Lewis Acid-Promoted, Stereocontrolled, Gram Scale, Diels−Alder Cycloadditions of Electronically Matched 2-Pyrones and Vinyl Ethers: The Critical Importance of Molecular Sieves and the Temperature of Titanium Coordination with the Pyrone

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(*R*)-(+)-Binol−titanium coordinates with commercial methyl 2-pyrone-3-carboxylate and promotes mild, highly enantiocontrolled Diels−Alder cycloadditions with electron-rich vinyl ether CH_2=CHOCH_2-1-naphthyl and vinyl silyl ether CH_2=CHOSiMe_2Bu-*t* leading to valuable 1α,25-dihydroxyvitamin D_3 (calcitriol) intermediate (−)-**2**. Unexpectedly, two subtle variables were found to be critical for obtaining reproducibly over 90% enantioselectivities in gram scale cycloadditions: (1) the moisture content (15−17% is best) of the molecular sieves used to prepare the binol−titanium complex according to the Mikami protocol and (2) the temperature (50 °C is best) at which the pyrone ester is mixed with the binol−titanium complex. Unsubstituted 2-pyrone undergoes ytterbium-promoted, high-pressure, regioselective, and stereoselective Diels−Alder cycloaddition with benzyl vinyl ether to form versatile bicyclic lactone (±)-**4** on gram scale.

We and others have been studying how to coax flat, stereochemically uninteresting, semiaromatic and thus normally unreactive 2-pyrone dienes into Diels−Alder cycloadditions and how to control the absolute stereochemistry of such cycloadditions to form synthetically useful, versatile, bicyclic lactone adducts.[1] Such bicyclic adducts can be converted into various enantiopure and biologically active compounds (*e.g.*, 1α,25-dihydroxyvitamin D_3 and various analogs).[2] To achieve high stereochemical results, chiral auxiliaries have been incorporated separately into the dienophiles,[3] into the pyrone diene,[4] and into the pyrone diene plus into the Lewis acid activator of the (4 + 2)-cycloaddition process.[5] Recently, in preliminary fashion, we reported an even better solution: use of a stereocontrol element on only the Lewis acid. In this way, using titanium complexes derived from chiral, nonracemic tartrates[6] and especially binaphthol,[7] Diels−Alder cycloadditions were achieved with electronically matched 2-pyrones and various dienophiles to form bicycloadducts on milligram scale in over 90% chemical yields and in over 95% enantiomeric purities. A major review of vitamin D synthesis refers to this approach as "highly attractive".[2c] Because this convenient approach uses readily available reactants and proceeds so favorably toward important vitamin D_3 intermediates, it was desirable to scale-up the procedures to form gram quantities of the cycloadducts. In attempting to do so, it quickly became clear that scale-up was unexpectedly complicated and difficult. In working out the surprising subtleties of scale up, we have discovered that these stoichiometric binaphthol−titanium complex-promoted (4 + 2)-cycloadditions are very sensitive, especially to two parameters: (1) the nature and moisture content of the molecular sieves used to prepare the complex and (2) the temperature of the initial coordination of the chiral titanium species with the pyrone diene. We report here details for performing these asymmetric induction Diels−Alder cycloadditions on gram scale with reproducibly high enantioselectivities (Scheme 1). We report also details for gram scale, Lewis acid-promoted cycloadditions of the unsubstituted parent 2-pyrone leading to racemic bicyclic lactone adducts valuable as intermediates for preparation of physiologically potent vitamin D_3 analogs.[2]

Results and Discussion

Dienophiles CH_2=CHOR were chosen so that, after cycloaddition, facile transformation of the OR protecting group into a free OH group could be achieved, thereby representing the synthetic equivalent of using CH_2=CHOH as dienophile.[8] Among the benzylic vinyl ethers used (including benzyl vinyl ether, 1-naphthylmethyl vinyl ether, fluorenyl vinyl ether, and diphenylmethyl vinyl ether), the highest asymmetric inductions were achieved with 1-naphthylmethyl vinyl ether; one added advantage of this dienophile is that it is consider-

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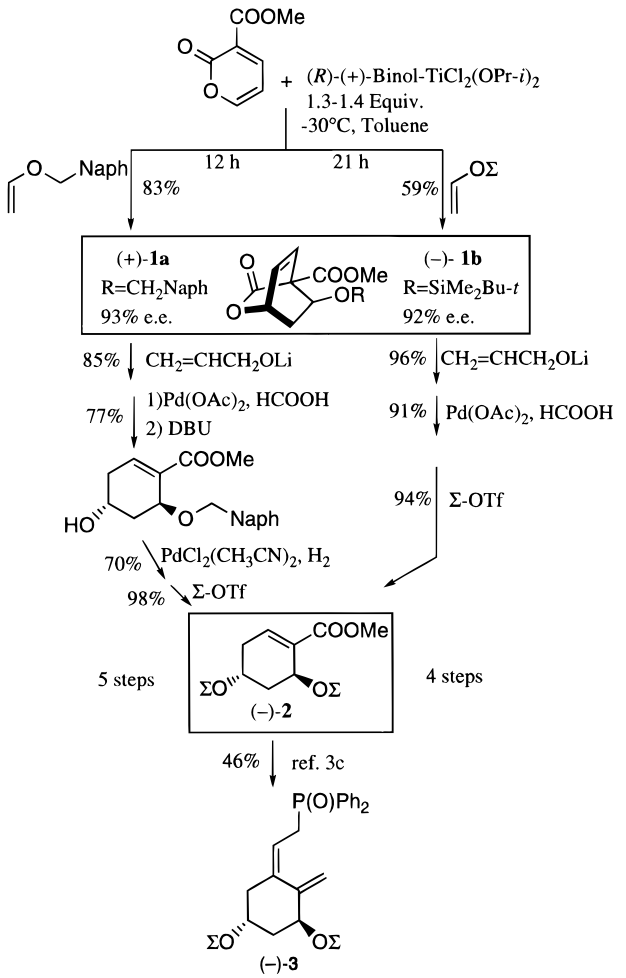
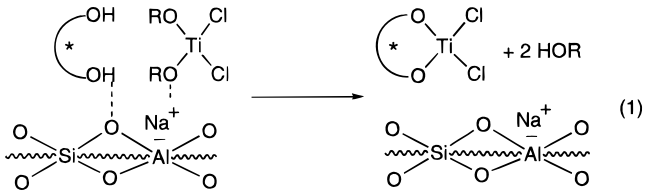
Scheme 1



ably easier to prepare than benzyl vinyl ether. Among the enol silyl ethers $CH_2{=}CHOSiR_3$ used [including $OSiMe_3$ (0% ee), $OSiPh_2Bu$-*t* (23% ee), $OSiMe_2Bu$-*t* (92% ee)], the *tert*-butyldimethylsilyl enol ether $CH_2{=}CHO\Sigma$ gave the highest asymmetric induction. Among the solvents tried (CH_2Cl_2, mesitylene, toluene) for the cycloadditions in Scheme I, toluene was the best.

1,1′-Bi-2-naphthol (binol) stands out as one of the most effective C_2-symmetric, chiral, nonracemic ligands useful for a variety of metal ion-mediated asymmetric reactions.[9] This diol ligand is now commercially available as the (*R*)- as well as the (*S*)-enantiomer. Binol−metal complexes, prepared in various ways, have been reported to promote normal electron-demand Diels−Alder cycloadditions.[10−12] We used this chiral auxiliary therefore in titanium-promoted inverse electron-demand (4 + 2)-cycloadditions with commercial methyl 2-pyrone-3-carboxylate. Diels−Alder cycloadditions with 1-naphthylmethyl vinyl ether directed by a binol−titanium complex in the presence of molecular sieves according to the general protocols of Narasaka[13] and Corey[14] gave bicycloadducts in no more than 60% ee. Preparation of the binol−titanium complex according to the protocol of Mikami,[10a] however, in which 4 Å molecular sieves are used only to assemble the complex but then are removed, gave 95−98% enantioselectivities in small scale (10 mg) reactions.[6] One troubling aspect of this process, however, was the lack of stereochemical reproducibility. As the Mikami group had reported,[10a] their enantiomeric excesses varied over a considerable range. While we achieved very high enantioselectivity (*i.e.*, 95% ee) occasionally and good enantioselectivity (≥90% ee) regularly, enantiomeric excesses as low as 70% were sometimes observed. The preparation of the complex is a multistep process involving reaction of $TiCl_2(OPr\text{-}i)_2$ with binol in the presence of 4 Å molecular sieves, centrifugation to remove the molecular sieves, and washing of the binol−titanium complex with a solvent capable of dissolving the achiral $TiCl_2(OPr\text{-}i)_2$ without dissolving the binol−titanium complex. The washing stage was found to be important in that unreacted $TiCl_2(OPr\text{-}i)_2$, which can promote the cycloaddition in an achiral fashion,[6] must be completely removed in order to achieve consistently high enantioselectivity. Another major factor contributing to reproducibly high enantioselectivity is the molecular sieves. Surface chemistry/morphology and control of the moisture content within the sieves proved to be extremely significant variables.

The molecular sieves used in this process (4 Å, type A) have the general composition $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]\cdot nH_2O$.[15a] Mikami and co-workers proposed the action of the sieves in this process to be as shown in eq 1, in which the asterisk represents the binol moiety.[10a]



The apparent simplicity of this process is complicated by variables present during the manufacture of the molecular sieves. While all 4 Å sieves have the same general composition, differences in trace elements and in crystallinity exist. We became aware of the effect of these "minor" variations when a new batch of 4 Å sieves

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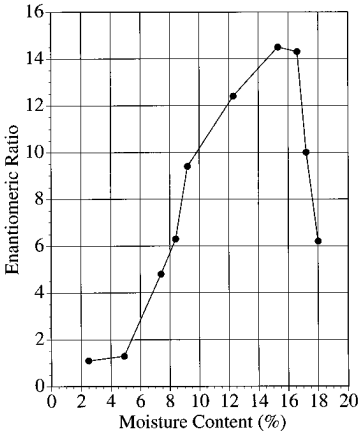


Figure 1. Enantioselectivity of cycloadditions *vs* hydration of molecular sieves used to prepare the binol−titanium complex.

Table 1. Characteristics of Davison 4 Å Molecular Sieves

crystallinity	100%
causticity (% as Na_2O)	0.57
chem compstn (%)	
Al_2O_3	36.112
Na_2O	22.815
CaO	0.061
MgO	0.010
Fe_2O_3	0.044
SO_4	0.035
K_2O	0.208
SiO_2	41.81
particle size distribtn	
90 vol % less than 22.8 μm	
50 vol % less than 11.5 μm	
10 vol % less than 1.7 μm	

failed to produce a chiral complex capable of exceeding 60% ee in our standard Mikami-based cycloaddition. By screening many different batches of 4 Å sieves from different manufacturers, several batches were identified that could produce highly efficient chiral titanium promoters. Commercially available Davison 4 Å molecular sieves, having the characteristics shown in Table 1 and giving the most reliable results, were used in our scale-up reactions.

Once a single batch of sieves was chosen for optimization, conditioning became a concern. Since the initial titanium species and the resulting chiral complex are both moisture sensitive, it was reasonable to assume that the sieves should contain as little water as possible. Therefore, our initial sieve drying protocol was standardized at a temperature of 175 °C for 16 h. Unfortunately, variable enantioselectivity was still a problem. The molecular sieve's moisture content was then precisely controlled through the entire range of hydration (*i.e.*, 2−22% by weight). Suprisingly, a maximum in enantioselectivity was observed in the range of 16−17% moisture content (Figure 1); a similar dependence on moisture content (15−17% being best) was observed also for the enantioselectivity of enol *tert*-butyldimethsilyl ether cycloaddition with methyl 2-pyrone-3-carboxylate. As far as we know, such an observation on the advantage of using molecular sieves of specific moisture content for maximum stereocontrol has been reported only once, in palladium-catalyzed diastereocontrolled cyclizations.[15d] This favorable effect of relatively high moisture content initially seemed counterintuitive, but it might be understandable because the accessibility of the sodium counterion is related to hydration. As moisture content increases, the sodium ions move away from the molecular sieve surface toward the center of the pore. Additionally, the hydrogen bonding of the binol with the surface may be attenuated at higher moisture contents, thus allowing the hydroxyl groups to be more available for complexation with titanium. Both of these possibilities are consistent with the Mikami model.[10a]

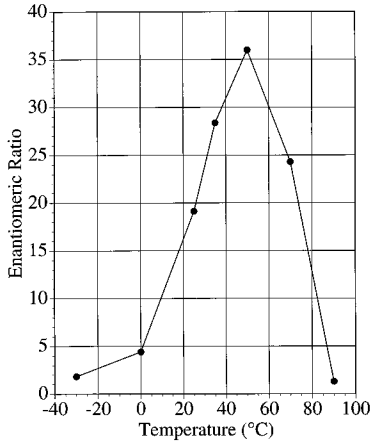


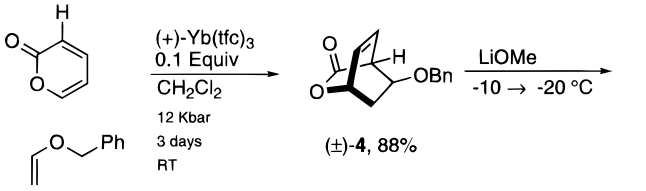
Figure 2. Enantioselectivity of cycloadditions *vs* temperature of mixing pyrone ester plus binol−titanium complex.

After very considerable trial and error in scale-up over a period of several months, it became clear that an additional but unexpected variable is crucial: the temperature at which the pyrone ester was mixed with the binol−titanium complex. Figure 2 graphically summarizes the dramatic and unanticipated sensitivity of the cycloadduct's enantiomeric purity to the temperature of mixing the pyrone ester with the binol−titanium complex. The data in Figure 1 are for room temperature mixing of the pyrone ester with the binol−titanium complex. Generally, 2−4 h of mixing at 50 °C was found to be optimal in gram scale cycloadditions. Unfortunately, ^{1}H NMR spectroscopy was not helpful in correlating the degree of pyrone ester coordination to the binol−titanium complex at various temperatures with the enantioselectivity of the cycloaddition. Thus, although this temperature effect of mixing the pyrone ester with the binol−titanium complex was reproducible and reliable at 50 °C in giving highly enantiocontrolled cycloadditions, unfortunately it has not been possible to develop a clear understanding of the relationship between the structure(s) of the binol−titanium−pyrone complex(es) and the enantioselectivity of cycloaddition.

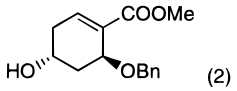
With these two major variables now under control, using Davison 4 Å molecular sieves of 15−17% moisture content to prepare the binol−titanium complex and mixing this complex, freed from molecular sieves, with methyl 2-pyrone-3-carboxylate at 45−50 °C for 2−4 h allowed cycloaddition to occur as in Scheme 1 leading finally to gram quantities of the desired bicycloadducts in 59−83% chemical yields and, most significantly, reproducibly with 92−93% enantioselectivity (Scheme 1). Although only four steps are required to prepare chiron (−)-**2** using the vinyl silyl ether as dienophile, this pathway gave more variable enantioselectivity than did the five-step pathway using the naphthylmethyl vinyl ether as dienophile. Up to 80% of binaphthol of unchanged rotation was recovered after the cycloadditions. It is worth emphasizing that the absolute stereochemistry of the cycloadducts in these gram scale Diels−Alder

reactions (Scheme 1) is consistent with the Seebach mechanistic generalization for titanium-promoted cycloadditions of bidentate ligands such as methyl 2-pyrone-3-carboxylate.[16a] When only 0.1 equiv instead of the usual 1.3−1.4 equiv of the titanium complex was used, surprisingly but reproducibly the mirror image cycloadducts were formed with ee's values in the 50−60% range; this stereochemical reversal may be due to a change from bidentate to monodentate coordination of the titanium Lewis acid to the pyrone ester when excess pyrone ester is present.

Scale-up of our recently reported cycloaddition of unsubstituted 2-pyrone with benzyl vinyl ether[17] to produce racemic cycloadduct (±)-**4** was much less troublesome. Multigram cycloaddition was achieved smoothly as in eq 2, with methanolysis of the initially formed bicyclic lactone (±)-**4** proceeding at −10 to −20 °C in a substantially improved 81% yield.[17] Trisubstituted cyclohexene (±)-**5** is a useful A-ring synthon for construction of 1α,25-dihydoxyvitamin D_3 analogs, including unnatural but biologically active 1β-hydroxy versions.[2]



(±)-**4**, 88%



(2)

(±)-**5**, 81%

Thus, the art of organic synthesis has been pictured here in some of its subtle complexity within the framework of stereocontrolled, atom-economical Diels−Alder cycloadditions. These results forcefully emphasize the experimental nature of organic chemistry, even though great advances in theoretical understanding and in computer-assisted design have been made. For the increasing number of chemists using molecular sieves in organic reactions[15] and the many now using chiral, nonracemic Lewis acids for asymmetric Diels−Alder cycloadditions,[18] these results serve as a warning about the importance of seemingly minor experimental variables, such as the moisture content of molecular sieves, for optimizing chemical reactions. The unanticipated difficulties in finding the best experimental conditions for these gram scale cycloaddition reactions strongly emphasize the importance of demonstrating any new synthetic method not only on milligram scale but also on at least gram scale as a measure of its practical utility.

Experimental Section[3b]

The purity of products was judged to be at least 95% on the basis of their chromatographic homogeneity.

Preparation of the Molecular Sieves. Davison molecular sieves were hydrated fully (22% water content) by exposing them to air in a Petri dish for 1−2 days at room temperature. Partial dehydration was achieved by heating the sieves for different times at 105 °C in a drying oven. Typically about 2−3 h at 105 °C was needed to achieve 15−17% water content. Monitoring the water content of a given batch of molecular sieves was done by heating a weighed portion of these sieves in a commercial electric Bunsen burner (VWR) at 950 °C to remove all moisture and to collapse the microporous structure, thus preventing rehydration upon handling in air. The weight loss after this procedure represents the amount of water originally in this batch of sieves.

Preparation of Binol−Titanium Complex. *R*-(+)-Binaphthol (5.0 g, 17.5 mmol, Aldrich, 98% ee) and 4 Å Davison molecular sieves (MS, 77.5 g) that had been dehydrated to 16.5% moisture were dissolved/suspended in 500 mL of CH_2Cl_2 under argon. After 1 h of stirring at room temperature, Ti(OPr-*i*)$_2$Cl$_2$[19] (4.1 g, 17.5 mL of a 1 M solution in toluene) was added over 10 min via argon-flushed syringe. The slurry immediately changed from white to orange and finally to dark red-brown. Stirring was continued for a total of 2 h, after which the reaction mixture was cannulated into argon-filled septum-capped 150 mL centrifuge tubes. The MS were then sedimented via centrifugation at 5000 rpm for 1 h. The supernatant was then cannulated into a dry 1 L round bottom flask, and the solvent was removed under reduced pressure (0.1 mmHg) with gentle heating. Once the volume was reduced to ∼25 mL, the solution was cannulated into a dry 30 mL centrifuge tube and again centrifuged at 5000 rpm for 20 min to ensure complete removal of the MS. Following careful cannulation of the supernatant into a septum-capped 250 mL flask, the CH_2Cl_2 was completely removed. The flask was then opened under argon, and the dark red-brown solid was thoroughly scraped from the flask wall with a spatula; this scraping process is essential for optimal enantioselectivity in the cycloaddition step. The solid product was then suspended via magnetic stirring in 200 mL of anhydrous pentane. After 15 min of stirring, the suspension was cannulated into a septum-capped Buchner funnel and washed with an additional 500 mL of pentane and dried at reduced pressure (0.1 mmHg) for 16 h. The chiral titanium species was obtained in 78% yield (5.9 g).

Coordination of Methyl 2-Pyrone-3-carboxylate with the Binol−Titanium Complex. Methyl 2-pyrone-3-carboxylate (500 mg, 3.2 mmol, Aldrich, sublimed, mp 74.5 °C) was added to a dry argon-filled 250 mL flask and dissolved in 50 mL of anhydrous toluene. Separately, the chiral binol−titanium dichloride species (1.97 g, 4.4 mmol) was dissolved in 50 mL of toluene. Upon dissolution of the pyrone, it was equilibrated to 50 °C and the chiral titanium species solution was cannulated into the vigorously stirring pyrone solution. Stirring at 50 °C was maintained for 4 h.

Cycloaddition with 1-Naphthylmethyl Vinyl Ether. The above heterogeneous mixture was cooled to −30 °C, and the 1-naphthylmethyl vinyl ether (3.0 g, 16.3 mmol)[19] was added via an argon-flushed syringe at a rate slow enough to maintain −30 °C (∼5 min). The reaction was allowed to proceed for 12 h, after which it was quenched with 100 mL of saturated NaCl. The reaction mixture was extracted with two additional aliquots of brine followed by 2 × 100 mL of H_2O. The aqueous extracts were extracted with 3 × 100 mL of CH_2Cl_2. The organic layers were combined, dried with $MgSO_4$, filtered, concentrated, and purified via column chromatography using 0−25% EtOAc in hexanes as the eluent to yield 910 mg (83% yield) of the cycloadduct (+)-**1a** as a solid: mp 110.1−111.0 °C: ^{1}H NMR ($CDCl_3$) δ 1.67 (dt, J = 14.0, 1.6 Hz, 1H), 2.48 (ddd, J = 13.6, 7.6, 3.6 Hz, 1H), 3.52 (s, 3H), 4.53 (dt, J = 7.2, 1.6 Hz, 1H), 4.85/4.98 (AB, J =12.0 Hz, 2H), 5.22 (m, 1H), 6.60 (dd, J = 7.6, 5.2 Hz, 1H), 6.83 (dt, J = 7.6, 1.6 Hz, 1H), 7.37−7.44 (m, 2H), 7.48−7.55 (m, 2H), 7.83−7.88 (m, 2H), 7.98−8.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 35.0, 52.6, 61.3, 70.3, 71.3, 74.1, 124.1, 125.1, 125.9, 126.3, 127.4, 128.5, 129.3, 129.7,

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130.6, 131.9, 132.4, 133.7, 167.3, 168.6; HRMS calcd for $C_{20}H_{18}O_5$ 338.1154, found 338.1158. Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 70.95; H, 5.36. The ratio of enantiomers was determined by chiral HPLC (Daicel Chiralpak AS, 250 mm × 4.6 mm) using 90:10 hexane:ethanol as the eluent. The minor enantiomer eluted at 16.7 min followed by the major enantiomer at 25.8 min. Recrystallization from ethanol gave a white solid, mp 110.9−112.4 °C. Preparative chiral HPLC gave the major enantiomer, mp 112.1 °C; $[\alpha]^{30}_D$ +13.9° (c = 1.8, $CHCl_3$).

Preparation of Cyclohexene (−)-2 from Cycloadduct (+)-1a. To 910 mg (2.7 mmol) of bicyclic lactone (+)-**1a** in 20 mL of CH_2Cl_2 at 0 °C was added 5.4 mL (5.4 mmol) of a freshly prepared 1.0 M solution of lithium allyloxide in allyl alcohol. After completion of the reaction (∼2 h), the reaction was quenched with 10 mL of aqueous NH_4Cl and the solution was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude product was purified by column chromatography using 0−20% EtOAc in hexane as the eluent. The purified mixed malonate product was obtained in 85% yield (912 mg, 2.3 mmol): ^{1}H NMR ($CDCl_3$) δ 1.83 (ddd, J = 13.6, 10.0 1.6 Hz, 1H), 2.54 (dtd, J = 13.6, 4.4, 0.8 Hz, 1H), 3.36 (s, 3H), 4.44 (m, 1H), 4.58 (m, 4H), 4.91/5.08 (AB, J = 12.4 Hz, 2H), 5.24 (ddq, J = 17.6, 10.0, 1.2 Hz, 2H), 5.82 (m, 1H), 6.02 (ddt, J = 26.8, 10.0, 2.0 Hz, 2H), 7.39−7.54 (m, 4H), 7.79−7.86 (m, 2H), 8.00 (dd, J = 8.4, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.2, 52.9, 59.5, 64.0, 66.5, 67.4, 70.1, 76.0, 118.9, 123.4, 124.4, 125.6, 126.2, 127.1, 128.9, 129.1, 131.6, 132.0, 133.5, 134.0, 135.2, 168.2, 169.3; $[\alpha]^{30}_D$ +97.2° (c = 8.6 $CHCl_3$).

The mixed malonate (900 mg, 2.3 mmol), formic acid (150 μL, 2.8 mmol), triethylamine (410 μL, 2.9 mmol), palladium(II) acetate (12.7 mg, 0.06 mmol),[20] triphenylphosphine (48.7 mg, 0.19 mmol), and 10 mL of dioxane were added to a 25 mL, three-neck flask fitted with a reflux condenser. The mixture was heated to reflux (105 °C). The reaction mixture turned black after ∼25 min, and heating was continued for a total of 23 h. Following cooling and concentration via rotary evaporator, 10 mL of 1.0 N HCl was added and the mixture was extracted with CH_2Cl_2 until the extract was colorless. The organic layers were combined, washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated. The crude conjugated cyclohexenol ester product was dissolved in 10 mL of CH_2Cl_2 and cooled to −78 °C, and DBU (50 μL) was added.[21] After 1 h, the reaction was allowed to warm to rt and stirring was continued for 12 h. The reaction mixture was then washed with aqueous NH_4Cl, extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated. Column chromatography using silica eluted with a gradient of 0−20% EtOAc in hexane provided the purified product in an overall yield of 77% (553 mg, 8 mmol): ^{1}H NMR ($CDCl_3$) δ 1.51 (ddd, J = 25.2, 12.0, 3.6 Hz, 1H), 1.60 (bs, 1H), 2.07 (dddd, J = 13.2, 8.4, 2.4, 1.2 Hz, 1H), 2.30 (d, J = 13.2 Hz, 1H), 2.65 (dtd, J = 19.2, 5.6, 1.2 Hz, 1H), 3.62 (s, 3H), 4.20 (m, 1H), 4.64 (t, J = 2.8 Hz, 1H), 5.05/5.10 (AB, J = 11.2 Hz, 2H), 6.97 (dd, J = 5.6, 2.4 Hz,1H), 7.40−7.53 (m, 4H), 7.78−7.85 (m, 2H), 8.16 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 35.6, 36.7, 52.1, 63.6, 71.1, 71.8, 124.8, 125.6, 126.1, 126.5, 127.4, 128.8, 129.2, 131.0, 132.4, 134.4, 134.3, 141.3, 167.1; $[\alpha]^{30}_D$ −77.2° (c = 4.3, $CHCl_3$); mp 82.4−82.7 °C. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06, H, 6.45. Found: C, 73.01, H, 6.51.

To a vigorously stirred solution of the cyclohexenol ester (550 mg, 1.8 mmol) in 40 mL of EtOAc under H_2 was added 40 mL (0.72 mmol) of a 0.018 M solution of $PdCl_2(CH_3CN)_2$ in EtOH. This latter solution was prepared immediately prior to use by the addition of 405 μL (1% v/v) of glacial acetic acid to a solution of $PdCl_2(CH_3CN)_2$ (207 mg, 0.09 mmol, 0.5% w/v) in 40 mL of EtOH. The reaction was closely monitored by TLC to avoid overreduction. The reaction color proceeded from translucent orange to a grey suspension that eventually formed a black precipitate that, upon settling, resulted in a colorless solution. Upon completion of the reaction (∼45 min), the reaction mixture was filtered through Celite, which was then rinsed with ∼75 mL of EtOAc. After concentration of the filtrate, the cyclohexenediol ester was purified by column chromatography on silica gel (EM Science silica gel 60) using a gradient of 80−100% EtOAc in hexane. The yield of the white solid diol was 70% (217 mg, 1.26 mmol): ^{1}H NMR ($CDCl_3$) δ 1.79 (ddd, J = 13.2, 10.4, 4.8 Hz, 2H), 2.09−2.15 (m, 2H), 2.19 (ddd, J = 8.4, 2.8, 1.2 Hz, 1H), 2.64 (dt, J = 19.2, 5.2 Hz, 1H), 3.78 (s, 3H), 4.18−4.25 (m, 1H), 4.72 (m, 1H), 6.97 (dd, J = 5.2, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.8, 38.6, 51.9, 63.2, 64.3, 131.8, 139.8, 167.2; IR ($CHCl_3$, cm^{-1}) 3606, 3454, 1702; mp 112.5−113.5 °C; $[\alpha]^{30}_D$ −88.7° (c = 1.5, $CHCl_3$); HRMS calcd for $C_8H_{12}O_4$ (M − H_2O) 154.0630, found 154.0631. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80, H, 7.02. Found: C, 55.57, H, 6.98.

To the cyclohexenediol ester (217 mg, 1.26 mmol) in 20 mL of CH_2Cl_2 was added 910 μL (7.8 mmol) of 2,6-lutidine. To this stirred solution was added *tert*-butyldimethylsilyl triflate (1200 μL, 5.2 mmol). The reaction was allowed to proceed for 20 h after which only a trace of starting material was evident by TLC. The reaction was worked up by dilution in CH_2Cl_2, followed by washing the organic layer with 5% HCl and deionized water. The organic phase was then dried with $MgSO_4$, filtered, and concentrated. Purification was accomplished by column chromatography using silica eluted with a gradient of 0−5% EtOAc in hexane, which yielded 98% (495 mg, 1.24 mmol) of the bis-protected diol (−)-**2** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.05 (s,3H), 0.07 (s, 6H), 0.14 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.58 (dd, J = 13.2, 4.0 Hz, 1H), 1.96 (dtd, J = 12.9, 2.5, 1.4 Hz, 1H), 2.08 (ddd, J = 19.2, 9.2, 2.5 Hz, 1H), 2.55 (dtd, J = 19.2, 5.5, 1.3 Hz, 1H), 3.73 (s, 3H), 4.20 (m, 1H), 4.76 (bt, J = 3.0 Hz, 1H), 6.88 (dd, J = 5.4, 2.8 Hz, 1H); ^{13}C ($CDCl_3$) δ −4.8 (2C), −4.6 (2C), 18.0, 25.8 (3C), 25.9 (3C), 36.1, 41.3, 51.5, 63.4, 64.9, 132.4, 139.8, 166.9; IR ($CHCl_3$, cm^{-1}) 1713; $[\alpha]^{30}_D$ −42.3° (c = 3.0, $CHCl_3$). These data are consistent with those reported previously.[3c] HRMS: calcd for $C_{20}H_{40}O_4Si_2$ (M − CH_3) 385.2230, found 385.2235.

Cycloaddition with Enol *tert*-Butyldimethylsilyl Ether. To a solution of methyl 2-pyrone-3-carboxylate (0.55 g, 3.6 mmol) in 80 mL of anhydrous toluene was added the solution of binol−Ti complex (2.1 g, weighed in air, 4.8 mmol, 1.35 equiv) in anhydrous toluene (35 mL) at 45 °C for 1 h. After being stirred for 4 h at 45−48 °C, the resulting solution was cooled to −30 °C. To the cooled solution was added CH_2=CHOSiMe$_2$Bu-*t* (3.0 mL, 18 mmol, 5 equiv).[22] The reaction mixture was stirred at −30 °C for 21 h with monitoring by TLC. After being warmed to rt, the reaction mixture was purified by silica gel chromatography (15% EtOAc/hexanes) without aqueous workup to give 0.66 g (59%) of bicycloadduct (−) **-1b** as a white solid, mp 88−89 °C: 92% ee by HPLC on a Daicel Chiralpak AS column, eluent = 3% EtOH in hexanes, flow rate = 1 mL/min, (+)-**1b** 7.0 min, (−) **-1b** 9.2 min, with detection at 230 nm: $[\alpha]^{28}_D$ −4.15 ° (c = 11.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dt, J = 7.6, 1.6 Hz, 1H), 6.59 (dd, J = 7.6, 5.2 Hz, 1H), 5.21 (dddd, J = 5.2, 3.6, 1.6, 1.6 Hz, 1H), 4.72 (dt, J = 7.2, 1.6 Hz, 1H), 3.89 (s, 3H), 2.61 (ddd, J = 14.0, 7.6, 3.6 Hz, 1H), 1.53 (dt, J = 13.6, 1.6 Hz, 1H), 0.79 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.86, 167.47, 130.00, 129.68, 74.11, 66.21, 62.59, 52.73, 38.11, 52.34, 17.60, −4.54, −5.44; IR ($CHCl_3$, cm^{-1}) 3028, 2956, 2931, 2887, 2856, 1626; MS, m/z (70 eV, EI) 255 (M − t-Bu$^+$, 31.30), 211 (M − t-Bu − CO_2^+, 100); HRMS calcd for $C_{24}H_{40}O_2Si$ − C_4H_9 255.0689, found 255.0686.

Preparation of Cyclohexene (−)-2 from Cycloadduct (−)-1b. To 1.5 mL of allyl alcohol was added 3 mL (3.9 mmol, 1.3 equiv) of a 1.6 M solution of *n*-BuLi in hexanes dropwise at −78 °C with stirring, and then the solution was warmed up to rt for 20 min. To the solution of 0.97 g (3.1 mmol) of two batches of bicyclic lactone (−)-**1b**, 90% ee, in 4.5 mL of CH_2Cl_2:allyl alcohol (2:1) was added the freshly prepared allyloxide solution at 0 °C. After the solution was stirred for 20 min, the reaction was quenched with water, extracted with

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EtOAc (×2), washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by short path chromatography (20% EtOAc/hexanes) gave 1.10 g (96%) of the mixed allyl methyl malonate as a white solid: mp 45−48 °C; $[\alpha]^{28}_D$ +105 ° (*c* = 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddt, *J* = 29.2, 10.4, 1.6 Hz, 2H), 5.85 (m, 1H), 5.28 (dq, *J* = 17.2, 1.6 Hz), 5.23 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.78 (d, *J* = 4.8 Hz, 1H), 4.60 (qdt, *J* = 13.2, 5.2, 1.6 Hz, 1H), 4.41 (bs, 1H), 3.72 (s, 3H), 2.31 (m, 1H), 1.89 (ddd, *J* = 13.6, 9.6, 1.6 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 1H of OH), 0.82 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.93, 168.06, 134.24, 131.25, 123.05, 118.46, 69.68, 65.96, 63.76, 59.80, 52.52, 37.31, 25.56, 17.78, −4.13, −5.56; IR ($CHCl_3$, cm^{-1}) 3027, 3012, 2931, 2887, 1650; MS, *m*/*z* (70 eV, EI) 313 (M − *t*-Bu^+, 100); HRMS *m*/*z* (M^+) calcd for $C_{18}H_{30}O_6Si - C_4H_9$ 313.1107, found 313.1108.

A 20 mL hydrolysis tube was charged with 1.05 g (2.85 mmol) of the mixed malonate, 3.5 mL of dioxane, 0.15 mL (2.5 mmol, 1.25 equiv) of 88% formic acid, 0.55 mL (3.92 mmol, 1.4 equiv) of trimethylamine, triphenylphosphine (74 mg, 0.1 equiv) and palladium diacetate (32 mg, 0.05 equiv) with stirring. This was sealed under argon and stirred for 16 h at 105−110 °C. The reaction mixture was cooled to rt, extracted with EtOAc (×2), washed with 10% HCl and brine, dried over anhydrous Na_2SO_4, and then concentrated *in vacuo* to give 0.81 g of monosilylated hydroxy α,β-unsaturated ester as a pale yellow oil. To a solution of the crude ester (0.81 g, 2.83 mmol) and 2,6-lutidine (1.6 mL, 14.2 mmol, 5 equiv) in 30 mL of CH_2Cl_2 was added *t*-$BuMe_2SiOTf$ (0.8 mL, 3.25 mmol, 1.15 equiv) at 0 °C. After being stirred for 10 min, the reaction mixture was diluted with ether (100 mL) and then the reaction was quenched with water. The solution was washed with 5% HCl (×2), and the aqueous layer was extracted with ether (100 mL). The combined solution was washed with saturated aqueous $NaHCO_3$ solution, and brine, dried over $NaSO_4$, concentrated *in vacuo*, and then purified by chromatography (5% EtOAc/hexanes) to give 0.98 g (86%) of cyclohexene (−)-**2** as a colorless oil. Spectral data are identical with those reported previously.[3c]

Cycloaddition of 2-Pyrone with Benzyl Vinyl Ether: Bicycloadduct (±)-4. A piece of heat-shrinkable Teflon tubing was sealed on one end with a glass plug by using a heat gun. A solution of 0.95 g (1.04 mmol, 0.1 equiv) of (+)-$Yb(tfc)_3$ (Aldrich) in 3 mL of CH_2Cl_2, followed by 1.0 g (10.4 mmol) of 2-pyrone and 2.8 g (20.9 mmol, 2.0 equiv) of benzyl vinyl ether were introduced into it. The open end of the tubing was sealed with a second glass plug in a similar way. The reaction vessel was then pressurized at 12 kbar at rt for 3 days. The reaction mixture, purified by column chromatography (silica gel, eluting solvent 10−20% EtOAc/hexane), gave 2.1 g (9.12 mmol, 88%) of cycloadduct (±)-**4** as a white solid (mp 77−78 °C) having spectroscopic and physical properties identical to those reported previously.[17]

Cyclohexenol Benzyl Ether (±)-5. To 20 mL of methanol at 0 °C was added dropwise 3.0 mL of *n*-BuLi (1.6 M in hexane, 4.8 mmol, 2.2 equiv). After stirring at 0 °C for 30 min, the mixture was diluted with 80 mL of CH_2Cl_2 and cooled to −78 °C, to which a precooled (−78 °C) solution of 0.5 g (2.17 mmol) of (±)-**4** in 15 mL of CH_2Cl_2 was added dropwise over 20 min via cannula. The resulting mixture was warmed to −10 °C, and the progress of the reaction was closely monitored by TLC: R_f (50% EtOAc/hexane) = 0.50, (±)-**4**; 0.33, β,γ-unsaturated ester; 0.26, (±)-**5**. After 5 h, just before the complete conversion of β,γ-unsaturated ester to the product (±)-**5**, the mixture was cooled to −20 °C and stirred for 3 h. The reaction was then quenched with saturated aqueous NH_4Cl at −20 °C. The combined extracts were dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel, eluting solvent 20−50% EtOAc/hexane) to yield 0.46 g (1.75 mmol, 81%) of cyclohexenol benzyl ether (±)-**5** as a pale yellow oil: IR ($CHCl_3$, cm^{-1}) 1708; ^{1}H NMR ($CDCl_3$) δ 1.53 (ddd, *J* = 13.2, 12.0, 3.6 Hz, 1H), 2.10 (ddd, *J* = 19.2, 9.6, 2.4, 1.2 Hz, 1H), 2.31 (dm, *J* = 13.2 Hz, 1H), 2.69 (dtd, *J* = 19.2, 5.6, 1.2 Hz, 1H), 3.74 (s, 3H), 4.23 (m, 1H), 4.54 (t, *J* = 3.2 Hz, 1H), 4.62 and 4.67 (AB, *J* = 11.2 Hz, 1H), 6.99 (dd, *J* = 5.6, 2.4 Hz, 1H), 7.24−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 35.3, 36.5, 51.7, 63.2, 71.7, 72.4, 127.6, 128.0 (2C), 128.3 (2C), 130.6, 138.5, 140.6, 166.6; HRMS calcd for $C_{15}H_{18}O_4$ (M − OCH_3) 231.1021, found 231.1023.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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