JOC Article

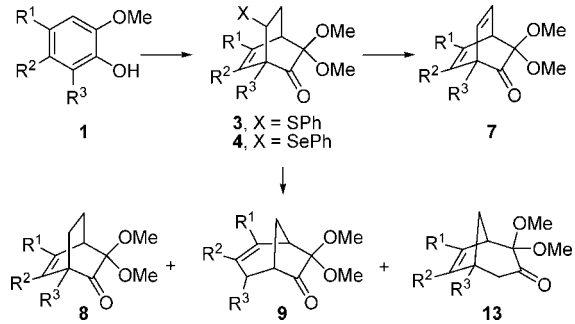
Efficient Synthesis and Subsequent Transformations of Phenylsulfanylbicyclo[2.2.2]octenones and Phenylselenylbicyclo[2.2.2]octenones

Shih-Yu Gao, Santhosh Kumar Chittimalla, Gary Jing Chuang, and Chun-Chen Liao*

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan, and Department of Chemistry, Chung Yuan Christian University, Chungli 32023, Taiwan

ccliao@mx.nthu.edu.tw

Received October 15, 2008



Inverse-electron-demand Diels−Alder reactions of masked *o*-benzoquinones **2** with phenyl vinyl sulfide and phenyl vinyl selenide furnished highly functionalized bicyclo[2.2.2]octenone derivatives **3** and **4**, respectively, in excellent regio- and stereoselectivities and yields up to 90%. The bicyclo[2.2.2]octenone derivatives **3** with the sulfur functionality were subjected to an oxidation−elimination process to furnish bicyclo[2.2.2]octadienone systems **7** in good yields. During the reduction process, the Diels−Alder adducts **3e** and **4e** led to **8**, whereas the carbon-centered radicals generated from the other adducts **3a**−**d** and **4a**−**d** provided various rearranged products **9**−**13** depending on the substitution pattern and reagents utilized (Raney-Ni or *n*-Bu_3SnH). Surprisingly these radicals showed preference for the carbonyl functionality to the olefinic double bond, leading to interesting rearrangement reactions of mechanistic importance and possible synthetic utility. Interestingly the alcohols obtained from the reduction of Diels−Alder adducts **3a**−**d** underwent desulfurization smoothly to give desulfurized products in high yields; thus a detoured method of "reduction−desulfurization−oxidation" provides an entry to desulfurized bicyclo[2.2.2]octenones without rearrangement.

Introduction

Designing effective and short routes for the stereoselective construction of polycyclic molecules is one of the main challenges in synthetic organic chemistry. Conceptually new methods for the construction of highly functionalized systems need to be developed. In this perspective, as a building block for rapid and efficient synthesis of structurally complex frameworks, bicyclo[2.2.2]octenone systems hold great promise for eventual applications in the total syntheses of natural products.[1] These bicyclic derivatives can be obtained via the Diels−Alder reactions of suitably substituted masked *o*-benzoquinones (MOBs) with appropriate dienophiles. Our laboratory has succeeded in developing several strategies based on bicyclo[2.2.2]-octenone derivatives and as a part of the effort to demonstrate the versatility of the developed strategies, these processes were utilized as key steps in the synthesis of *cis*-decalin natural products such as (±)-clerodane diterpenic acids,[2a,b] (±)-eremopetasidione,[2c] (±)-3β-methacryloyloxyfuranoeremophilane,[2d] (±)-3β-angeloyloxyfuranoeremophilane,[2d] refuted (±)-bilosespenes A and B,[2e] triquinane-based natural products like (±)-magellanine[3] and (±)-capnellene,[1h] and other natural products such as (±)-reserpine,[4a] (±)-forsythide aglucone dimethyl ester,[4b] (±)-annuionone, and (±)-tanarifuranonol.[4c] Another area of our interest is the photochemical rearrangements of highly substituted heteroarene-fused barrelenes.[5] Compared to barrelenes and benzobarrelenes, heteroarene-fused barrelenes may have complicated reaction mechanisms due to the additional

10.1021/jo802295p CCC: $40.75
Published on Web 01/20/2009

n,π^* states.[5g,i] In the context of studying the competitive aptitude of several possible reaction pathways in these reactions, easy access to bicyclo[2.2.2]octadienones were needed as suitable precursors for further manipulations to deliver the necessary heteroarene-fused barrelenes.[5g,i]

Organosulfur compounds are used as versatile reagents in organic synthesis and bio-organic and medicinal chemistry.[6] They can be prepared with great ease and possess a large range of applications, as the sulfur functionality can easily be removed or subjected to a variety of reactions to achieve interconversions of useful functional groups. Phenyl vinyl sulfide was extensively used as an electron-rich alkene in [1 + 2],[7a] [2 + 2],[7b−d] [3 + 2],[7e,f] and [4 + 2][7g] cycloaddition reactions. Organoselenium and organosulfur chemistries are closely related, and yet each one has its own advantages and disadvantages.[8] Phenyl vinyl sulfide or phenyl vinyl selenide are valuable dienophiles that can both act as ethylene and acetylene equivalents. With the extensive sulfide and selenide chemistry and highly reactive MOB building blocks in hand, we have investigated the Diels−Alder reactions of phenyl vinyl sulfide/selenide with various MOBs and contemplated that their cycloadducts would be potentially useful. Initially the bicyclo[2.2.2]octenones were sought and subsequently converted to the bicyclo[2.2.2]-octadienones, which can be further transformed to the desired heteroarene-fused barrelenes for photochemical studies. A C−S or C−Se bond can also be homolytically cleaved to generate a radical. For many years, radical reactions have drawn the attention of organic chemists from both mechanistic and synthetic perspectives.[9] Though radical species are known to be reactive in both neucleophilic and electrophilic fashions, radicals are not solvated like cations, and the rates of radical reactions are thus less solvent-dependent. Addition of carbon-centered radicals to alkenes and alkynes are usually exothermic and irreversible, whereas the addition to carbon heteroatom multiple bonds can be reversible.[9e] The addition of a radical to a π-bond followed by fragmentation of a different bond accomplishes a group transfer reaction. A radical generated on these functionally rich bridged cycloadducts could in principle give rise to several interesting transformations through usual or unusual mechanisms. The sulfide or the selenide functionality present in the phenylsulfanyl or selenylbicyclo[2.2.2]octenones can be exploited for the generation of bicyclo[2.2.2]octenone radicals. Thus, we proposed a systematic study on the fate of the bicyclo[2.2.2]octenone radicals generated from phenylsulfanyl/selenyl bicyclo[2.2.2]octenones, which in turn were obtained from the Diels−Alder reactions between MOBs and phenyl vinyl sulfide/selenide. Recently Marko and co-workers found that lactone-group-bearing compounds of the bicyclo[2.2.2] skeleton embedded with a sulfide/selenide underwent radical rearrangement with reducing agents Raney nickel (Raney-Ni) or *n*-Bu_3SnH to give bicyclo[3.3.0]octane derivatives in good yields.[10] Herein we present a full account of our investigations on the Diels−Alder reactions of MOBs with phenyl vinyl sulfide[12] and phenyl vinyl selenide. Interestingly, the radical generated on these systems showed preferential addition to carbonyl functionality (oxa-di-π-methane type) rather than the olefinic double bond (di-π-methane type) in the reaction. This unusual behavior was studied by selecting differently substituted bicyclo[2.2.2]octenone systems with the hope of finding a proper reason for their unique reaction pathway in radical chemistry. These reactions at first sight look to have a di-π-methane or oxa-di-π-methane rearrangement-type reaction pathways. Though the fate of electronically excited triplets cannot be compared with that of the radicals in the ground states, we recently reported, during our study of photochemical reactions on bicyclo[2.2.2]octadienones, the competition between di-π-methane and oxa-di-π-methane bridgings.[5,11]

Results and Discussion

Diels−Alder Reactions of MOBs 2a−g with Phenyl Vinyl Sulfide and Phenyl Vinyl Selenide. At the outset, the inverse-electron-demand Diels−Alder reactions of various MOBs generated in situ from 2-methoxyphenols with phenyl vinyl sulfide were studied. In most cases, the competition between self-dimerization of MOB and the Diels−Alder reaction with the added dienophile is often observed, though to a varying degree. To avoid or suppress the undesired dimerization, several

(1) (a) Ho, T.-L. In *Carbocyclic Ring Construction in Terpene Synthesis*; VCH: Weinheim, Germany, 1988. (b) Deslongchamps, P.; Belanger, A.; Berney, D. J. F.; Boreschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; Maclachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 115. and 127. (c) Liao, C.-C. In *Modern Methodology in Organic Synthesis* ; Kodansha: Tokyo, 1992, p 409. (d) Quideau, S.; Pouységu, L. *Org. Prep. Proced. Int.* **1999**, *31*, 617. (e) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324. (f) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (g) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (h) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221. (i) Hsu, D.-S.; Liao, C.-C. *Org. Lett.* **2007**, *9*, 4563. (j) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292.

(2) (a) Lee, T.-H.; Liao, C.-C. *Tetrahedron Lett.* **1996**, *37*, 6869. (b) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912. (c) Hsu, D.-S.; Hsu, P.-Y.; Liao, C.-C. *Org. Lett.* **2001**, *3*, 263. (d) Hsu, D.-S.; Hsu, P.-Y.; Lee, Y.-C.; Liao, C.-C. *J. Org. Chem.* **2008**, *73*, 2554. (e) Hsu, D.-S.; Liao, C.-C. *Org. Lett.* **2003**, *5*, 4741.

(3) Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090.

(4) (a) Chu, C.-S.; Liao, C.-C.; Rao, P. D. *Chem. Commun.* **1996**, 1537. (b) Liao, C.-C.; Wei, C.-P. *Tetrahedron Lett.* **1989**, *30*, 2255. (c) Shiao, H.-Y.; Hsieh, H.-P.; Liao, C.-C. *Org. Lett.* **2008**, *10*, 449.

(5) (a) Liao, C.-C.; Hsieh, H.-P.; Lin, S.-Y. *J. Chem. Soc., Chem. Commun.* **1990**, 545. (b) Liao, C.-C.; Lin, S.-Y.; Hsieh, H.-P.; Yang, P.-H. *J. Chin. Chem. Soc. (Taipei)* **1992**, *39*, 275. (c) Liao, C.-C. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Soon, P. S., Eds.; CRC Press: New York, 1995; pp 194−203. (d) Chou, C.-H.; Peddinti, R. K.; Liao, C.-C. *Heterocycles* **2001**, *54*, 61. (e) Liao, C.-C. *Chemistry (Chem. Soc., Taipei; in Chinese)* **2001**, *59*, 163–179. (f) Lin, S.-Y.; Hsieh, H.-P.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron Lett.* **2003**, *44*, 8761. (g) Liao, C.-C.; Peddinti, R. K. *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; CRC Press: Boca Raton, FL, 2004,pp 32/1−32/17. (h) Chen, A.-C.; Chuang, G. J.; Villarante, N. R.; Liao, C.-C. *J. Org. Chem.* **2007**, *72*, 9690. (i) Chen, A.-C.; Lin, S.-Y.; Villarante, N. R.; Chuang, G. J.; Wu, T.-C.; Liao, C.-C. *Tetrahedron* **2008**, *64*, 8907.

(6) (a) McReynolds, M. D.; Doughtery, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (b) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: New York, 1996; pp 1−262. (c) Oae, S.; Okuyama, T. *Organosulfur Chemistry: Biochemical Aspects*; CRC Press: Boca Raton, FL, 1992; pp 1–260. (d) *Handbook of Chalcogen Chemistry: New Perspectives in Sulfur, Selenium and Tellurium*; Devillanova, F. A., Ed.; Royal Society of Chemistry: London, 2006.

(7) (a) Weber, A.; Sabbioni, G.; Galli, R.; Stampfli, U.; Neuenshwander, M. *Helv. Chim. Acta* **1988**, *71*, 2026. (b) Bruckner, R.; Huisgen, R. *Tetrahedron Lett.* **1990**, *31*, 2561. (c) Sugimura, H.; Osumi, K. *Tetrahedron Lett.* **1989**, *30*, 1571. (d) Pabon, R. A.; Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1984**, *106*, 2730. (e) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (f) Tsuge, O.; Kanemasa, S.; Sakamoto, K.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2513. (g) Gupta, R. B.; Franck, R. W.; Onan, K. D.; Soll, C. E. *J. Org. Chem.* **1989**, *54*, 1097, and references therein.

(8) (a) Comasseto, J. V. *J. Organomet. Chem.* **1983**, *253*, 131. (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*: Pergamon Press: New York, 1986. (c) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

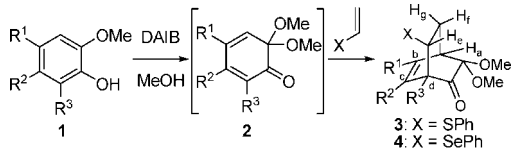
(9) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, Chapters 4.1 and 4.2. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Giese, B. *Tetrahedron* **1985**, *41*, 3887. (e) Giese, B. *Angew. Chem., Int. Ed.* **1983**, *22*, 753.

(10) Marko, I. E.; Warriner, S. L.; Augustyns, B. *Org. Lett.* **2000**, *20*, 3123.

(11) (a) Chang, S.-Y.; Huang, S.-L.; Villarante, N. R.; Liao, C.-C. *Eur. J. Org. Chem.* **2006**, 4648. (b) Yang, M.-S.; Lu, S.-S.; Rao, C. P.; Tsai, Y.-F.; Liao, C.-C. *J. Org. Chem.* **2003**, *68*, 6543.

(12) Gao, S.-Y.; Lin, Y.-L.; Rao, P. D.; Liao, C.-C. *Synlett* **2000**, 421.

TABLE 1. Diels−Alder reactions of MOBs 2a−g with Phenyl Vinyl Sulfide and Phenyl Vinyl Selenide



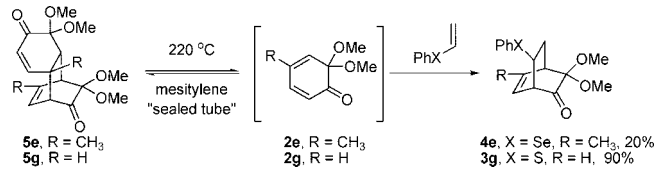
	R^1	R^2	R^3
a	CO_2Me	H	H
b	COMe	H	H
c	CO_2Me	H	OMe
d	H	CO_2Me	H
e	Me	H	H
f	CN	H	H
g	H	H	H

entry	phenol	MOB	dienophile/ equiv	method[a]/ temp	time, h	adduct (yield %[b])
1	**1a**	**2a**	X = SPh/4	B/rt	1	**3a** (85)
2	**1b**	**2b**	X = SPh/4	A/rt	0.5	**3b** (84)
3	**1c**	**2c**	X = SPh/4	B/50 °C	1	**3c** (89)
4	**1d**	**2d**	X = SPh/4	B/50 °C	1	**3d** (90)
5	**1e**	**2e**	X = SPh/4	B/reflux	1	**3e** (58)
6	**1f**	**2f**	X = SPh/20	B/rt	1	**3f** (58)
7	**1g**	**2g**	X = SPh/10	B/rt	1	**3g** (30)
8	**1a**	**2a**	X = SePh/10	A/rt	0.5	**4a** (87)
9	**1a**	**2a**	X = SePh/4	A/rt	0.5	**4a** (87)
10	**1a**	**2a**	X = SePh/10	B/50 °C	1	**4a** (50)
11	**1b**	**2b**	X = SePh/4	A/rt	0.5	**4b** (90)
12	**1b**	**2b**	X = SePh/10	B/50 °C	1	**4b** (24)
13	**1c**	**2c**	X = SePh/10	A/rt	1	**4c** (6)
14	**1c**	**2c**	X = SePh/10	B/50 °C	2	**4c** (70)
15	**1d**	**2d**	X = SePh/10	A/rt	1	**4d** (7)
16	**1d**	**2d**	X = SePh/10	B/50 °C	1	**4d** (16)
17	**1d**	**2d**	X = SePh/10	B/50 °C	3	**4d** (30)
18	**1e**	**2e**	X = SePh/10	A/rt	4.5	**4e** (7)

[a] See Experimental Section. [b] The yields are of isolated products.

procedures were developed to obtain the desired DA adducts in good yields.[13,14] Owing to the electron-rich nature of phenyl vinyl sulfide, initially we envisioned that electron-deficient MOB **2a** generated from methyl vanillate could be a potential starting point. Consequently, the inverse-electron-demand Diels−Alder reaction between phenyl vinyl sulfide with MOB **2a** gave 85% yield of the expected adduct **3a**. As a result, the present reaction was investigated with variously substituted MOBs. The reaction conditions providing the optimal results in each case are listed in Table 1. In general, 4 equiv of phenyl vinyl sulfide was used. Except for 6,6-dimethoxycyclohexa-2,4-dienone (**2g**), which is prone to self-dimerization to give **5g**, other MOBs **2a−f** provided good to excellent yields of Diels−Alder adducts with phenyl vinyl sulfide. In our recent studies on the inverse-electron-demand Diels−Alder reactions, dienophiles benzyl vinyl ether and dihydrofuran provided lower yields of cycloadducts with MOB **2g**, along with substantial amounts of dimer. A marginal improvement in the yield of bicyclo[2.2.2]octenone **3g** was observed by utilizing a domino rDA/DA protocol (Scheme 1) recently developed in our laboratory.[14] The reactivity of MOB **2e** with an electron-donating methyl group toward inverse-electron-demand Diels−Alder reaction was lower than expected, and only 58% of the Diels−Alder adduct was obtained. The reason for the low yield of adduct **3f** is not clear,

SCHEME 1. Domino Retro-Diels−Alder/Diels−Alder Procedure To Generate 3g and 4e



but MOB **2f** has shown similar results in our previous studies.[13a] The importance of this method, which allows the one-pot assembly of the highly substituted bicyclo[2.2.2]octenone framework from readily available starting materials under mild conditions in high yields, may be underscored. The encouraging results obtained with phenyl vinyl sulfide and MOBs prompted us to attempt to explore the effectiveness of phenyl vinyl selenide in the inverse-electron-demand Diels−Alder reaction. Phenyl vinyl selenide, prepared following the reported procedure,[15] though closely related to phenyl vinyl sulfide, was found to be less reactive in the inverse-electron-demand Diels−Alder reaction with MOBs. Nevertheless, the reactions worked smoothly, and the corresponding products could be isolated in excellent to moderate yields with high selectivities when 10 equiv of the dienophile was utilized (Table 1). Though MOBs **2a−c** furnished good yields of expected Diels−Alder adducts with phenyl vinyl selenide, MOBs **2d** and **2e** afforded the corresponding adducts in much lower yields. Attempts at improving the yield of **4e** utilizing the detour method (domino retro-Diels−Alder/Diels−Alder procedure)[14] from the dimer of MOB **2e** with phenyl vinyl selenide proved to be partially successful furnishing adduct **4e** in 20% yield (Scheme 1).

It is noteworthy that in all cases studied the Diels−Alder reactions of MOBs with both phenyl vinyl sulfide and phenyl vinyl selenide had excellent regio- and stereoselectivity. Structures of all the adducts were unambiguously identified with ^{1}H NMR, ^{13}C NMR, DEPT, and high- and low-resolution mass spectroscopy. For most of the high-resolution mass spectra recorded in electron impact mode (70 eV), the peaks corresponding to the molecular ion (M^+) could not be seen; instead the peaks corresponding to $[M - CO]^+$ were observed, indicating that the extrusion of CO resulted from facile fragmentation. All the cycloadducts exhibited IR absorptions at 1732−1755 cm^{-1} due to the characteristic features of the carbonyl functional group adjacent to α,α-dimethoxyl groups in a functionalized bicyclo[2.2.2]octenone skeleton. Stereo- and regioselectivities were ascertained by extensive decoupling experiments and comparing the δ and J coupling constants with that of similar reported compounds.[13] As a result of the deshielding effect by the methoxy group, H_f appeared at δ 2.51−2.64, whereas H_e appeared at δ 1.21−1.65, thus proving the assigned regiochemistry (structure of compound **3/4** depicted in Table 1). The coupling constants $J(H_e-H_f)$ = 9.0−9.6 Hz and $J(H_e-H_g)$ = 4.8−6.0 Hz showing the *cis* and *trans* relation, respectively, could confirm the assigned stereochemistry. The regioselectivities observed in the present study have literature precedents, due to the greater influence of the carbonyl functionality than the two methoxy groups present on the MOB moiety.[13]

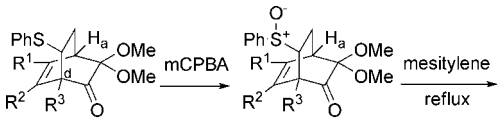
Synthesis of Bicyclo[2.2.2]octadienones 7a−d,f from Bicyclo[2.2.2]octenones 3a−d,f. With the installation of sulfur

(13) (a) Gao, S.-Y.; Ko, S.; Lin, Y.-L.; Peddinti, R. K; Liao, C.-C. *Tetrahedron* **2001**, *57*, 297. (b) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Hsiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102. (c) Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Rao, N. S. K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 6493.

(14) (a) Chittimalla, S. K.; Liao, C.-C. *Synlett* **2002**, 565. (b) Chittimalla, S. K.; Shiao, H.-Y.; Liao, C.-C. *Org. Biomol. Chem.* **2006**, *6*, 2267.

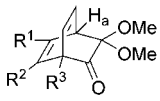
(15) (a) Hagiwara, H.; Sakai, H.; Kirita, M.; Suzuki, T.; Ando, M. *Tetrahedron* **2000**, *56*, 1445. (b) Keefer, L. K.; Lunn, G. *Chem. Rev.* **1989**, *89*, 459.

SCHEME 2. Versatile Synthesis of Bicyclo[2.2.2]octadienones 7 from Bicyclo[2.2.2]octenones 3



3 6

	R^1	R^2	R^3
a	CO_2Me	H	H
b	COMe	H	H
c	CO_2Me	H	OMe
d	H	CO_2Me	H
f	CN	H	H



7

Yield for two steps
7a, 68%: **7b**, 59%: **7c**, 39%, **7d**, 57%: **7f**, 66%

and selenide functionalities in the bicyclic systems, a selected set of adducts **3a**−**d** and **3f** were subjected to the oxidation−elimination reaction sequence. The oxidation of the sulfide moiety to the corresponding sulfoxides **5** was accomplished by standard *m*CPBA reaction condition, and the obtained crude reaction mixtures were refluxed in mesitylene; much to our satisfaction, the bicyclo[2.2.2]octadienones **7** were obtained in good yields (Scheme 2) in all the cases studied irrespective of the nature and the position of the substitution. The appearance of two newly formed olefinic protons at 6.41−6.53 ppm and the proton shift changes of the bridge-head hydrogens (Scheme 2, H_a changed from 2.98−3.67 to 4.51−4.72 and H_d changed from 3.25−3.83 to 4.13−4.14) confirmed the formation of the bicyclo[2.2.2]octadienone systems. Similar to their parent compounds, these bicyclo[2.2.2]octadienones have also shown the $[M - CO]^+$ peak instead of the molecular ion (M^+) in the high-resolution mass spectra recorded. Thus, this reaction sequence provides an expedient route to highly functionalized bicyclo[2.2.2]octadienone systems. These structural frameworks are highly promising as the key starting points for the synthesis of heteroarene-fused barrelenes of photochemistry interest.[5h] To explore the possibility of reducing a synthetic step, phenyl vinyl sulfoxide was subjected for the Diels−Alder reaction with MOB **2a**, but only exclusive formation of dimer **5a** and no trace of expected adduct **6a** was observed. We then expected the formation of the bicyclo[2.2.2]octadienone system **7a** from domino retro-Diels−Alder/Diels−Alder procedure from the dimer **5a** and phenyl vinyl sulfoxide as shown in Scheme 1. Unfortunately, this method led only to untractable reaction mixtures.

Reduction of Diels−Alder Adducts 3a−g with Raney Nickel. Raney-Ni is a versatile reducing reagent, capable of many interesting transformations conveniently with unique selectivity among various functional groups, including hydrogenolysis of the C−S bond. Intrigued by the possibility that the phenylthio moiety present in **3** could be hydrogenolyzed to generate bicyclo[2.2.2]octenone **8,** a cycloadduct formally derived from ethylene and a masked *o*-benzoquinone, we carried out the reactions of **3** with Raney-Ni. Thus, treatment of **3a** with Raney-Ni in ethanol for 15 min provided 36% of desulfurization product **8a** along with 10% of rearranged bicyclo[3.2.1]octenone **9a** and the over-reduced compound bicyclo[2.2.2]octanone **10a** in 25% yield. The reduction of conjugated double bonds in the presence of Raney-Ni is a well-known phenomenon,[15b] and thus the formation of compound **10a** was not surprising. At shorter exposures to Raney-Ni or at a higher concentration of **3a**, **8a** was produced in higher yields without affecting the chemical yield of **9a**. Thus, to improve the yield of compound **8a**, the reaction was carried out in the presence of pyrrolidine to reduce the reactivity of Raney-Ni, which could potentially increase the selectivity of the reduction of the sulfides.[18] Interestingly, this procedure increased selectivity for the formation of rearranged product **9a** to 30%. Formation of the bicyclo[3.2.1]octane skeleton from the bicyclo[2.2.2]octane system is a very useful method in organic synthesis,[16a−c] as these moieties are found as a subunit in many bioactive sesqui- and diterpenes.[17] Though the yield of **9a** is synthetically not acceptable, we obtained an interesting and unique sequence to obtain bicyclo[3.2.1]octene skeleton from the corresponding bicyclo[2.2.2]octene. Similarly, the reaction of acetovanillin-derived cycloadduct **3b** with Raney-Ni furnished **8b** in 42% yield along with 16% of **9b**. However, after considerable experiments, the yield of bicyclo[3.2.1]octenone **9b** could be successfully improved to 50% by performing the reaction in the presence of pyrrolidine. We were able to obtain **8c** and **11c** in better quantities from **3c** based on the reaction conditions. When the position of electron-withdrawing substitution was changed as in cycloadduct **3d**, treatment with Raney-Ni provided desulfurization product **8d** in 39% yield; however, the bicyclo[3.2.1]octenone **9d** was formed in poor yield. Consequently, a change in product distribution could be found with the variation of the reaction conditions. The extent to which the products are formed reflects the competition between the hydrogen abstraction and radical isomerization. Regardless of the position of the substitution in the starting compounds, in all cases studied, the reactions showed the same types of products formed from competing mechanistic pathways. Interestingly, no rearrangement was observed for the reduction of creosol-derived adduct **3e**, from which the clean reaction gave **8e** in 90% yield. Hence, the position and nature of substitution in the starting compound plays a role in this rearrangement reaction.

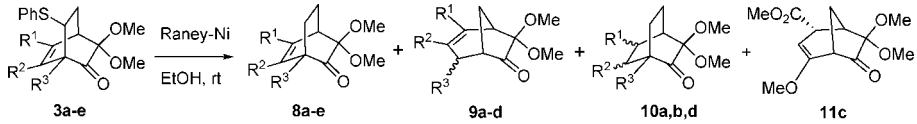
Reduction of Diels−Alder Adducts 3a−g with *n*-Bu_3SnH. We then examined the reactions of **3** with tri-*n*-butyltin hydride (*n*-Bu_3SnH) in the presence of radical initiator azobisisobutyronitrile (AIBN). Thus treatment of **3a** with *n*-Bu_3SnH and AIBN in refluxing toluene for 15 min yielded 17% of bicyclo[3.2.1]octenone **9a** and 60% of bicyclo[3.2.1]octadienol **12a** together with 7% of **11a**. Interestingly, no **8a** was observed. At first view, the reaction looks to have taken a complicated pathway, but at closer observation it is clear that compounds **9a** and **11a** are different only at the double bond position and could have been derived from a common intermediate as in the case of Raney-Ni. Compound **12a** should have been formed via a completely different mechanism. Even when the reaction was carried out in benzene for 5.5 h, compounds **9a** and **12a** were isolated in similar quantities; however, **11a** was not observed. The reaction of **3b** provided **9b** exclusively, albeit in moderate yield. The cycloadduct **3c**, upon treatment with *n*-Bu_3SnH and AIBN, afforded 58% of **12c** and 18% of a separable 5:1 epimeric mixture of **11c**. Interestingly, the reaction of **3d** in toluene provided **9d** in 52% together with 30% of bicyclo[3.2.1]octenone **13d**. In a similar observation as in the case of Raney-Ni reduction, the adduct **3e** bearing methyl

(16) (a) Hariprakash, H. K.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1997**, *38*, 5343. (b) Kim, D.; Hong, S. W.; Park, C. W. *J. Chem. Soc., Chem. Commun.* **1997**, 2263. (c) Bickel, A. F.; Knotnerus, J.; Kooyman, E. C.; Vegter, G. C. *Tetrahedron* **1960**, *9*, 230.

(17) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27.

(18) Humber, D. C.; Pinder, A. R.; Williams, R. A. *J. Org. Chem.* **1967**, *32*, 2335.

TABLE 2. Reductions of Adducts 3 with Raney Nickel



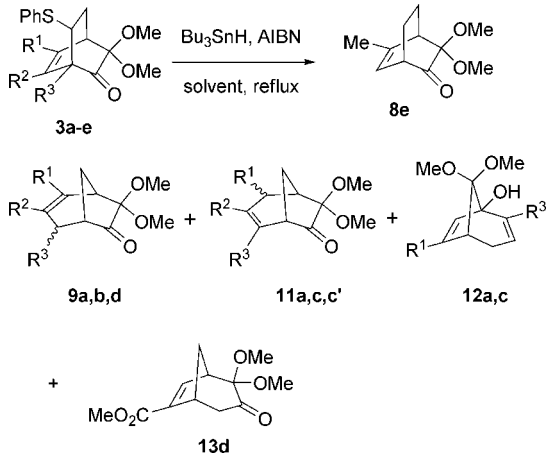
3a-e 8a-e 9a-d 10a,b,d 11c

	R^1	R^2	R^3
a	CO_2Me	H	H
b	COMe	H	H
c	CO_2Me	H	OMe
d	H	CO_2Me	H
e	Me	H	H

entry	cycloadduct	concn (M)	pyrrolidine	rxn time	yield (%)[a] 8	9 (11c)	10
1	**3a**	0.02		15 min	36	10	25
2	**3a**	0.02		6 min	58	12	7
3	**3a**	0.04		10 min	57	10	<1
4	**3a**	0.04	1 mL/14 g Raney-Ni	3 h	34	30	
5	**3b**	0.02		7 min	28	21	28
6	**3b**	0.04			42	16	16
7	**3b**	0.04	1 mL/9 g Raney-Ni	4 h	10	42	
8	**3b**	0.04	1 mL/14 g Raney-Ni	5 h	24	50	
9	**3c**	0.04		10 min	49	32[b]	
10	**3c**	0.04	1 mL/14 g Raney-Ni	2.5 h	17	49[b]	
11	**3d**	0.04		11 min	39	7	27
12	**3d**	0.04	1 mL/14 g Raney-Ni	3 h	10	22	
13	**3e**	0.04		8 min	90		

[a] Yields are of isolated products. [b] Yield of **11c.**

TABLE 3. Reductions of Adducts 3 with Tributyltin Hydride in the Presence of AIBN



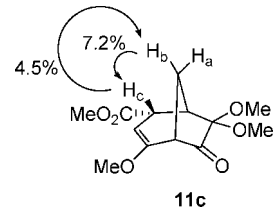
3a-e 8e 9a,b,d 11a,c,c' 12a,c 13d

entry	cyclo-adduct	concn (M)	solvent	rxn time	yield (%)[a] 8	9	11	12	13
1	**3a**	0.02	toluene	15 min		17	7	60	
2	**3a**	0.02	benzene	5.5 h		17		65	
3	**3b**	0.02	toluene	15 min		23			
4	**3c**	0.02	toluene	15 min			15 + 3[b]	65	
5	**3c**	0.02	benzene	2 h			14 + 5[b]	58	
6	**3d**	0.02	toluene	15 min		52			30
7	**3d**	0.02	benzene	2 h		48			32
8	**3e**	0.02	benzene	3 h	88				

[a] Yields are of isolated products. [b] Yields of major and minor epimers.

substitution again furnished the desulfurized product **8e** exclusively in 88% yield.

Structural Effects on the Rearrangements of Radicals Generated. All structures of the rearranged products were thoroughly characterized by standard analytical data including NOE experiments for compound **11c** and CH-COSY and HH-COSY in the case of compound **12a**. For **11c** in the NOE experiment, saturation of H_c gave rise to increased signal intensity of H_b (4.5%), while saturation of H_b brought about significant NOE effect in H_c (7.2%), proving the assigned stereochemistry (Figure 1).



11c

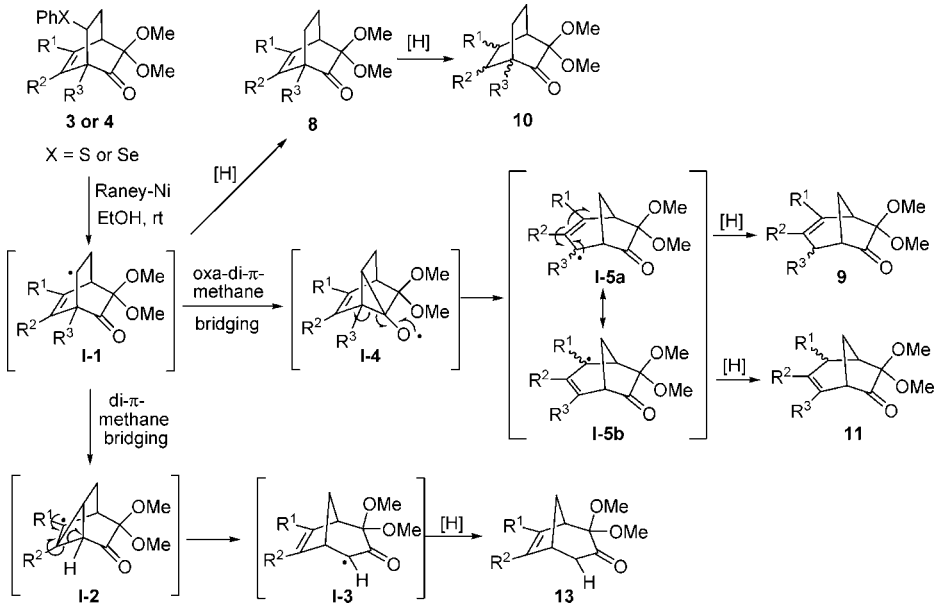
FIGURE 1. NOE experiment of **11c**.

A reasonable mechanism for the conversion using Raney-Ni of **3** into bicyclo[2.2.2]octane derivatives **8** and **10** and bicyclo[3.2.1]octenones **9** and **11** is shown in Scheme 3. The radical **I-1** generated from **3** may undergo hydrogen abstraction to form **8**, which may subsequently give **10** upon hydrogen-atom transfer. On the other hand, **I-1** may proceed through an oxa-di-π-methane type of mechanism, in which the β-scission of the C−C bond and following C−C bond cleavage led to the formation of bicyclo[3.2.1]octenones **9** and/or **11**. The generated radical can in principle undergo intramolecular addition to either the carbonyl group or the vinyl group.[19] In the present study, the bridging toward the ketone or the olefinic moiety are equally possible, leading to a cyclopropane intermediate with high strain. While it is a well-known phenomena that radicals readily add to alkenes and addition to carbonyls is usually less common because the C═O π-bond is much stronger than the C═C π-bond;[20] there are also examples of intramolecular cyclization

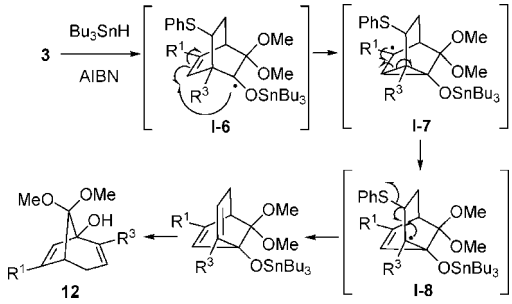
(19) (a) Tsang, R.; Dickson, J. K., Jr.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230.

(20) (a) Cottrell, T. L. *The Strengths of Chemical Bonds*, 2nd ed.; Butterworths: London, 1958; A-21 to A-34. (b) Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502.

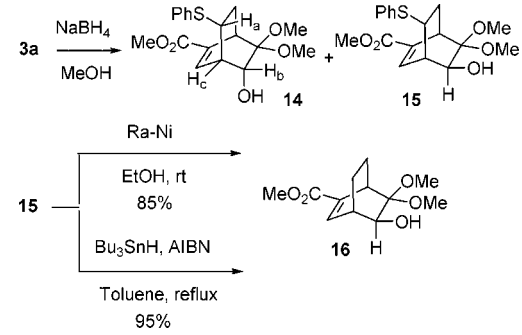
SCHEME 3. A Plausible Mechanism for the Formation of Compounds 9, 10, 11, and 13



SCHEME 4. A Plausible Mechanism for the Formation of Compounds 12



SCHEME 5. Desulfurization of the Reduced Compound 15



process where the carbon radical in sterically congested substrates showed preference of carbonyl group over olefin.[19a] A possible explanation could be that the intramolecular addition of the carbon-centered radical onto a olefinic double bond might be highly prone to reversible reaction to regenerate the original radical, and hence di-π-methane bridging products **13** are not observed from the reaction of **3** with Raney-Ni. Though the olefinic moiety does not take place in the reaction, it might be playing a major role in dictating the reaction pathway depending on the substitution present on it. The electron-poor olefin due to an electron-withdrawing substitution (regardless of the position of the substitution) in compounds **3a**−**d** may provide a stabilizing factor to the rearranged radical centers, whereas the lacking of such an effect in **3e** leads to a high yield of **8e** from the Raney-Ni or Bu_3SnH reduction of **3e**.

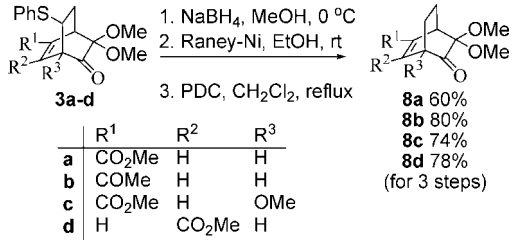
In the *n*-Bu_3SnH reduction reactions, formation of the observed bicyclo[3.2.1]octadienol products **12** could be rationalized by the attack of *n*-Bu_3Sn on the carbonyl oxygen to generate radical **I-6** followed by cyclopropane ring formation and release of phenylthio radical (Scheme 4). In the absence of such a preference to oxygen atom, in the case of Raney-Ni, no **12** could be obtained. Compound **13d** might have arisen from the radical intermediate **I-1** ($R^1 = R^3 = H$, $R^2 = CO_2Me$) via di-π-methane bridging (Scheme 3). Here in the *n*-Bu_3SnH reduction reaction of adduct **3d**, the oxa-di-π-methane and di-π-methane bridging seems to be competing and in favor of the former. For the radical intermediate **I-1**, the competing processes of hydrogen abstraction to form **8** or bridging process toward **I-2** should be controlled by reaction kinetics. Hence the rate of the bridging process is faster in a substrate having an electron-withdrawing group, yielding mainly the rearrangement products **9**−**13**.

To confirm the suggested mechanism that the radical prefers the carbonyl functionality rather than the olefinic double bond and interference of carbonyl function is the reason for the rearranged products, the carbonyl functionality in compound **3a** was reduced with $NaBH_4$ to provide separable isomers **14** (63%) and **15** (30%) in excellent combined yield (Scheme 5). The stereochemistry in the compound **14** was confirmed by NOE experiments. Irradiating H_a brought about significant NOE on the signal intensities of H_b (12%) and when H_b was saturated, enhancement in the signal intensity of H_a (9%) and H_c (7%) could be observed. Thus the stereochemistry in compound **15** could be assigned as shown. The hydroxyl compound **15** provided a single nonrearranged reaction product **16** in both the sulfide reduction conditions in high yield (Scheme 5). Neither oxa-di-π-methane nor di-π-methane-like rearrangement products were observed.

We then applied the detoured strategy to **3a**−**d** (Scheme 6); in all cases, the sulfide groups were removed by Raney-Ni smoothly and the resulting alcohols were oxidized to ketones using pyridinium dichromate (PDC). The desire products **8a**−**d** were obtained in good yield via a three-step procedure.

Effect of C−S and C−Se Bond Strengh on the Reduction. The C−S bond energy is 264 KJ mol^{-1}, whereas the C−Se

SCHEME 6. Detoured Desulfurization Method



	R^1	R^2	R^3
a	CO_2Me	H	H
b	COMe	H	H
c	CO_2Me	H	OMe
d	H	CO_2Me	H

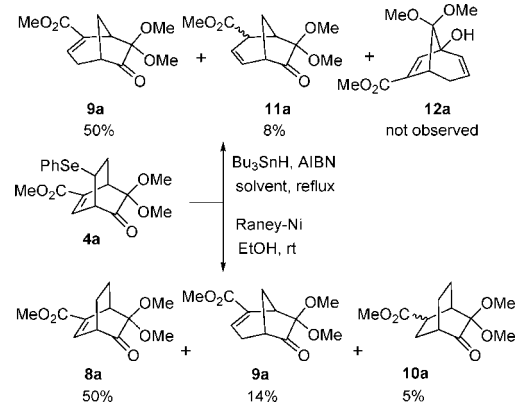
bond energy is around 222 KJ mol^{-1}.[7d] Therefore, processes involving cleavage of the latter type of bond is expected to occur at a greater rate than the former. Thus, in the case of organosulfur substrate, the slower cleavage of the C−S bond as compared with the C−Se bond by the *n*-Bu_3Sn radical could potentially result in competition from other reactions, such as direct addition of the *n*-Bu_3Sn radical to the carbonyl group.[21] The formation of intermediate **I-1** (Scheme 2) should be more favorable than that of intermediate **I-6** (Scheme 2) for selenide adducts. Consequently, the Diels−Alder adducts **4** were subjected to similar reduction conditions described previously. The deselenation reaction of compound **4a** with Raney-Ni provided the same products as for desulfurization with almost similar yields. The interesting part of the result is when *n*-Bu_3SnH was utilized, no **12a** was observed. This result suggests that intermediate **I-6** is not favored during *n*-Bu_3SnH reduction of selenide compounds **4**. The expected selectivity in the rearrangement reaction was also observed with the other set of selenium-containing compounds as shown in Table 3. Compound **9b** could be obtained in improved yield of 40% from selenium reduction in **4b** compared to sulfur reduction in **3b**. Compound **4c** provided 2.2:1 ratio of **11c** to **11c′** which is different from the 5:1 ratio obtained with **3c**. It is also important to note that no **12c** was observed, and the combined yield of **11c** and **11c′** was improved. Interestingly, compound **4e** furnished deselenized product **8e** in 90% yield, which is in accord with the high yield of **8e** from the reductions of **3e**. These results were presumably due to the lack of stabilizing factor caused by the electron-withdrawing group in other cases.

Conclusion

In conclusion, highly regio- and stereoselective inverse-electron-demand Diels−Alder reactions of MOBs with phenyl vinyl sulfide and phenyl vinyl selenide as dienophilic partners were studied in detail. The Diels−Alder adducts thus obtained from the above reaction sequence have proven to be important synthetic intermediates. We could successfully prepare highly substituted bicyclo[2.2.2]octadienones, which can be potential starting materials for synthesis of heteroarene-fused barrelenes. In the course of developing approaches to bicyclo[2.2.2]octanone derivatives by desulfurization/deselenation, a number of possible reaction pathways have been discovered, ranging from simple hydrogenolysis of a C-X (X = S or Se) bond to rearrangement reactions, including di-π-methane and oxa-di-π-methane-like rearrangements. The scope and limitation of these novel rearrangement reactions is presented with a set of selected examples.

(21) (a) Sugawara, T.; Otter, B. A.; Ueda, T. *Tetrahedron Lett.* **1988**, *29*, 75. (b) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939. (c) Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; p69.

TABLE 4. Reductions of Adducts 4 with *n*-Bu_3SnH in the Presence of AIBN



entry	cyclo-adduct	concn (M)	solvent	rxn time	yield (%)[a] 8	9	11	12	13
1	**4b**	0.02	toluene	15 min		40			
2	**4c**	0.02	toluene	15 min			45 + 20[b]		
3	**4d**	0.02	toluene	15 min		42			21
4	**4e**	0.02	benzene	3 h	90				

[a] Yields are of isolated products. [b] yields of major and minor epimers.

This study reveals unknown skeletal rearrangements of bicyclo[2.2.2]octenones derived from MOBs. It is also demonstrated, while changing the sulfide to a selenide function, that the diversed reaction pathway leading to bicyclo[3.2.1]octenones could be avoided. The radical reaction condition with *n*-Bu_3SnH, on a reactant bearing both selenide and carbonyl function, effects the cleavage of selenide faster due to the weaker C−Se bond. However, clean desulfurizations could be applied to the sulfide groups on bicyclo[2.2.2]octenols derived from a simple reduction of the Diels−Alder adducts. Thus the desired bicyclo[2.2.2]-octenones could also be accomplished by the detoured route of "reduction of ketone−Raney-Ni reduction−PDC oxidation" procedure. It is pertinent to mention that the transformation of bicyclo[2.2.2]octenones bearing no bridghead methoxy group into bicyclo[3.2.1]octenones have been successfully achieved as compared to reported examples in which the bridgehead methoxy group is a crucial factor to transform bicyclo[2.2.2]-octenones into bicyclo[3.2.1]octenones.[22]

Experimental Section

General Procedure for Raney-Ni Mediated Transformations. A solution of cycloadduct **3** or **4** (0.5 mmol) in EtOH (7 mL) was added to Raney-Ni (3.58 g, washed 4 times with EtOH) in EtOH (8 mL) and the contents were stirred for appropriate time. Then the suspension was filtered and the residue was washed with ether. The filtrate was evaporated and subjected to column chromatography to afford compounds **8**, **9**, and **10**.

General Procedure for *n*-Bu_3SnH Mediated Transformations. To a solution of cycloadduct **3** or **4** (0.5 mmol) in toluene (20 mL) was added a toluene (20 mL) solution of *n*-Bu_3SnH (1.0 mmol) and AIBN (35 mg) during a time interval of 15 min at reflux temperature. The reaction was stopped after the TLC analysis indicated the disappearance of starting material. After the removal

(22) (a) Singh, V.; Jagadish, B. *Tetrahedron* **1996**, *52*, 3693. (b) Uyehara, T.; Murayama, T.; Sakai, K.; Ueno, M.; Sato, T. *Tetrahedron Lett.* **1996**, *37*, 7295. (c) Uyehara, T.; Osanai, K.; Sugimoto, M.; Suzuki, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 7264. (d) Hua, D. H.; Gung, W.-Y.; Ostrander, R. A.; Takusagawa, F. *J. Org. Chem.* **1987**, *52*, 2509. (e) Monti, S. A.; Dean, T. R. *J. Org. Chem.* **1982**, *47*, 2679.

of solvent the crude reaction mixture was chromatographed to afford compounds **9**, **11**, **12**, and **13**.

Methyl (1*R,4*S**)-6,6-Dimethoxy-5-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate (8a).** IR (film) 3064, 1745, 1716, 1626, 1438, 1263, 1226, 1082, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (dddd, J = 3.1, 4.1, 12.0, 12.2 Hz, 1H), 1.61 (dddd, J = 3.2, 3.3, 12.2, 12.3 Hz, 1H), 1.95−2.08 (m, 2H), 3.27 (s, 3H), 3.27−3.29 (m, 1H), 3.73 (dd, J = 3.2, 6.8 Hz, 1H), 7.13 (dd, J = 1.8, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 22.4, 38.4, 48.7, 49.9, 50.2, 51.9, 93.8, 137.3, 137.7, 164.5, 202.2; MS (70 eV) *m*/*z* (relative intensity) 212 ($[M - CO]^+$, 76), 181 (18), 165 (100), 153 (21), 137 (17), 121 (15), 93 (13), 79 (22), 77 (37), 59 (23); HRMS (EI) calcd for $C_{11}H_{16}O_4$ $[M - CO]^+$ 212.1207, found 212.0998.

(1*S,4*R**)-5-Acetyl-3,3-dimethoxybicyclo[2.2.2]oct-2-en-2-one (8b).** IR (film) 3064, 1745, 1668, 1615, 1462, 1380, 1260, 1100, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.29 (m, 1H), 1.61−1.70 (m, 1H), 1.98−2.08 (m, 2H), 2.33 (s, 3H), 3.22 (s, 3H), 3.30 (ddd, J = 2.0, 3.0, 6.6 Hz, 1H), 3.34 (s, 3H), 3.89 (ddd, J = 2.4, 4.8, 6.8 Hz, 1H), 7.06 (dd, J = 2.0, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 22.5, 24.7, 36.4, 48.7, 50.0, 50.2, 93.8, 137.2, 146.4, 194.5, 202.3; MS (70 eV) *m*/*z* (relative intensity) 196 ($[M - CO]^+$, 100), 165 (33), 153 (14), 149 (84), 121 (20), 107 (11), 91 (16), 79 (20), 33 (77), 43 (62); HRMS (EI) calcd for $C_{11}H_{16}O_3$ $[M - CO]^+$ 196.1099, found 196.1096.

Methyl (1*R,4*S**)-4,6,6-Trimethoxy-5-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate (8c).** IR (film) 3070, 1757, 1717, 1629, 1439, 1264, 1139, 1057, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42−1.49 (m, 1H), 1.71−1.79 (m, 1H), 1.99−2.11 (m,. 2H), 3.27 (s, 3H), 3.36 (s, 3H), 3.67 (dd, J = 3.0, 5.0 Hz, 1H), 3.79 (s, 3H), 7.17 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 26.9, 37.7, 49.9, 50.4, 52.1, 53.7, 84.7, 93.9, 136.3, 138.4, 164.0, 200.1; MS (70 eV) *m*/*z* (relative intensity) 242 ($[M - CO]^+$, 61), 227 (100), 211 (26), 195 (34), 168 (17), 167 (17), 135 (12), 123 (23), 109 (17), 108 (15); HRMS (EI) calcd for $C_{12}H_{18}O_5$ $[M - CO]^+$ 242.1154, found 242.1153.

Methyl (1*S,4*R**)-5,5-Dimethoxy-6-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate (8d).** IR (film) 3073, 1741, 1716, 1718, 1628, 1438, 1266, 1110, 1085, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27−1.37 (m, 1H), 1.58−1.67 (m, 1H), 1.93−2.04 (m, 2H), 3.27 (s, 3H), 3.29−3.31 (m, 1H), 3.33 (s, 3H), 3.71−3.73 (m, 1H), 3.75 (s, 3H), 7.37 (dd, J = 1.8, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 22.5, 39.7, 46.8, 50.2, 51.9, 93.9, 131.7, 143.8, 164.2, 202.1; MS (70 eV) *m*/*z* (relative intensity) 212 ($[M - CO]^+$, 100), 181 (48), 165 (83), 153 (29), 149 (10), 137 (38), 121 (19), 107 (10), 93 (15), 77 (25); HRMS (EI) calcd for $C_{12}H_{16}O_5$ (M^+) 240.0998, found 240.0980.

(1*S,4*R**)-3,3-Dimethoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one (8e).** IR (film) 3051, 1735, 1582, 1439, 1131, 1190, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (ddt, J = 3.3, 9.0, 14.8 Hz, 1H), 1.52∼1.64 (m, 1H), 1.81 (d, J = 1.2 Hz, 1H), 1.83∼1.97 (m, 2H), 2.90 (ddd, J = 1.7, 1.9, 3.5 Hz, 1H), 2.97 (ddd, J = 2.1, 2.9, 7.2 Hz, 1H), 3.30 (s, 3H), 3.31 (s, 3H), 5.96 (dddd, J = 1.2, 1.9, 3.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 20.4, 21.7, 38.3, 49.8, 50.1, 53.2, 94.7, 126.9, 137.0, 203.4; MS (70 eV) *m*/*z* (relative intensity) 168 ($[M - CO]^+$, 100), 153 (30), 137 (39), 121 (17), 105 (11), 94 (11), 93 (87), 79 (24), 75 (16), 59 (12); HRMS (EI) calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1098.

Methyl (1*R,5*R**)-7,7-Dimethoxy-6-oxobicyclo[3.2.1]oct-2-ene-2-carboxylate (9a).** IR (film) 3046, 1752, 1700, 1630, 1280, 1240, 1128, 1066, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (dd, J = 0.8, 11.5 Hz, 1H), 2.34 (dddd, J = 0.8, 4.3, 5.2, 11.5 Hz, 1H), 2.43 (ddd, J = 0.8, 2.0, 4.0 Hz, 1H), 2.55 (dd, J = 3.0, 5.5 Hz, 1H), 2.60 (dd, J = 3.0, 5.5 Hz, 1H), 2.65 (ddd, J = 2.2, 5.0, 7.4 Hz, 1H), 3.26 (s, 3H), 3.33 (s, 3H), 3.55 (ddd, J = 1.8, 2.4, 4.4 Hz, 1H), 3.73 (s, 3H), 6.84 (dd, J = 3.0, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 33.6, 38.8, 42.3, 50.6, 51.2, 51.9, 105.2, 133.0, 137.6, 166.1, 212.1; MS (70 eV) *m*/*z* (relative intensity) 212 ($[M - CO]^+$, 100), 209 (42), 197 (21), 165 (53), 137 (53), 121 (21), 105 (30), 88 (34), 77 (49); HRMS (EI) calcd for $C_{11}H_{16}O_4$ $[M - CO]^+$ 212.1207, found 212.1050.

(1*R,5*R**)-2-Acetyl-7,7-dimethoxybicyclo[3.2.1]oct-2-en-6-one (9b).** IR (film) 3067, 1754, 1670, 1627, 1378, 1438, 1280, 1232, 1129, 1072, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (dd, J = 1.2, 11.4 Hz, 1H), 2.29 (s, 3H), 2.34 (ddd, J = 3.9, 3.9, 11.4 Hz, 1H), 2.44∼2.52 (m, 1H), 2.62 (dd, J = 2.8, 5.2 Hz, 1H), 2.65∼2.69 (m, 1H), 3.24 (s, 3H), 3.25 (s, 3H), 3.72∼3.74 (m, 1H), 6.71∼6.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 27.9, 34.0, 37.0, 42.3, 50.7, 51.3, 105.1, 138.2, 142.3, 196.8, 212.2; MS (70 eV) *m*/*z* (relative intensity) 196 ($[M - CO]^+$, 100), 193 (25), 153 (59), 149 (66), 121 (35), 107 (26), 91 (20), 88 (34), 79 (26), 77 (30); HRMS (EI) calcd for $C_{11}H_{16}O_3$ $[M - CO]^+$ 196.1099, found 196.1103.

Methyl (1*R,5*S**)-7,7-Dimethoxy-6-oxobicyclo[3.2.1]oct-2-ene-3-carboxylate (9d).** IR (film) 1763, 1700, 1717, 1653, 1250, 1128, 1131, 1089, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73 (dd, J = 1.4, 11.5 Hz, 1H), 2.28 (ddd, J = 3.8, 4.9, 11.5 Hz, 1H), 2.54 (dd, J = 2.5, 17.8 Hz, 1H), 2.62 (ddd, J = 1.9, 5.2, 17.8 Hz, 1H), 2.73 (ddd, J = 2.5, 4.9, 5.2 Hz, 1H), 3.01 (dd, J = 2.6, 7.0 Hz, 1H), 3.26 (s, 3H), 3.35 (s, 3H), 3.70 (s, 3H), 7.04 (ddd, J = 1.4, 1.9, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 32.6, 40.0, 42.4, 50.5, 51.1, 51.8, 105.3, 129.8, 139.2, 166.4, 211.4; MS (70 eV) *m*/*z* (relative intensity) 240 (M^+, 1), 212 ($[M - CO]^+$,100), 197 (14), 165 (18), 153 (33), 137 (20), 121 (14), 88 (20), 77 (19), 58 (13); HRMS (EI) calcd for $C_{12}H_{16}O_5$ (M^+) 240.0998, found 240.1010.

Acknowledgment. We gratefully acknowledge financial support from the National Science Council of Taiwan (NSCT). S.K.C. and G.J.C. thank NSCT for postdoctoral fellowships. We thank Dr. R. K. Peddinti for helpful discussion.

Supporting Information Available: General procedures, characterization data, and copies of ^1H NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802295P