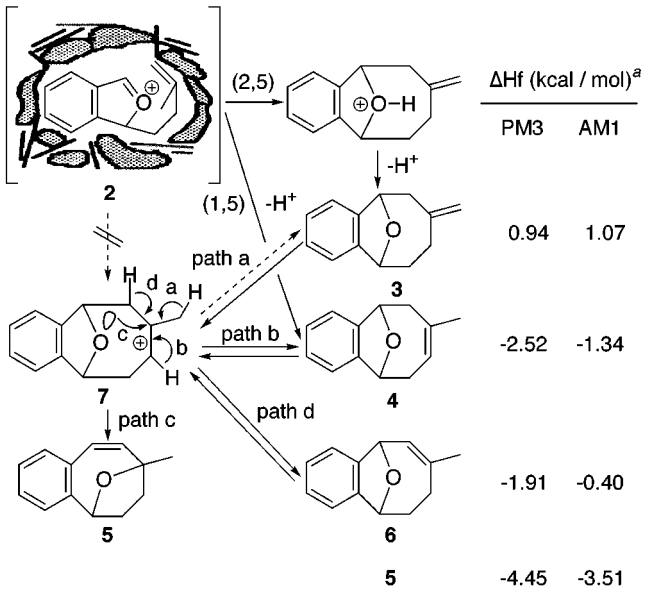


Figure 1. Isomerization of **3**.

Scheme 4



[a] Heat of formation calculated by PM3 or AM1 Hamiltonians

ever, the addition of MS4A is effective in trapping an excess amount of water generated during dehydration from the ene substrate.

Upon treatment of the purified (2,5) ene product **3**[17] under the same reaction conditions as in entries 6 and 7 (Table 2), the isomerization of **3** to **5** via **4** was observed with essentially no loss of total amount (Figure 1). The heats of formation of **3**−**6** thus deduced by PM3 and AM1 calculations indicate that the product **3** is the least thermodynamically stable product (Scheme 4). Therefore, it is unlikely that **3** was derived from the carbenium ion **7** by elimination of a proton from the terminal methyl (path a) in preference to the internal methylene group (path b or d). By contrast, **5** is found to be the most thermodynamically stable. It should be emphasized here again that almost no starting lactol **1** remained under these experimental conditions, even after 30 s! It is safe to say that the ene cyclization is so rapid that it gives the (2,5) ene product **3** as the kinetic product and that the isomerization follows to give **4**, **6**, and eventually **5**.

(17) The (2,5) ene product **3** was isolated by column chromatography on silver nitrate-doped silica gel (Et_2O−hexane, 1:10).

Conclusions

The present K10-catalyzed ene cyclization of the oxonium ion is the first example of the (2,5) ene cyclization. This regiochemical fidelity is consistent with the direct conversion of the oxonium ion to the (2,5) ene product by an intramolecular ene pathway involving the hydrogen shift of the methyl protons with close proximity to the oxonium ion in the mesopore of K10[16] (Scheme 4). A solid acid catalyst makes the reaction and the following workup easy to carry out, and the catalyst can be recycled to reduce the waste material. Therefore, this newly developed reaction is regarded as an environmentally benign reaction.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on a glass plate precoated with silica gel 60 (70−230 mesh) purchased from Kanto Chemical Co., Inc. Column chromatography was performed on Merck Kieselgel 650. Silver nitrate-doped silica gel was prepared by suspending silica gel in acetonitrile, adding 10 wt % of silver nitrate dissolved in acetonitrile, stirring thoroughly, and then removing the solvent in vacuo at 50 °C. Molecular sieves (MS4A, activated powder) were purchased from Aldrich Chemical Co. All experiments were carried out under argon atmosphere unless otherwise noted.

Preparation of 3-(3-methyl-3-butenyl)-1,3-dihydro-2-benzofuran-1-ol (1). 3-(3-Methyl-3-butenyl)-2-benzofuran-1(3*H*)-one. To a stirring solution of diisopropylamine (4.95 mmol, 37.8 mmol) and dry THF (60 mL) at −78 °C was added *n*-BuLi (11.7 mL of 1.54 M solution in hexane, 17.96 mmol). The reaction mixture was maintained at −78 °C for 20 min, at 0 °C for 20 min, and at −78 °C again. The solution of *o*-phthalaldehydic acid (2.84 g, 18.9 mmol) and dry THF (50 mL) was then added. The resulting solution was maintained at −78 °C for 1 h, and 3-methyl-3-butenylmagnesium bromide (50.4 mL of 0.45 M solution in ether, 22.68 mmol) was added and allowed to warm to room temperature. The reaction mixture was immersed for 2.5 h and then poured into 1 N HCl. The aqueous phase was extracted with ethyl acetate several times, and the combined organic phase was rinsed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (Et_2O−hexane, 1:3) to afford 2.72 g (71.1%) of 3-(3-methyl-3-butenyl)-2-benzofuran-1(3*H*)-one: ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.85−1.92 (m, 1H), 2.16−2.28 (m, 3H), 4.73 (s, 1H), 4.78 (s, 1H), 5.51 (dd, J = 3.0, 8.1 Hz, 1H), 7.46 (dd, J = 0.9, 7.5 Hz, 1H), 7.54 (dd, J = 7.5, 7.5 Hz, 1H), 7.69 (dd, J = 0.9, 7.5, 7.8, 1H), 7.91 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 32.7, 32.8, 80.7, 110.9, 121.6, 125.6, 126.1, 129.0, 133.9, 144.0, 149.8, 170.4; IR (neat) 2942, 1763, 1651, 893 cm^{-1}.

3-(3-Methyl-3-butenyl)-1,3-dihydro-2-benzofuran-1-ol (1). To a stirring solution of 3-(3-methyl-3-butenyl)-2-benzofuran-1(3*H*)-one (659.4 mg, 3.26 mmol) and dry toluene (22.0 mL) at −78 °C was added DIBAL-H (2.6 mL of 1.5 M solution in toluene, 3.91 mmol). The reaction was maintained at −78 °C for 1.5 h, then quenched by the addition of sat. Na_2SO_4 and allowed to warm to room temperature. To the mixture was added Na_2SO_4. The mixture was stirred for 1 h, then filtered, and concentrated. The residue was purified by column chromatography (Et_2O−hexane, 1:2) to afford 657.1 mg (99%) of 3-(3-methyl-3-butenyl)-1,3-dihydro-2-benzofuran-1-ol (**1**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3H),1.75 (s, 3H), 1.79−2.29 (m, cis/trans-4H), 3.43−3.58 (bs, cis/trans-1H), 4.69−4.73 (m, cis/trans-2H), 5.17 (dd, J = 3.8, 7.7 Hz, trans-1H), 5.43 (ddd,

J = 2.1, 2.4, 7.2 Hz, cis-1H), 6.42 (d, J = 8.4 Hz, trans-1H), 6.48 (dd, J = 2.1, 8.1 Hz, cis-1H), 7.20−7.44 (m, cis/trans-4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 32.9, 33.3, 34.0, 35.5, 82.0, 82.7, 100.5, 100.6, 109.9, 110.0, 121.0, 121.1, 122.9, 123.0, 127.9, 129.1, 129.2, 139.1, 139.3, 142.2, 142.3, 145.2, 145.3; IR (neat) 3388, 2934, 1651, 1114, 888 cm^{-1}; FAB-MS m/z = 227 ([M + Na]$^+$); HRMS (FAB$^+$) calcd for $C_{13}H_{16}O_2Na$ 227.1049, found 227.1042 ([M + Na]$^+$).

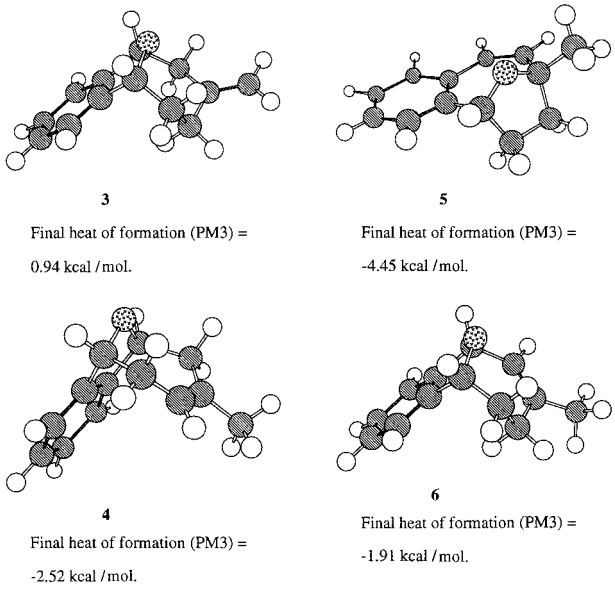
General Procedure for the Montmorillonite K10-Catalyzed Oxonium Ene Reaction of the 3-(3-Methyl-3-butenyl)-1,3-dihydro-2-benzofuran-1-ol (1). To a stirring solution of 3-(3-methyl-3-butenyl)-1,3-dihydro-2-benzofuran-1-ol (**1**) (113 mg, 0.55 mmol) and toluene (5.5 mL) at room temperature in the presence of MS4A (0.55 g, 1 g/mmol) was added Montmorillonite K10 (0.44 g, 0.8 g/mmol) which was activated by heating in vacuo. The reaction was maintained at room temperature for 10 min, then quenched by filtration through Celite, and concentrated. The residue was purified by column chromatography on silica gel (Et_2O−hexane, 1:10) to afford the mixture of cyclized products.

(2,5) Ene Product 3. The (2,5) ene product was separated by column chromatography on silver nitrate-doped silica gel (Et_2O−hexane, 1:10) to obtain (2,5) ene product (**3**): 96% purity by GC analysis; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64−1.74 (m, 2H), 2.06−2.23 (m, 2H), 2.45 (dd, J = 0.9, 14.4 Hz, 1H), 2.98 (dd, J = 6.6, 14.4 Hz, 1H), 4.55 (s, 1H), 4.68 (s, 1H), 5.44 (d, J = 6.6 Hz, 1H), 5.48 (d, J = 5.7 Hz, 1H), 7.12−7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 36.1, 45.7, 80.3, 82.3, 114.6, 120.3, 120.4, 127.4, 127.5, 142.7, 143.5, 146.6; IR (neat) 2932, 1642, 1046, 893 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{13}H_{15}O$ 187.1123, found 187.1121 ([M + H]$^+$).

Isomerized Product 5. To the solution of the mixture of cyclized products (91.4 mg, 0.491 mmol, **3**:**4**:**5**:**6** = 83:10:5:2) and CH_2Cl_2 (6 mL) at 0 °C was added TMSOTf (104 μL, 0.54 mmol). The reaction was allowed to warm to room temperature and was then heated to reflux for 7 h. The reaction was cooled and was poured into saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (Et_2O−hexane, 1:10) to afford 71.7 mg (78.4%) of pure isomerized product **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 3H), 1.87−1.98 (m, 1H), 2.02−2.14 (m, 1H), 2.30−2.48 (m, 2H), 5.13 (dd, J = 5.7, 8.7 Hz, 1H), 5.88 (d, J = 12 Hz, 1H), 6.32 (d, J = 12 Hz, 1H), 7.08−7.24 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 34.3, 46.7, 82.1, 84.6, 126.1, 127.0, 127.1, 128.0, 132.2, 133.4, 138.5, 144.8; IR (neat) 2974, 1638, 1106, 731 cm^{-1}; FAB-MS m/z = 187 ([M + H]$^+$), 186 ([M$^{\bullet}$]$^+$); HRMS (FAB$^+$) calcd for $C_{13}H_{15}O$ 187.1123, found 187.1128 ([M + H]$^+$).

Isomerized Products 4 and 6. The ^{1}H NMR, H−H COSY, and C−H COSY spectra for the mixture of **3**, **4**, and **6** (see the Supporting Information) show that the difference between **4** and **6** is the existence of the coupling between olefinic proton and methylene protons of **4**. For the mixture of **3**, **4**, and **6**: FAB-MS m/z = 187 ([M + H]$^+$).

PM3 and AM1 Calculations on the Heats of Formation. The structures were fully optimized by PM3 and AM1 calculations (Mopac version 6.10 ran on a Tektronix CAChe: CAChe MOPAC version 94 molecular modeling workstation).



Supporting Information Available: ^{1}H NMR, H−H COSY, and C−H COSY spectral data for the mixture of **3**, **4**, and **6** (4 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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