# Generation, Stability, Dimerization, and Diels−Alder Reactions of Masked *o*-Benzoquinones. Synthesis of Substituted Bicyclo[2.2.2]octenones from 2-Methoxyphenols

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Diels−Alder reactions of labile and readily dimerizing masked *o*-benzoquinones, i.e., substituted 6,6-dimethoxy-2,4-cyclohexadienones with electron-deficient dienophiles that resulted in the development of an efficient and reliable one-pot method for the preparation of highly functionalized bicyclo[2.2.2]octenones, are described. Oxidation of 2-methoxyphenols **8**, **9**, **11**, **13**, and **14** with (diacetoxy)iodobenzene in methanol afforded the corresponding masked *o*-benzoquinones **1**, **2**, **4**, **6**, and **7**, which are not stable enough to be isolated and are found to dimerize under reaction conditions in a highly regio- and stereoselective manner to provide the Diels−Alder dimers **22**, **23**, **25**, **27**, and **28** respectively. On the other hand, masked *o*-benzoquinones **3** and **5**, derived from phenols **10** and **12**, respectively, were found to be quite labile and provided a complex mixture of products. However, masked *o*-benzoquinones **1**−**7**, when generated in the presence of dienophiles such as methyl acrylate, methyl methacrylate, and methyl vinyl ketone, underwent highly regio- and stereoselective intermolecular Diels−Alder reactions to furnish variously substituted bicyclo-[2.2.2]octenones **15**−**21(a**−**c)**. While the Diels−Alder reactions of masked *o*-benzoquinone **5** were found to be low-yielding, masked *o*-benzoquinones **1**−**4**, **6**, and **7** provided the desired adducts in good to high yields. Attempts are made to explain the observed regio- and stereoselectivity of these Diels−Alder reactions in terms of frontier molecular orbital theory.

## Introduction

The Diels−Alder reaction has become one of the most frequently used reactions in organic synthesis since it provides easy access to a wide variety of cyclic compounds.[1−4] The art of utilizing the Diels−Alder reaction in the synthesis of natural products lies in the design and preparation of suitable dienes and dienophiles.[5] A large variety of dienes and dienophiles bearing an array of functionalities have been used to construct different types of ring structures.[6] Nevertheless, Diels−Alder reaction of 2,4-cyclohexadienones with activated alkenes has been used as one of the methods for the synthesis of bicyclo[2.2.2]octenones,[7,8] which have wide range of applications in the synthesis of natural products.[5] In addition, bicyclo[2.2.2]octenones undergo interesting and useful photochemical reactions, viz., 1,3-acyl migration and oxadi-$\pi$-methane rearrangement.[9] On the other hand, 2,4-cyclohexadienones themselves are very important compounds from both synthetic and biological points of view.[10−12] They were recently identified as a potential new class of receptor tyrosine kinase inhibitors.[11] They can in principle participate in (i) cycloaddition reactions,[7,10] (ii) nucleophilic, electrophilic, and radical addition reactions,[13] and (iii) photochemical reactions.[14] Despite their vast potential, they are a relatively underutilized class of compounds.

Although not extensively, the Diels−Alder chemistry of cyclohexadienones **I**−**VII** (Figure 1) has been studied and used in the total synthesis of natural products.[7,10,15−21]

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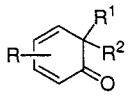
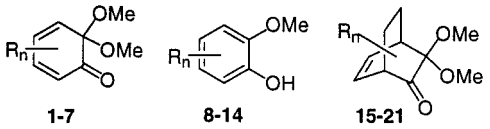


**I** ($R^1$ = $R^2$ = alkyl)
**II** ($R^1$ = alkyl, $R^2$ = ester or amido group)
**III** ($R^1$, $R^2$ = $-CH_2O-$)
**IV** ($R^1$ = alkyl, $R^2$ = OAc)
**V** ($R^1$ = $R^2$ = OAc)
**VI** ($R^1$ = alkoxy, $R^2$ = OAc)
**VII** ($R^1$ = $R^2$ = alkoxy)

**Figure 1.** Various types of 2,4-cyclohexadienones.

The use of cyclohexadienones **I**−**IV** in a general way is constrained in that their preparation requires strategic placement of substituents, which cannot be removed easily. On the other hand, 2,4-cyclohexadienones of type **V**−**VII**, which may also be called as *o*-quinone monoacetals or masked *o*-benzoquinones (MOBs), could be ideal compounds for use in Diels−Alder reactions because the unavoidable acetal group, being positioned next to a keto group, could be removed by reduction if not required or modified into a desired functionality at a latter stage with relative ease.[22,23] However, lack of efficient methods for their preparation and their high propensity to dimerize are main deterrents for their use in organic synthesis.[24,25]



**1-7** **8-14** **15-21**

**Figure 2.**

Prior to our entry into this area,[26] relatively little Diels−Alder chemistry of masked *o*-benzoquinones has been reported.[19−21] Deslongchamps and co-workers have used Diels−Alder reaction of a masked *o*-benzoquinone as one of the key steps in their synthesis of ryanodol.[20a,b] Andersson reported dimers of some simple MOBs of type **VII** and studied Diels−Alder reactions of 5,6,6-trimethoxy-2,4-cyclohexadienone with dimethyl acetylenedicarboxylate and substituted maleic anhydrides.[21] For the past decade or so, we have been interested in exploiting the synthetic potential of masked *o*-benzoquinones in general and their Diels−Alder chemistry in particular.[22,23,26−28]

In the begining, our efforts were mainly focused on synthesis of stable MOBs and their photo- and Diels−Alder chemistry with the emphasis laid on unraveling their basic nature.[26] Spirolactone moiety, which needs additional synthetic steps and results in mixtures of diastereomeric products, was employed as the mask in those studies. Consequently, our attention was shifted to MOBs **VII**, which are achiral and easily accessible. It was soon realized that MOBs **VII** have a very high propensity to dimerize. As a result, attempts were made to trap rather than isolate them. This change in direction has brought remarkable success, and over the years we have made a systematic study of Diels−Alder chemistry of in situ generated unstable MOBs. We herein present a detailed account of our investigations on the generation, stability, and dimerization of masked *o*-benzoquinones **1**−**7** derived from 2-methoxyphenols **8**−**14** and their Diels−Alder reactions with electron-deficient dienophiles to facilitate the synthesis of various bicyclo[2.2.2]-octenones **15**−**21** (Figure 2).[28]

## Results

Oxidation of 2-methoxy-4-methylphenol (**8**) in methanol using (diacetoxy)iodobenzene (DAIB)[23,29] at 0 °C produced MOB **1** exclusively as shown by $^1$H NMR spectrum of the reaction mixture. Attempts to isolate **1** in a pure state resulted in the production of its dimer, **22**.[25] Instead of isolating **1**, an excess (25 equiv) of methyl acrylate (MA) was added to the oxidation reaction mixture of **8** and the reaction was allowed to proceed at 0 °C. The reaction was found to be rather sluggish, and

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**Scheme 1**

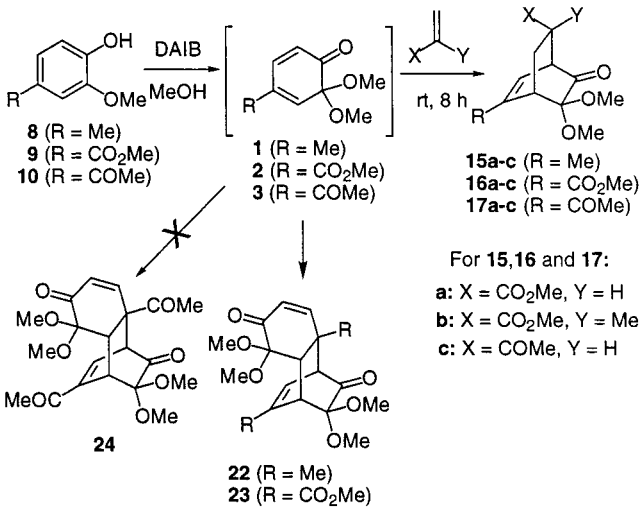



**Table 1. Intermolecular Diels–Alder Reactions of Masked *o*-Benzoquinones 1–7 with MA, MMA, and MVK**

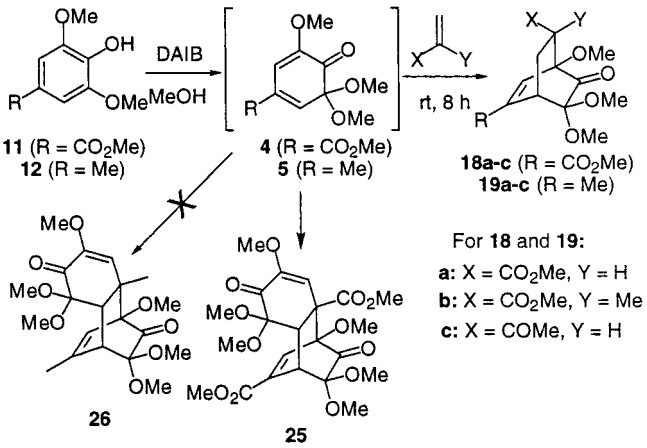
| entry | phenol | MOB | dienophile | product | yield (%) |
|---|---|---|---|---|---|
| 1 | **8** | **1** | MA | **15a** | 88 |
| 2 | | | MMA | **15b** | 75 |
| 3 | | | MVK | **15c** | 80 |
| 4 | **9** | **2** | MA | **16a** | 85 |
| 5 | | | MMA | **16b** | 90 |
| 6 | | | MVK | **16c** | 86 |
| 7 | **10** | **3** | MA | **17a** | 89 |
| 8 | | | MMA | **17b** | 87 |
| 9 | | | MVK | **17c** | 90 |
| 10 | **11** | **4** | MA | **18a** | 74 |
| 11 | | | MMA | **18b** | 78 |
| 12 | | | MVK | **18c** | 87 |
| 13 | **12** | **5** | MA | **19a** | 45 |
| 14 | | | MMA | **19b** | 33 |
| 15 | | | MVK | **19c** | 34 |
| 16 | **13** | **6** | MA | **20a** | 76 |
| 17 | | | MMA | **20b** | 60 |
| 18 | | | MVK | **20c** | 84 |
| 19 | **14** | **7** | MA | **21a** | 86 |
| 20 | | | MMA | **21b** | 84 |
| 21 | | | MVK | **21c** | 88 |

it produced substantial amounts of the Diels–Alder dimer **22** with some desired product **15a**. It was quite clear that the concentration of **1** in the reaction mixture should be reduced to avoid dimerization. To achieve this, a high dilution technique was employed. To maintain an appropriate concentration all through the course of reaction, a syringe pump was employed for the addition of phenol. The temperature was elevated to room temperature to increase the rate of Diels–Alder reaction.

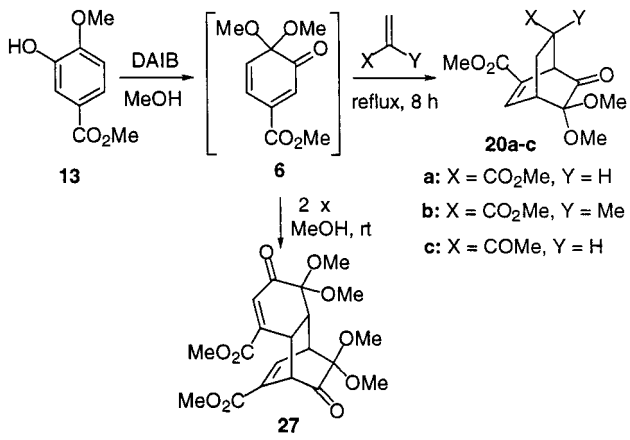
Accordingly, MOB **1** was generated in the presence of MA during 8 h by adding a solution of **8** in methanol using a syringe pump to a mixture of DAIB and MA in methanol at room temperature. These changes in reaction conditions provided the desired results. No trace of the dimer **22** could be detected in the $^1$H NMR spectrum of the crude reaction mixture. The reaction furnished a single Diels–Alder adduct **15a** in 74% isolated yield after column chromatography. These conditions were extended to other dienophiles such as methyl methacrylate (MMA) and methyl vinyl ketone (MVK) to afford adducts **15b** and **15c** in good yields (Scheme 1, Table 1).

The MOB **2**, generated from methyl vanillate (**9**) via oxidation with DAIB, was found to be highly reactive, and in the absence of dienophile it dimerized quite rapidly to produce dimer **23**. On the other hand, MOB **3** obtained via oxidation of acetovanillone (**10**) under similar conditions was found to be quite reactive and provided a complex mixture of products but not the dimer **24**. However, MOBs **2** and **3** furnished the expected products **16a–c** and **17a–c** in excellent yields when MA, MMA, and MVK were employed as dienophiles (Scheme 1).

**Scheme 2**




**Scheme 3**

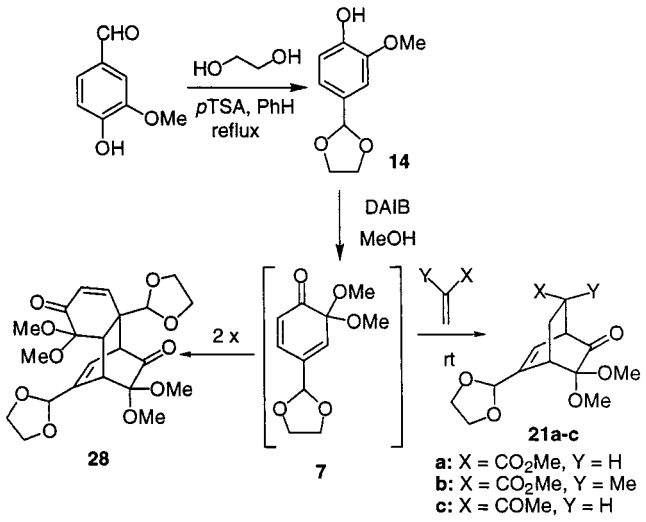



Under usual conditions, MOB **4**, derived from methyl syringate (**11**), reacted smoothly with MA, MMA, and MVK to furnish adducts **18a–c** in good yields. These cycloadditions of **4** also proceeded with excellent regio- and stereoselectivity. MOB **4** was found to be comparable to MOB **2** in Diels–Alder reactivity. However, MOB **4** dimerized quite rapidly to provide the dimer **25** when generated in the absence of dienophile (Scheme 2). On the other hand, MOB **5** generated from phenol **12** was found to be labile and furnished the desired products **19a–c** in very low yields in the reactions with MA, MMA, and MVK under the usual conditions. Dimer **26** was not discernible from any of the above reactions or from oxidation of **12** in the absence of dienophile.

The cycloaddition reactions of MOB **6**, generated from methyl isovanillate (**13**), were found to be rather sluggish when performed at room temperature and furnished a substantial amount of dimer **27**. However, MOB **6** reacted in a highly regio- and stereoselective manner at reflux temperature with MA, MMA, and MVK to provide bicyclo[2.2.2]octenones **20a–c** in good yields (Scheme 3). MOB **6** also exhibited a high propensity to dimerize.

Attempted oxidation of vanillin in the presence of MA at room temperature resulted in the production of a

**Scheme 4**




complex reaction mixture. Consequently, the aldehyde group was protected as an acetal,[30] and MOB **7** was generated in the presense of MA and anhydrous $NaHCO_3$ under the usual conditions. The MOB **7** was found to be less reactive and quite stable at room temperature in methanol. The best results were obtained when the MOB **7** was generated by the addition of phenol **14** in one portion to the mixture of DAIB and MA in methanol and the reaction was allowed to proceed until the MOB **7** reacted completely. This procedure was extended to MMA and MVK. The adducts **21a**−**c** were obtained in good yields (Scheme 4). No trace of dimer **28** was observed in any of the reactions performed at room temperature. The stability of **7** has attracted our attention. However, attempts to isolate it in pure form were unsuccessful.

The observed regioselectivity is in line with literature precedents.[7d,15d,20c,31d] However, it was thoroughly examined in each case using proton−proton decoupling experiments. The structures of all the new compounds were determined by their IR, $^1H$ and $^{13}C$ NMR, and low- and high-resolution mass spectral analyses. The assigned relative configuration of the epimeric carbon $C_7$ in all these adducts is based on previously confirmed structures of compounds **16a**[22] and **20b**.[31] The significant feature that could be seen in the $^1H$ NMR spectra is the W-type or allylic coupling between the vinylic protons and corresponding allylic protons on the bridgehead carbons. In the low-resolution mass spectra recorded in electron impact mode (12 or 70 eV) the peak corresponding to the molecular ion ($M^+$) could not be detected in general. Only the peak corresponding to $M^+ - 28$ could be seen, indicating rapid fragmentation resulting in the extrusion of CO. For the majority of these compounds, a satisfactory elemental analysis could be obtained.

## Discussion

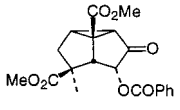
**Generation and Stability of MOBs.** Oxidation of 2-methoxyphenols in methanol by oxidants such as periodic acid[21] and thallium trinitrate (TTN)[32] is known to produce, among other products, 6,6-dimethoxy-2,4-cyclohexadienones and the corresponding dimers. In the initial stages of our studies, MOBs **VII** were generated in situ from 2-methoxyphenols by oxidation with TTN in methanol, and the yields of Diels−Alder reactions of thus generated MOBs were moderate.[22] This could be due to less stability of MOBs under the reaction conditions. Meanwhile, oxidation of phenols by organic hypervalent iodine reagents had come in for use.[29] Attracted by the mildness of this oxidation, we switched over to (diacetoxy)iodobenzene (DAIB) and bis(trifluoroacetoxy)iodobenzene (BTIB).[23,27b] These two reagents were found to be quite efficient. The oxidation had been spontaneous even at 0 °C (5−10 min), and the yields of MOBs were quite high as reflected by the yields of Diels−Alder adducts. Thus generated MOBs, except **5**, were found to be stable enough to undergo dimerization or Diels−Alder reactions with added dienophiles under the oxidation reaction conditions. However, due to problem of dimerization or high reactivity, the isolation of these MOBs in pure form was not possible.

**Dimerization and Diels−Alder Reactivity.** In the absence of dienophiles as well as in the presence of less reactive dienophiles, MOBs readily undergo dimerization in a highly regio- and stereoselective manner (Schemes 1−4). This is not a regular feature of all types of 2,4-cyclohexadienones. In fact, many 2,4-cyclohexadienones of types **IV**−**VI** or Schultz's 2,4-cyclohexadienones **II** are stable enough to be isolated in moderate yields and require relatively harsh conditions to undergo Diels−Alder reactions with added dienophiles.[7d,18−20] Apparently, the dimethoxy acetal group plays some role in increasing the reactivity as well as the propensity to dimerize. The reasons for this higher tendency of MOBs to dimerize could be reduced steric effects and increased secondary orbital overlap between the diene and unshared pair of electrons of the oxygen atom of the methoxy group of MOB acting as dienophile (Figure 3).[33,34]

However, the substituents present on other carbons of MOBs also have a profound influence on dimerization. MOBs **2**, **4**, and **6** undergo facile dimerization when compared to MOBs **1** and **7**. Expectedly, the parent MOB **29** (Figure 3) was found to dimerize quite readily, making its intermolecular Diels−Alder reactions with electron-deficient dienophiles inefficient.[27e,35] The MOBs isolated by us or others thus far are either strategically or highly

(30) Bozell, J. J.; Hames, B. R.; Dimmel, D. R. *J. Org. Chem.* **1995**, *60*, 2398.

(31) (a) Compound **20b** was stereoselectively transformed into compound **i** using oxadi-$\pi$-methane rearrangement as one of the key steps. The structure of **i** was unambiguously determined by its single-crystal X-ray diffraction analysis, and the details will be published elsewhere.[31b] (b) Chu, C.-S.; Liao, C.-C. Unpublished results. (c) Quite recently, Yamauchi and co-workers have studied Diels−Alder reactions of a 2,4-cyclohexadienone with methyl methacrylate, methacrolein, and methyl propen-2-yl ketone and reported identical regio- and stereoselectivities as described herein.[31d] (d) Katayama, S.; Hiramatsu, S.; Aoe, K.; Yamauchi, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 561.




i

(32) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282.

(33) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510.

(34) (a) Houk, K. N. *Tetrahedron Lett.* **1970**, 2621. (b) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095. (c) Fox, M. A.; Cardona, R.; Kiwiet, N. J. *J. Org. Chem.* **1987**, *52*, 1469. (d) Guner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1988**, *53*, 1129. (e) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129.

(35) Lai, C.-H.; Liao, C.-C. Unpublished results.

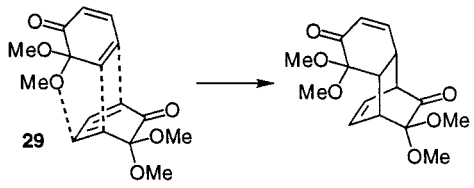



**Figure 3.** Dimerization of MOB **29**. Possible secondary interactions responsible for higher propensity of MOBs to dimerize.

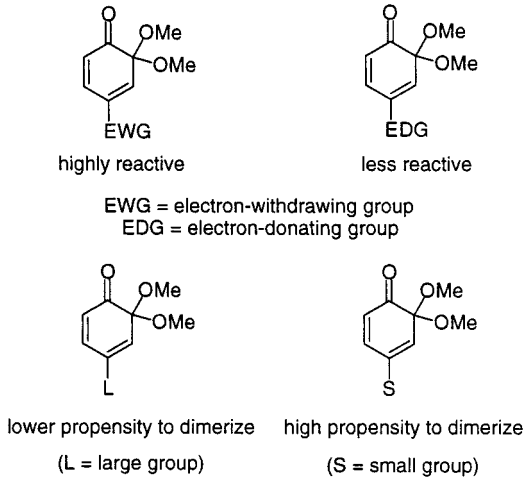



**Figure 4.**

substituted or have very bulky substituents.[13,21,26] Based on experience, it may be concluded that the presence of electron-withdrawing groups at $C_4$ of MOB increase the propensity of MOB to dimerize and the substituents that are electron releasing in nature exert an opposite effect. The presence of bulky substituents at $C_4$ of MOBs also reduce their propensity to dimerize (Figure 4).[13c] A similar conclusion was reached by Andersson from his own observations.[21b]

To prevent or reduce dimerization, the MOBs were generated in situ in very low concentrations by a very slow and regulated addition of phenol to a mixture of DAIB and an excess of dienophile in methanol. Under such reaction conditions, the dienophile is present in large excess (thousands of times) to MOB. As a result, the accumulation of MOB could be avoided in cases where the MOBs exhibited sufficient reactivity toward added dienophiles.

Despite the fact that the MOBs are electron-defficient dienes, they readily undergo both *normal* and *inverse-electron-demand* Diels−Alder reactions with electron-deficient dienophiles at room temperature and atmospheric pressure if generated in the presence of dienophiles (vide infra). However, different MOBs have exhibited different degrees of reactivity in their cycloaddition reactions with a given dienophile to produce highly substituted bicyclo[2.2.2]octenones. In addition, the competition between self-dimerization and Diels−Alder reaction with added dienophiles always exists except in case of MOB **7**. For example, the MOB **2** and **3** exhibited excellent reactivity in Diels−Alder reactions and produced only the desired bicyclo[2.2.2]octenones in very good yields at room temperature. On the other hand, MOBs **1** and **4**−**7** were found to be relatively less reactive. Obviously, these differences in reactivity are a result of nature, position, and size of the substituents. Although the relative reactivities are not rigorously assessed, our results clearly indicate that if the substituent attached to $C_4$ of MOB is an electron-withdrawing group as in **2**, the reactivity is much higher compared to when the substituent at $C_4$ is an electron-donating group as in MOB **1** (Figure 4).

**Table 2. Energies of FMOs of MOBs 1−7, MA, and MVK Obtained by Semiempirical PM3 and ab Initio RHF/3-21G* Level Calculations**

| compd | FMO | PM3 | 3-21G |
|---|---|---|---|
| **1** | HOMO | −9.9179 | −9.1671 |
| | LUMO | −0.8748 | 1.9099 |
| **2** | HOMO | −10.3082 | −9.5140 |
| | LUMO | −1.2899 | 1.3586 |
| **3** | HOMO | −10.1925 | −9.6321 |
| | LUMO | −1.2763 | 1.1981 |
| **4** | HOMO | −9.3278 | −8.7543 |
| | LUMO | −0.7856 | 1.6312 |
| **5** | HOMO | −9.6192 | −8.5393 |
| | LUMO | −0.8503 | 2.2056 |
| **6** | HOMO | −10.3225 | −9.5289 |
| | LUMO | −1.3340 | 1.1110 |
| **7** | HOMO | −9.8372 | −9.0949 |
| | LUMO | −0.9020 | 1.7428 |
| MA | HOMO | −11.0665 | −10.7733 |
| | LUMO | −0.0833 | 3.0393 |
| MVK | HOMO | −10.7234 | −10.5074 |
| | LUMO | −0.0561 | 2.7259 |

**Regio- and Stereoselectivity.** These cycloaddition reactions of MOBs appear to have followed all the ground rules of Diels−Alder reactions. To explain this high selectivity in all respects, an attempt was made to correlate the energies and coefficients of the frontier molecular orbitals.[36] HOMOs and LUMOs of MOBs **1**−**7**, MA, and MVK were calculated using both semiempirical (PM3) method and ab initio RHF (3-21G*) procedures.[37,38] The geometries were fully optimized by the AM1 semiempirical method[39] and used as the starting point for optimization at PM3 and 3-21G* levels. The energy levels derived from these calculations are summarized in Table 2.

In the majority of the cases examined, the difference in the energy gaps (DDE) for the two possible interactions remained around 0.5 eV. If these small differences are considered as preference for either interaction, the energy gaps indicate the preference for *normal-electron-demand* interaction, i.e., $HOMO_{diene}/LUMO_{dienophile}$ in the case of reactions of MOBs **1**, **4**, **5**, and **7** with dienophiles MA and MVK, while for the reactions of MOBs **2**, **3**, and **6** with both the dienophiles *inverse-electron-demand* interactions are preferred.[40] Figure 5 illustrates the FMO interactions of Diels−Alder reactions of MOBs **1** and **2** with MVK. However, in two cases the predictions made by the two methods are different (Table 3).

The relative magnitudes of HOMO and LUMO coefficients of MOBs **1**−**7**, MA and MVK derived from ab initio calculations performed at the 3-21G* level are listed

(36) (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57. (b) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (c) Alston, P. V.; Ottenbrite, R. M.; Guner, O. F.; Shillady, D. D. *Tetrahedron* **1986**, *42*, 4403.

(37) PM3 calculations were performed using PC Spartan Plus.[38a] (a) PC Spartan, v 1.5, Wave Function, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

(38) RHF/3-21G* calculations were performed using PC Spartan Plus.[39a] (a) PC Spartan, v 1.5, Wave Function, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

(39) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(40) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1975. (b) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

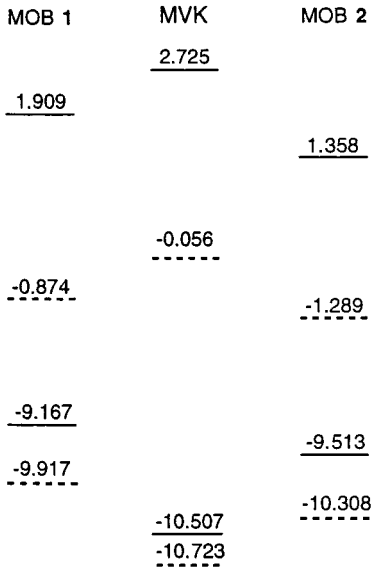



**Figure 5.** FMO interactions for the Diels−Alder reactions of MOBs **1** and **2** with MVK. The values shown on solid lines are derived by ab initio RHF/3-21G* level calculations, and those shown on dotted lines are derived by PM3 semiempirical calculations.

**Table 3. Energy Gaps (eV): FMO Interactions of MOBs 1−7 with MA and MVK**

| | | energy gaps to MA | | energy gaps to MVK | |
|---|---|---|---|---|---|
| MOB | method | $HOMO_{MOB}-LUMO_{MA}$ | $HOMO_{MA}-LUMO_{MOB}$ | $HOMO_{MOB}-LUMO_{MVK}$ | $HOMO_{MVK}-LUMO_{MOB}$ |
| **1** | PM3 | 9.8617 | 9.8487 | 9.8346 | 10.1917 |
| | 3-21G* | 11.8929 | 12.4173 | 12.2064 | 12.6831 |
| **2** | PM3 | 10.2521 | 9.4335 | 10.2249 | 9.7766 |
| | 3-21G* | 12.2399 | 11.8660 | 12.5533 | 12.1319 |
| **3** | PM3 | 10.1363 | 9.4471 | 10.1092 | 9.7902 |
| | 3-21G* | 12.3580 | 11.7055 | 12.6714 | 11.9713 |
| **4** | PM3 | 9.2717 | 9.9378 | 9.2445 | 10.2809 |
| | 3-21G* | 11.4802 | 12.1387 | 11.7936 | 12.4045 |
| **5** | PM3 | 9.5631 | 9.8731 | 9.5360 | 10.2162 |
| | 3-21G* | 11.2652 | 12.7131 | 11.5787 | 12.9789 |
| **6** | PM3 | 10.2663 | 9.3894 | 10.2392 | 9.7325 |
| | 3-21G* | 12.2548 | 11.6184 | 12.5683 | 11.8842 |
| **7** | PM3 | 9.9786 | 9.7469 | 9.9514 | 10.0990 |
| | 3-21G* | 11.9944 | 12.2957 | 12.3079 | 12.5615 |

in Table 4. While in the case of MOBs **1** and **6** the regioselectivity observed and predicted by calculations are the same, in other cases the predictions differed from observed regioselectivity. In fact, in the majority of the cases the relative magnitudes of $C_2$ and $C_5$ coefficients of both HOMO and LUMO of MOBs are very close. Similarly, $C_1$ and $C_2$ coefficients of HOMOs of MA and MVK are also very close. It is therefore clear that these calculations based on molecular orbitals of isolated reactants are just not enough to explain the exclusive formation of ortho adducts. It is pertinent to mention that the Diels−Alder reactions of dienes and alkenes terminally substituted with electron-demanding groups could not be explained in terms of simple FMO theory and no general solutions for such anamolies are available. However, Alston invoked secondary orbital interactions and Houk introduced the schizophrenic behavior of substituents to explain similar anomalies of regioselectivity.[41,42]

The extremely high stereoselectivity observed in these cycloaddition reactions clearly indicates overwhelming endo preference at the transition state. This high endo preference may be explained by invoking secondary orbital interactions between the carbonyl group in the dienophile and $C_3$'s of MOBs. Our calculations clearly indicate the possibility for such interactions. The ab initio RHF/3-21G* level calculations provided large coefficients for $C_3$'s of both HOMOs and LUMOs of MOBs. The large $C_3$ coefficient could involve in secondary orbital overlap with large coefficients in the carbonyl group of dienophiles and thereby participate in stabilizing the endo transition state (Figure 6). In fact, on similar lines regioselectivity can also be explained. However, it is wise to examine other factors before any conclusion could be reached. In fact, studies directed at evaluation of solvent effect and transition-state calculations are in progress and will form the basis of a future publication.

## Conclusion

In conclusion, these studies resulted in the development of a reliable method for the regio- and stereoselective preparation of a variety of bicyclo[2.2.2]octenones. The present methodology makes use of inexpensive 2-methoxyphenols and DAIB for the generation of a variety of highly reactive 2,4-cyclohexadienones in a simple and practical manner. Furthermore, these studies also helped in assessing the nature of this class of 2,4-cyclohexadienones especially with regard to their stability, propensity to dimerize, and Diels−Alder reactivity. This methodology has already been used as one of the key steps in the stereoselective synthesis of a variety of compounds including polysubstituted cyclohexane derivatives,[43] *cis*-decalins,[27a] bicyclo[4.2.2]decenones,[27a] tricyclo[3.3.0.$0^{2,8}$]octenones,[43,44] and bicyclo[4.2.0]octenones[44] and in the total synthesis of a clerodane diterpenic acid[45] and forsythide aglucone dimethyl ester.[22]

## Experimental Section

**General Procedures.** Unless stated otherwise, reagents were obtained from commercial sources and used without further purification. Methyl acrylate, methyl methacrylate, and methyl vinyl ketone were distilled from hydroquinone prior to use. All reactions were performed under a nitrogen atmosphere in anhydrous solvents, which were dried prior to use following standard procedures. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using 7% ethanolic phosphomolybdic acid as developing agent. The product composition of each reaction was determined by the $^1$H NMR (400 MHz) spectrum of the crude reaction mixture. Standard column chromatography was performed using 230−400 mesh silica gel obtained from E. Merck. Melting points are uncorrected. IR spectra were recorded as films on NaCl plates. $^1$H and $^{13}$C NMR spectra were recorded at 300 or 400 MHz and 75 or 100 MHz, respectively, in $CDCl_3$, and chemical shifts are reported in $\delta$ (ppm) using solvent resonance as the internal reference. Mass spectra were recorded by the NSC Instrumentation Center at Hsinchu, Taiwan. Elemental analyses were performed by the NSC Instrumentation Center at Taichung, Taiwan.

(41) Alston, P. V.; Ottenbrite, R. M.; Shillady, D. D. *J. Org. Chem.* **1973**, *38*, 4075 and references therein.
(42) Houk, K. N.; Domelsmith, L. N.; Strozier, R. W.; Patterson, R. T. *J. Am. Chem. Soc.* **1978**, *100*, 6531 and references therein.
(43) Lee, T.-H.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1999**, in press.
(44) Song, L.-D. Master Thesis, National Tsing Hua University, Hsinchu, Taiwan, 1993.
(45) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912.

**Table 4. Coefficients ($C_i$) of HOMOs and LUMOs of MOBs 1−7, MA, and MVK[a]**

| | HOMO | | | | | | | LUMO | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | $C_O$ | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $\Delta C_i$[b] | $C_O$ | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $\Delta C_i$[b] |
| **1** | 0.090 | 0.012 | 0.239 | 0.172 | 0.211 | 0.266 | 0.027 | 0.189 | 0.180 | 0.184 | 0.220 | 0.137 | 0.181 | −0.003 |
| **2** | 0.111 | 0.012 | 0.257 | 0.197 | 0.196 | 0.231 | −0.027 | 0.156 | 0.142 | 0.155 | 0.176 | 0.145 | 0.243 | 0.089 |
| **3** | 0.138 | 0.006 | 0.267 | 0.194 | 0.192 | 0.234 | −0.032 | 0.169 | 0.154 | 0.143 | 0.185 | 0.140 | 0.236 | 0.092 |
| **4** | 0.069 | 0.002 | 0.231 | 0.247 | 0.158 | 0.222 | −0.009 | 0.165 | 0.156 | 0.174 | 0.136 | 0.158 | 0.230 | 0.056 |
| **5** | 0.058 | 0.005 | 0.216 | 0.229 | 0.169 | 0.255 | 0.040 | 0.195 | 0.193 | 0.207 | 0.180 | 0.154 | 0.162 | −0.045 |
| **6** | 0.086 | 0.016 | 0.237 | 0.187 | 0.212 | 0.258 | 0.022 | 0.180 | 0.158 | 0.219 | 0.200 | 0.095 | 0.151 | −0.068 |
| **7** | 0.103 | 0.014 | 0.253 | 0.188 | 0.202 | 0.248 | −0.005 | 0.181 | 0.169 | 0.178 | 0.209 | 0.142 | 0.195 | 0.017 |
| MA | 0.194 | 0.294 | 0.311 | 0.036 | | | 0.017 | 0.192 | 0.286 | 0.197 | 0.237 | | | −0.089 |
| MVK | 0.209 | 0.292 | 0.301 | 0.052 | | | 0.009 | 0.224 | 0.265 | 0.162 | 0.246 | | | −0.103 |

[a] Obtained from 3-21G* calculations and only absolute values are given. [b] $\Delta C_i = C_5 - C_2$ for MOBs **1**−**7** and $\Delta C_i = C_2 - C_1$ for MA and MVK.

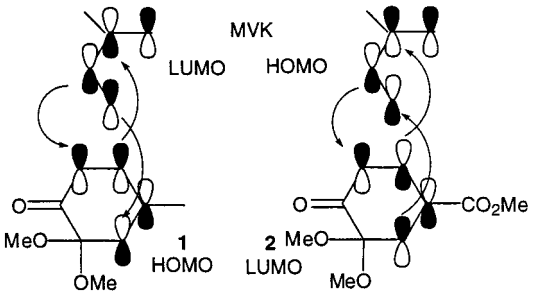



**Figure 6.** Possible endo transition states of Diels−Alder reactions of MOBs **1** and **2** with MVK.

**General Procedure for Diels−Alder Reactions. Procedure A. For the Reactions of Phenols 8−13.** To a mixture of DAIB (6 mmol) and a dienophile (125 mmol) in anhydrous methanol (30 mL) was added a solution of a 2-methoxyphenol (5 mmol) in MeOH (70 mL) during 8 h using a syringe pump at room temperature (in the case of phenol **6** at reflux) under a nitrogen atmosphere. The stirring was continued for a further 2 h. Then solvent, excess dienophile, and other volatile products were stripped off under reduced pressure. After the $^1$H NMR spectrum of the residue was recorded, it was subjected to purification by column chromatography on silica gel using 15−40% ethyl acetate in hexanes as eluent.

**Procedure B. For the Reactions of Vanillin Derivative 14.** Unlike in procedure A, the phenol **14** (5 mM) in MeOH (25 mL) was added in one portion to a mixture of DAIB (6 mM), anhydrous $NaHCO_3$ (15 mM), and dienophile (125 mM) in MeOH (25 mL), and stirring was continued at room temperature until MOB **7** disappeared (TLC). Then solvent and excess dienophile were removed under reduced pressure. The residue was suspended in ether (50 mL) and washed with brine. The organic layer was dried and concentrated. After the $^1$H NMR spectrum of the residue was recorded, it was subjected to purification by column chromatography on silica gel using 20% ethyl acetate in hexanes as eluent.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-methoxycarbonyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (15a).** This was prepared from phenol **8** and methyl acrylate in 88% yield as a colorless solid: mp 67−68 °C (from ethyl acetate−hexanes); IR (film) 2956, 1738 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.70 (ddd, $J$ = 13.3, 6.1, 3.0 Hz, 1H), 1.85 (d, $J$ = 1.5 Hz, 3H), 2.15 (ddd, $J$ = 13.3, 10.0, 3.0 Hz, 1H), 2.88 (m, 1H), 2.94 (ddd, $J$ = 10.0, 6.1, 1.8 Hz, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.34 (dd, $J$ = 6.3, 1.8 Hz, 1H), 3.66 (s, 3H), 5.64 (m, 1H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 21.06, 23.88, 39.00, 43.45, 49.64, 50.45, 52.10, 93.93, 117.40, 145.91, 173.45, 201.00; MS (EI, 12 eV) *m*/*z* (relative intensity) 226 ($M^+$ − CO, 100); HRMS (EI) calcd for $C_{13}H_{18}O_5$ ($M^+$) 254.1154, found 254.1154. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.38; H, 7.14.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-methoxycarbonyl-5,7-dimethylbicyclo[2.2.2]oct-5-en-2-one (15b).** This was prepared from phenol **8** and methyl methacrylate in 75% yield as a colorless solid: mp 37−38 °C (from ethyl acetate−hexanes); IR (film) 2936, 1724 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.25 (s, 3H), 1.74 (dd, $J$ = 13.6, 2.1 Hz, 1H), l.83 (d, $J$ = 1.5 Hz, 3H), 2.26 (dd, $J$ = l3.6, 3.4 Hz, 1H), 2.83 (dd, $J$ = 3.4, 2.1 Hz, 1H), 3.22 (d, $J$ = 6.3 Hz, 1H), 3.29 (s, 3H), 3.30 (s, 3H), 3.63 (s, 3H), 5.69 (dd, $J$ = 6.3, l.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.15, 25.42, 31.17, 43.66, 46.62, 49.41, 50.49, 52.34, 56.12, 94.19, 119.40, 145.32, 176.44, 202.49; MS (EI, 12 eV) *m*/*z* (relative intensity) 268 ($M^+$, 1), 240 ($M^+$ − CO, 100); HRMS (EI) calcd for $C_{14}H_{20}O_5$ ($M^+$) 268.1311, found 268.1310. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.65; H, 7.51.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-ethanoyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (15c).** This was prepared from phenol **8** and methyl vinyl ketone in 80% yield as a colorless solid: mp 61−62 °C (from ethyl acetate−hexanes); IR (film) 2927, 1724 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.62 (ddd, $J$ = 12.9, 6.6, 2.6 Hz, 1H), 1.79 (d, $J$ = 1.2 Hz, 3H), 1.99−2.12 (m, 1H), 2.05 (s, 3H), 2.85 (dd, $J$ = 2.6, 2.3 Hz, 1H), 2.94 (ddd, $J$ = 8.9, 6.6, 1.7 Hz, 1H), 3.22 (s, 3H), 3.24 (s, 3H), 3.26 (dd, $J$ = 5.7, 1.7 Hz, 1H), 5.55 (dd, $J$ = 5.7, 1.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.94, 22.62, 28.18, 43.51, 47.00, 49.16, 49.66, 50.43, 94.11, 117.03, 145.45, 201.21, 205.99; MS (EI, 12 eV) *m*/*z* (relative intensity) 238 ($M^+$, 1), 210 ($M^+$ − CO, 100); HRMS (EI) calcd for $C_{13}H_{18}O_4$ ($M^+$) 238.1205, found 238.1205. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.46; H, 7.60.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5,7-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-en-2-one (16a).** This was prepared from methyl vanillate (**9**) and methyl acrylate in 85% yield as a colorless liquid: IR (film) 2950, 1740, 1730, 1710 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.68 (ddd, $J$ = 13.2, 6.0, 2.9 Hz, 1H), 2.35 (ddd, $J$ = 13.2, 10.2, 2.9 Hz, 1H), 3.07 (ddd, 10.2, 3.3, 1.9 Hz, 1H), 3.25 (s, 3H), 3.31 (s, 3H), 3.61 (m, 1H), 3.63 (s, 3H), 3.74 (s, 3H), 3.75 (m, 1H), 7.06 (dd, $J$ = 6.3, 1.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.81, 38.25, 39.16, 50.05, 50.24, 50.80, 52.00, 52.40, 93.19, 135.32, 138.11, 164.07, 172.77, 199.70; MS (EI, 12 eV) *m*/*z* (relative intensity) 270 ($M^+$ − CO, 100); HRMS (EI) calcd for $C_{13}H_{18}O_6$ ($M^+$ − CO) 270.1103, found 270.1105.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (16b).** This was prepared from methyl vanillate (**9**) and methyl methacrylate in 90% yield as a colorless liquid: IR (film) 2975, 1727 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31 (s, 3H), 1.93 (dd, $J$ = 18.1, 2.2 Hz, 1H), 2.19 (dd, $J$ = 18.1, 3.1 Hz, 1H), 3.26 (s, 3H), 3.34 (s, 3H), 3.48 (d, $J$ = 6.5 Hz, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 3.65−3.71 (m, 1H), 7.09 (dd, $J$ = 6.5, 1.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.92, 31.58, 38.03, 46.29, 49.32, 49.77, 51.58, 52.21, 56.93, 93.17, 137.27, 137.36, 164.22, 175.67, 200.98; MS (EI, 20 eV) *m*/*z* (relative intensity) 284 ($M^+$ − CO, 70), 252 (8), 225 (100); HRMS calcd for $C_{14}H_{20}O_6$ ($M^+$ − CO) 284.1260, found 284.1260.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-ethanoyl-5-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (16c).** This was prepared from methyl vanillate (**9**) and methyl vinyl ketone in 86% yield as a colorless liquid: IR (film) 2947, 1741, 1714, 1671 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.52 (ddd, $J$ = 13.1, 6.8, 3.0 Hz, 1H), 2.09 (s, 3H), 2.36 (ddd, $J$ = 13.1, 10.2, 3.0

Hz, 1H), 3.13 (m, 1H), 3.24 (s, 3H), 3.31 (s, 3H), 3.54 (dd, $J$ = 6.2, 1.3 Hz, 1H), 3.72 (s, 3H), 3.75 (m, 1H), 7.05 (dd, $J$ = 6.2, 1.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.08, 28.12, 38.22, 47.48, 50.04, 50.23, 51.94, 93.33, 135.82, 136.92, 164.05, 200.11, 205.10; MS (EI, 70 eV) *m/z* (relative intensity) 254 ($M^+$ − CO, 9), 252 (8), 43 (100); HRMS calcd for $C_{13}H_{18}O_5$ ($M^+$ − CO) 254.1154, found 254.1148.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5-ethanoyl-7-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (17a).** This was prepared from acetovanillone (**10**) and methyl acrylate in 89% yield as a yellowish liquid: IR (film) 2951, 1738 (br), 1673 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.55 (ddd, $J$ = 13.2, 6.4, 2.8 Hz, 1H), 2.32 (s, 3H), 2.39 (ddd, $J$ = 13.2, 10.4, 2.8 Hz, 1H), 3.13 (ddd, $J$ = 10.4, 6.4, 1.8 Hz, 1H), 3.23 (s, 3H), 3.32 (s, 3H), 3.64 (dd, $J$ = 6.8, 1.8 Hz, 1H), 3.65 (s, 3H), 3.94 (m, 1H), 7.05 (dd, $J$ = 6.8, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.65, 24.80, 35.98, 39.19, 50.04, 50.11, 50.70, 52.30, 93.10, 135.53, 146.20, 172.90, 194.10, 199.78; MS (EI, 70 eV) *m/z* (relative intensity) 254 ($M^+$ − CO, 74), 195 (100); HRMS calcd for $C_{13}H_{18}O_5$ ($M^+$ − CO) 254.1154, found 254.1162.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5-ethanoyl-7-methoxycarbonyl-7-methylbicyclo[2.2.2]oct-5-en-2-one (17b).** This was prepared from acetovanillone (**10**) and methyl methacrylate in 87% yield as a yellowish liquid: IR (film) 2953, 1737 (br), 1674 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33 (s, 3H), 1.96 (dd, $J$ = 14.0, 2.0 Hz, 1H), 2.06 (dd, $J$ = 14.0, 3.6 Hz, 1H), 2.29 (s, 3H), 3.21 (s, 3H), 3.34 (s, 3H), 3.50 (d, $J$ = 6.4 Hz, 1H), 3.65 (s, 3H), 3.85 (m, 1H), 7.05 (dd, $J$ = 6.4, 2.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.65, 25.27, 31.94, 36.27, 46.80, 49.71, 50.04, 52.48, 57.22, 93.31, 137.57, 145.40, 175.63, 194.32, 201.02; MS (EI, 70 eV) *m/z* (relative intensity) 268 ($M^+$ − CO, 49), 209 (100); HRMS calcd for $C_{14}H_{20}O_5$ ($M^+$ − CO) 268.1311, found 268.1312.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5,7-diethanoylbicyclo[2.2.2]-oct-5-en-2-one (17c).** This was prepared from acetovanillone (**10**) and methyl vinyl ketone in 90% yield as a yellowish liquid: IR (film) 2947, 1741, 1714, 1671 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (ddd, $J$ = 13.2, 6.8, 2.8 Hz, 1H), 2.11 (s, 3H), 2.29 (s, 3H), 2.42 (ddd, $J$ = 13.2, 10.4, 2.8 Hz, 1H), 3.19 (m, 1H), 3.22 (s, 3H), 3.33 (s, 3H), 3.56 (dd, $J$ = 6.8, 1.6 Hz, 1H), 3.94 (m, 1H), 7.05 (dd, $J$ = 6.8, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.14, 24.54, 28.08, 35.91, 47.60, 50.08, 93.24, 136.48, 144.96, 194.14, 200.33, 205.46; MS (EI, 70 eV) *m/z* (relative intensity) 238 ($M^+$ − CO, 13), 195 (100); HRMS calcd for $C_{13}H_{18}O_4$ ($M^+$ − CO) 238.1205, found 238.1202.

**(1*R**,4*S**,7*S**)-1,3,3-Trimethoxy-5,7-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-en-2-one (18a).** This was prepared from methyl syringate (**11**) and methyl acrylate in 74% yield as a colorless solid: mp 124−125 °C (from ethyl acetate−hexanes); IR (film) 2961, 1734 cm$^{-1}$; $^1$H NMR (400 MHz, CDC1$_3$) $\delta$ 1.65 (ddd, $J$ = 13.0, 6.3, 2.9 Hz, 1H), 2.43 (ddd, $J$ = 13.0, 10.1, 2.9 Hz, 1H), 3.17 (ddd, $J$ = 10.1, 6.3, 1.2 Hz, 1H), 3.32 (s, 3H), 3.37 (s, 3H), 3.61 (s, 3H), 3.69 (s, 3H), 3.79 (m, 1H), 3.83 (s, 3H), 7.22 (d, $J$ = 1.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.17, 37.60, 43.27, 49.89, 50.02, 51.98, 52.07, 54.42, 85.71, 92.94, 135.06, 136.12, 163.54, 172.28, 197.84; MS (EI, 12 eV) *m/z* (relative intensity) 300 ($M^+$ − CO, 83), 285 (100); HRMS (EI) calcd for $C_{14}H_{20}O_7$ ($M^+$ − CO) 300.1209, found 300.1203. Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.88; H, 6.15.

**(1*R**,4*S**,7*S**)-1,3,3-Trimethoxy-5,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (18b).** This was prepared from methyl syringate (**11**) and methyl methacrylate in 78% yield as a colorless solid: mp 86−87 °C (from ethyl acetate−hexanes); IR (film) 2966, 1731 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.30 (s, 3H), 1.95−2.05 (m, 2H), 3.31 (s, 3H), 3.40 (s, 3H), 3.58 (s, 3H), 3.66 (s, 3H), 3.73 (dd, $J$ = 2.7, 2.0 Hz, 1H), 3.83 (s, 3H), 7.43 (d, $J$ = 2.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.28, 35.86, 37.57, 49.65, 49.92, 50.14, 52.04, 52.32, 55.20, 89.45, 92.75, 134.02, 137.15, 163.85, 174.26, 199.08; MS (EI, 12 eV) *m/z* (relative intensity) 314 ($M^+$ − CO, 71), 299 (100); HRMS (EI) calcd for $C_{15}H_{22}O_7$ ($M^+$ − CO) 314.1366, found 314.1367. Anal. Calcd for $C_{16}H_{22}O_8$: C, 56.l3; H, 6.48. Found: C, 56.11; H, 6.49.

**(1*R**,4*S**,7*S**)-1,3,3-Trimethoxy-7-ethanoyl-5-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (18c).** This was prepared from methyl syringate (**11**) and methyl vinyl ketone in 87% yield as a colorless solid: mp 93−94 °C (from ethyl acetate−hexanes); IR (film) 2959, 1757, 1717 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.63 (ddd, $J$ = 13.0, 6.2, 2.9 Hz, 1H), 2.20 (s, 3H), 2.20−2.28 (m, 1H), 3.23−3.29 (m, 1H), 3.29 (s, 3H), 3.38 (s, 3H), 3.56 (s, 3H), 3.78−3.82 (m, 1H), 3.82 (s, 3H), 7.20 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 25.72, 31.73, 37.71, 49.49, 49.70, 50.01, 51.93, 54.75, 86.62, 92.74, 134.52, 135.24, 163.39, 198.25, 206.32; MS (EI, 12 eV) *m/z* (relative intensity) 284 ($M^+$ − CO, 48), 43 (100); HRMS (El) calcd for $C_{15}H_{20}O_7$ ($M^+$) 312.1209, found 312.1210. Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45. Found: C, 57.67; H, 6.47.

**(1*R**,4*S**,7*S**)-1,3,3-Trimethoxy-7-methoxycarbonyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (19a).** This was prepared from phenol **12** and methyl acrylate in 45% yield as a colorless solid: mp 73−74 °C (from ethyl acetate−hexanes); IR (film) 2956, 1741 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.67 (ddd, $J$ = 12.9, 6.3, 2.9 Hz, 1H), 1.97 (s, 3H), 2.26 (ddd, $J$ = 12.9, 9.9, 2.9 Hz, 1H), 2.92 (m, 1H), 3.10−3.14 (m, 1H), 3.32 (s, 3H), 3.36 (s, 3H), 3.57 (s, 3H), 3.69 (s, 3H), 5.79 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.99, 26.62, 42.38, 42.90, 49.62, 50.44, 51.91, 53.92, 84.42, 93.88, 118.77, 143.04, 173.04, 198.84; MS (EI, 12 eV) *m/z* (relative intensity) 256 ($M^+$ − 28, 18), 209 (100); HRMS (EI) calcd for $C_{14}H_{20}O_6$ ($M^+$) 284.1260, found 284.1252.

**(1*R**,4*S**,7*S**)-1,3,3-Trimethoxy-7-methoxycarbonyl-5,7-dimethylbicyclo[2.2.2]oct-5-en-2-one (19b).** This was prepared from phenol **12** and methyl methacrylate in 33% yield as a colorless solid: mp 41−42 °C (from ethyl acetate−hexanes); IR (film) 2957, 1736 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.21 (s, 3H), 1.78 (dd, $J$ = 13.4, 2.9 Hz, 1H), 1.90 (s, 3H), 2.00 (dd, $J$ = 13.4, 2.9 Hz, 1H), 2.81 (m, 1H), 3.28 (s, 3H), 3.29 (s, 3H), 3.44 (s, 3H), 3.59 (s, 3H), 5.91 (s, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.40, 21.07, 35.12, 42.89, 49.29, 49.38, 50.29, 51.99, 54.57, 88.19, 93.62, 118.78, 142.15, 174.95, 200.23; MS (EI, 12 eV) *m/z* (relative intensity) 298 ($M^+$, 1), 270 ($M^+$ − CO, 71), 223 (100); HRMS (EI) calcd for $C_{15}H_{22}O_6$ 298.1416, found 298.1429.

**(1*R**,4*S**,7*S**)-1,3,3-Trimethoxy-7-ethanoyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (19c).** This was prepared from phenol **12** and methyl vinyl ketone in 34% yield as a colorless liquid: IR (film) 2952, 1728 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.68 (ddd, $J$ = 13.1, 6.3, 3.0 Hz, 1H), 1.97 (s, 3H), 2.05 (ddd, $J$ = 13.1, 9.6, 3.0 Hz, 1H), 2.21 (s, 3H), 2.92 (m, 1H), 3.18 (dd, $J$ = 9.6, 6.3 Hz, 1H), 3.33 (s, 3H), 3.34 (s, 3H), 3.52 (s, 3H); 5.77 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.19, 24.99, 31.81, 43.16, 49.29, 49.57, 50.54, 54.24, 85.35, 93.81, 116.88, 143.73, 199.66, 207.73; MS (EI, 12 eV) *m/z* (relative intensity) 240 ($M^+$ − 28, 41), 193 (100); HRMS (EI) calcd for $C_{13}H_{20}O_4$ ($M^+$ − CO) 240.1362, found 240.1369.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-6,7-bis(methoxycarbonyl)-bicyclo[2.2.2]oct-5-en-2-one (20a).** This was prepared from methyl isovanillate (**13**) and methyl acrylate in 76% yield as a colorless liquid: IR (film) 2953, 1732 (br) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.74 (ddd, $J$ = 13.2, 5.6, 2.8 Hz, 1H), 2.25 (ddd, $J$ = 13.2, 10.0, 2.8 Hz, 1H), 3.07 (ddd, $J$ = 10.0, 5.6, 2.0 Hz, 1H), 3.27 (s, 3H), 3.32 (s, 3H), 3.32 (m, 1H), 3.63 (s, 3H), 3.74 (s, 3H), 4.05 (apparent t, $J$ = 2.0 Hz, 1H), 7.36 (dd, $J$ = 6.8, 2.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 23.41, 38.60, 39.22, 49.17, 49.64, 50.37, 51.90, 52.23, 93.20, 129.48, 143.43, 163.69, 172.61, 199.56; MS (EI, 70 eV) *m/z* (relative intensity) 270 ($M^+$ − 28, 100); HRMS (EI) calcd for $C_{14}H_{18}O_7$ ($M^+$) 298.1053, found 298.1045.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-6,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (20b).** This was prepared from methyl isovanillate (**13**) and methyl methacrylate in 60% yield as a colorless liquid: IR (film) 2960, 1740, 1730, 1720 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H), 1.83 (dd, $J$ = 13.9, 2.2 Hz, 1H), 2.27 (dd, $J$ = 13.9, 3.6 Hz, 1H), 3.25 (m, 1H), 3.26 (s, 3H), 3.32 (s, 3H), 3.58 (s, 3H), 3.72 (s, 3H), 3.87 (d, $J$ = 1.5 Hz, 1H), 7.27 (dd, $J$ = 8.7, 1.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.94, 31.12, 39.51, 46.19, 49.56, 50.45,

51.98, 52.40, 55.56, 93.61, 131.70, 143.37, 163.80, 175.49, 200.60; MS (EI, 12 eV) *m/z* (relative intensity) 284 ($M^+$ − CO, 100).

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-ethanoyl-6-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (20c).** This was prepared from methyl isovanillate (**13**) and methyl vinyl ketone in 84% yield as a colorless solid: mp 69−70 °C (from ethyl acetate−hexanes); mp 69−70 °C; IR (film) 2950, 1740, 1730, 1720 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.85 (ddd, $J$ = 13.3, 5.5, 3.0 Hz, 1H), 2.03 (ddd, $J$ = 13.3, 9.5, 2.7 Hz, 1H), 2.19 (s, 3H), 3.11 (ddd, $J$ = 9.5, 5.5, 2.0 Hz, 1H), 3.27 (s, 3H), 3.33 (m, 1H), 3.36 (s, 3H), 3.72 (s, 3H), 4.06 (dd, $J$ = 2.0, 1.7 Hz, 1H), 7.31 (dd, $J$ = 7.1, 1.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.25, 28.32, 39.46, 46.68, 49.04, 49.73, 50.60, 52.08, 93.58, 128.77, 143.61, 163.85, 200.00, 205.01; MS (EI, 70 eV) *m/z* (relative intensity) 254 ($M^+$ − CO); HRMS (EI) calcd for $C_{14}H_{18}O_6$ ($M^+$) 282.1103, found 282.1087. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.57; H, 6.43.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-methoxycarbonyl-5-(2,5-dioxacyclopentyl)bicyclo[2.2.2]oct-5-en-2-one (21a).** This was prepared from phenol **14** and methyl acrylate in 86% yield as a colorless solid: reaction time 60 h; mp 121−123 °C (from ethyl acetate−hexanes); IR (film) 2955, 1740, 1730 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.73 (ddd, $J$ = 13.1, 6.1, 2.9 Hz, 1H), 2.33 (ddd, $J$ = 13.1, 10.0, 3.5 Hz, 1H), 3.06 (ddd, $J$ = 10.0, 6.1, 2.0 Hz, 1H), 3.27 (dd, $J$ = 3.5, 2.9 Hz, 1H), 3.33 (s, 3H), 3.34 (s, 3H), 3.55 (dd, $J$ = 6.5, 2.0 Hz, 1H), 3.68 (s, 3H), 3.90−4.10 (m, 4H), 5.43 (s, 1H), 6.19 (d, $J$ = 6.5 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 25.24, 38.17, 39.17, 49.76, 49.96, 52.22, 64.75, 64.83, 93.56, 102.01, 122.80, 144.95, 173.14, 200.44; MS (EI, 70 eV) *m/z* (relative intensity) 284 ($M^+$ − CO, 30), 253 (100); HRMS (EI) calcd for $C_{15}H_{20}O_7$ ($M^+$) 312.1209, found 312.1208. Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.69, H, 6.45. Found: C, 57.71, H, 6.41.

**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-7-methoxycarbonyl-7-methyl-5-(2,5-dioxacyclopentyl)bicyclo[2.2.2]oct-5-en-2-one (21b).** This was prepared from phenol **14** and methyl methacrylate in 84% yield as a colorless solid: reaction time 72 h; mp 97−98 °C (from ethyl acetate−hexanes); IR (film) 2975, 1725 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H), 1.89 (dd, $J$ = 13.6, 2.8 Hz, 1H), 2.27 (dd, $J$ = 13.6, 3.6 Hz, 1H), 3.20 (m, $J$ = 3.6, 2.8, 1.6 Hz, 1H), 3.34 (s, 3H), 3.35 (s, 3H), 3.40 (d, $J$ = 6.8 Hz, 1H), 3.67 (s, 3H), 3.90−4.00 (m, 4H), 5.41 (d, $J$ = 0.8 Hz, 1H), 6.22 (ddd, $J$ = 6.8, 1.6, 0.8 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 25.04, 32.07, 38.19, 46.60, 49.37, 49.70, 52.20, 56.06, 64.45, 64.58, 93.55, 101.83, 124.40, 144.19, 175.75, 201.52; MS (EI, 70 eV) *m/z* (relative intensity) 298 ($M^+$ − CO, 75), 267 (100); HRMS (EI) calcd for $C_{16}H_{22}O_7$ ($M^+$) 326.1366, found 326.1360. Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89, H, 6.79. Found: C, 58.84, H, 6.73.

**(1*R**,4*S**,7*S**)-7-Ethanoyl-3,3-dimethoxy-5-(2,5-dioxacyclopentyl)bicyclo[2.2.2]oct-5-en-2-one (21c).** This was prepared from phenol **14** and methyl vinyl ketone in 88% yield as a colorless solid: reaction time 20 h; mp 104−105 °C (from ethyl acetate−hexanes); IR (film) 2975, 1738 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.61 (ddd, $J$ = 12.8, 6.4, 3.2 Hz, 1H), 2.12 (s, 3H), 2.27 (ddd, $J$ = 12.8, 9.6, 3.2 Hz, 1H), 3.07 (ddd, $J$ = 9.6, 6.4, 2.0 Hz, 1H), 3.26 (m, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 3.47 (dd, $J$ = 6.4, 2.0 Hz, 1H), 3.80−4.00 (m, 4H), 5.37 (d, $J$ = 0.8 Hz, 1H), 6.16 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 24.31, 28.22, 38.13, 47.26, 49.16, 49.93, 64.70, 64.82, 93.71, 101.99, 123.01, 144.65, 200.77, 205.56; MS (EI, 70 eV) *m/z* (relative intensity) 281 ($M^+$ − $CH_3$, 5), 73 (100); HRMS (EI) calcd for $C_{15}H_{20}O_6$ ($M^+$) 296.1260, found 296.1180. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80, H, 6.80. Found: C, 60.83, H, 6.84.

**Dimer 22.** This was obtained in 72% yield during attempted isolation of MOB **1**, which was generated by adding DAIB (1.1 mM) to a solution of phenol **8** in MeOH (10 mL) at room temperature:[21a] $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.94, 26.00, 44.25, 44.92, 44.99, 48.25, 49.59, 49.88, 50.14, 59.30, 94.54, 98.27, 122.01, 126.20, 142.54, 152.04, 193.13, 201.68; MS (EI, 70 eV) *m/z* (relative intensity) 336 ($M^+$, 2), 308 (100); HRMS (EI) calcd for $C_{18}H_{24}O_6$ ($M^+$) 336.1573, found 336.1577.

**Dimer 23.** This was obtained in 85% yield during attempted isolation of MOB **2**, which was generated by adding DAIB (1.1 mM) to a solution of phenol **9** in MeOH (10 mL) at room temperature: mp 129−131 °C (from ethyl acetate−hexanes); IR (film) 2952, 1735, 1719 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.03 (s, 3H), 3.24 (s, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 3.47 (d, $J$ = 6.8 Hz, 1H), 3.75 (s, 3H), 3.77 (m, 1H), 3.80 (s, 3H), 4.02 (m, 1H), 6.00 (d, $J$ = 10.4 Hz, 1H), 6.55 (dd, $J$ = 10.4, 1.2 Hz, 1H), 6.85 (dd, $J$ = 6.8, 2.4 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 39.95, 42.97, 48.55, 49.31, 49.97, 50.99, 52.23, 53.43, 54.74, 57.44, 93.75, 97.39, 128.50, 136.00, 137.13, 143.80, 163.14, 171.44, 192.50, 198.36; MS (EI, 70 eV) *m/z* (relative intensity) 409 ($M^+$ − $CH_3$, 11), 396 ($M^+$ − CO, 57), 59 (100); HRMS (EI) calcd for $C_{20}H_{24}O_{10}$ ($M^+$) 424.1370, found 424.1378.

**Dimer 25.** This was obtained in 78% yield during attempted isolation of MOB **4**, which was generated by adding DAIB (1.1 mM) to a solution of phenol **11** in MeOH (10 mL) at room temperature: mp 153−154 °C (from ethyl acetate−hexanes); IR (film) 1726 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.05 (s, 3H), 3.26 (s, 3H), 3.39 (s, 3H), 3.58−3.59 (m, 6H), 3.66 (s, 3H), 3.72 (s, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 3.85 (s, 1H), 5.73 (s, 1H), 6.99 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 38.94, 44.80, 48.64, 49.12, 50.43, 51.28, 52.51, 53.29, 55.63, 55.89, 58.25, 92.02, 92.94, 97.79, 109.77, 134.48, 138.14, 151.25, 162.78, 172.18, 187.93, 197.89; MS (EI, 70 eV) *m/z* (relative intensity) 456 ($M^+$ − 28, 53); HRMS (EI) calcd for $C_{22}H_{28}O_{12}$ ($M^+$) 484.1581, found 484.1577.

**Dimer 27.** This was obtained in 82% yield during attempted isolation of MOB **6**, which was generated by adding DAIB (1.1 mM) to a solution of phenol **13** (1 mM) in MeOH (10 mL) at room temperature: mp 104−106 °C (from ethyl acetate−hexanes); IR (film) 2955, 1725 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.92 (s, 3H), 3.08 (s, 3H), 3.17 (dd, $J$ = 7.0, 1.5 Hz, 1H), 3.22 (dd, $J$ = 6.0, 3.1 Hz, 1H), 3.28 (s, 3H), 3.33 (s, 3H), 3.53 (s, 3H), 3.70 (m, 1H), 3.74 (s, 3H), 3.83 (m, 1H), 6.61 (d, $J$ = 1.0 Hz, 1H), 6.94 (dd, $J$ = 6.8, 1.7 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 38.00, 38.06, 40.72, 48.92, 49.72, 50.10, 50.38, 51.41, 51.92, 52.64, 94.13, 98.33, 132.09, 132.54, 140.41, 144.18, 163.12, 164.61, 193.63, 200.10; MS (EI, 70 eV) *m/z* (relative intensity) 424 ($M^+$, 11), 396 (100); HRMS (EI) calcd for $C_{20}H_{24}O_{10}$ ($M^+$) 424.1370, found 424.1386.

**Dimer 28.** This was obtained in 69% yield during attempted isolation of MOB **7**, which was generated by adding DAIB (1.1 mM) to a solution of phenol **14** (1 mM) in MeOH (10 mL) at room temperature: IR (film) 2987, 1737, 1706 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.04 (s, 3H), 3.15 (t, $J$ = 1.8 Hz, 1H), 3.27 (s, 3H), 3.32 (d, $J$ = 6.8 Hz, 1H), 3.38 (s, 3H), 3.39 (s, 3H), 3.58 (t, $J$ = 1.2 Hz, 1H), 3.78−3.92 (m, 7H), 4.11−4.15 (m, 1H), 5.21 (d, $J$ = 0.8 Hz, 1H), 5.23 (s, 1H), 5.99 (ddd, $J$ = 7.1, 2.1, 1.1 Hz, 1H), 6.02 (d, $J$ = 10.4 Hz, 1H), 6.35 (dd, $J$ = 10.4, 1.2 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 39.84, 41.85, 48.16, 48.42, 49.77, 51.16, 51.56, 53.70, 64.19, 64.55, 64.99, 66.06, 94.49, 97.46, 101.35, 104.76, 125.43, 129.22, 142.91, 146.73, 191.94, 199.12; MS (EI, 70 eV) *m/z* (relative intensity) 421 ($M^+$ − OMe, 13), 350 (100); HRMS (EI) calcd for $C_{22}H_{28}O_{10}$ ($M^+$) 452.1683, found 452.1691.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR and DEPT spectra of compounds **15**−**21**(**a**−**c**). This material is available free of charge via the Internet at http://pubs.acs.org.

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