An Enantioselective Synthetic Route to Atractyligenin Using the Oxazaborolidine-Catalyzed Reduction of β-Silyl- or β-Stannyl-Substituted α,β-Enones as a Key Step

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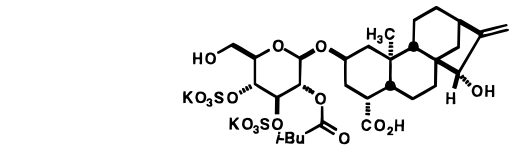
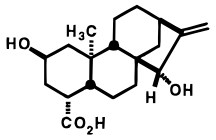
Abstract: In this paper, we describe a novel catalytic enantioselective synthetic route to the bicyclic tetraene ester **3**, a key intermediate for the synthesis of the naturally occurring adenosine diphosphate transport inhibitor atractyligenin (**2**). The success of this route depended on the extension of the oxazaborolidine-catalyzed (CBS) reduction of an achiral β-stannyl-substituted α,β-enone (**6c**) to form a chiral allylic alcohol and further steps to effect simultaneous transfer of chirality, carbocycle formation, and quaternary stereocenter formation, which led to the triene acid **13**. The conversion of **13** to **3** was carried out efficiently by a four-step sequence involving iodolactonization, double elimination, and esterification. The combined use of the CBS reduction of appropriate α,β-enones and Claisen rearrangement provides an important synthetic avenue to many types of natural products containing quaternary stereocenters embedded in cyclic networks.

Introduction

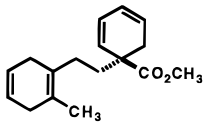
Atractyloside (**1**) and carboxyatractyloside are found in the thistle *Atractylis gummifera* (Plunderer of Life), which has been renowned since ancient times for its deadly toxicity.[1] Atractyloside is highly poisonous by virtue of its strychnine-like action, producing convulsions of a hypoglycemic type.[2] It functions as an inhibitor of oxidative phosphorylation by blocking the translocation of adenosine diphosphate (ADP) into mitochondria, and thus impairing the production of ATP.[1,3] Atractyloside and other related compounds containing atractyligenin (**2**) as the aglycon are common in nature.[4] Atractylosides are present in *Wedelia glauca*,[5] *Iphinona aucheri*,[6] and *Drymaria arenariodes*,[7] and were implicated in the death of cattle, camels, and other livestock that accidentally ingested these plants. In addition, **1** is a component of *Callilepis laureola*, which has been employed by the Zulus and other African people as an herbal medicine. Many patients who have used this remedy have suffered serious and often fatal liver lesions.[8] Unfortunately, atractylosides are also present in *Coffea* beans (*arabica* and to a lesser extent *robustica*)[9] and are unwittingly ingested by coffee drinkers, as confirmed by the detection of a metabolite of **2** in the urine of human coffee consumers.[9a,10] It has been suggested that atractylosides may possibly be responsible for the statistical link between coffee drinking and pancreatic cancer,[11] although further work is clearly necessary to fully establish the detrimental effects of atractylosides on the health of coffee consumers. The intriguing biochemistry and the challenging structures of these compounds have attracted the interest of our group, which reported the only total synthesis of atractyligenin, as the racemate, to date.[12] This paper describes an enantioselective route to **3**, the first chiral intermediate in the synthesis of **2**, and thus establishes the first synthetic route to the natural form of **2**. The enantioselective synthesis of **3** demonstrates a new method for the generation of quaternary stereocenters using the enantioselective oxazaborolidine-catalyzed (CBS) reduction of an enone followed by chirality transfer via an Ireland−Claisen rearrangement, which promises to be widely applicable.[13]



Atractyloside (1)



Atractyligenin (2)



Key intermediate 3

The CBS catalytic reduction of ketones using catalysts **4** (Scheme 1) is a remarkable transformation due to the high enantioselectivities it provides, as well as the detailed mechanistic understanding, broad scope, and predictability of the

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(9) (a) Ludwig, H.: Obermann, H.; Spiteller, G. *Chem. Ber.* **1974**, *107,* 2409. (b) Obermann, H.; Spiteller, G. *Chem. Ber.* **1976**, *109,* 3450. (c) Richter, H.; Spiteller, G. *Chem. Ber.* **1978**, *111,* 3506.

(10) Obermann, H.; Spiteller, G.; Hoyer, G.-A. *Chem. Ber.* **1973**, *106,* 3506.

(11) Pegel, K. H. *Chem. Eng. News* **1981** (July 20), 4.

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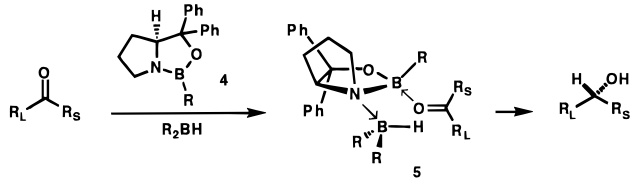
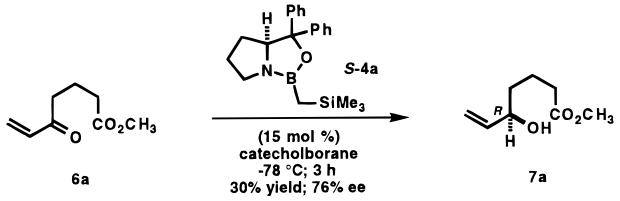
Scheme 1. Enantioselective Oxaborolidine-Catalyzed Reduction of Ketones



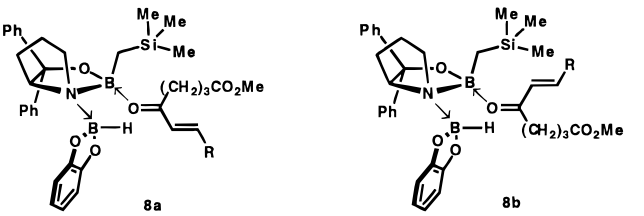
reaction.[14] It represents a powerful tool for the synthesis of a wide variety of simple and complex molecules.[15] A summary of the mechanistic model that has been presented for the reduction of ketones catalyzed by oxazaborolidines **4** is depicted in Scheme 1. The model has the following characteristics: (1) coordination of the stoichiometric reducing agent R_2BH to the nitrogen atom of the catalyst, thereby activating one boron as a hydride donor and the other as a Lewis acid; (2) coordination of the prochiral ketone to the Lewis acidic catalyst at the α-face of the boron in the oxazaborolidine ring and in an *exo* arrangement, which minimizes unfavorable steric interactions between ketone and catalyst while activating the carbonyl group, as shown in **5**; (3) preferential coordination of oxygen via the electron lone pair *syn* to the ketone substituent with the smaller effective steric bulk (R_S), thereby placing the larger substituent (R_L) at a distance from the group on boron (R), as indicated in **5**; and (4) stereoelectronically favorable hydride transfer from the R_2BH unit to the proximate ketone face. The rate acceleration of this pathway relative to other modes is derived from (1) the simultaneous activation of the reductant and ketone by the catalyst and (2) the reduced entropic cost of the reaction when the reagents are held in close proximity as in structure **5**.[14a,16]

Results and Discussion

Our synthetic plan for the asymmetric construction of key intermediate **3** required the CBS reduction of ketone **6a**. Initial experiments were disappointing; the reduction proceeded in only 30% yield and 76% enantiomeric excess (ee).[17] Careful



consideration of the aforementioned mechanistic model for the CBS reduction suggested a reason for the low selectivity: the ketone substituents of **6a** are not sufficiently size-differentiated, and consequently, the reaction proceeds with only a moderate preference for complex **8a** versus **8b** (R = H). In addition, the



model predicts that the use of a bulky and *removable* substituent at the enone β-position, such as a β-trimethylsilyl (TMS) or β-tri-*n*-butylstannyl (*n*-Bu_3Sn) group, would significantly increase the steric presence of the vinyl substituent so as to discourage the pathway that proceeds via complex **8b**. For example, complex **8a** (R = TMS) should be more favorable than **8b** (R = TMS) due to the unfavorable *remote* interactions that exist between the TMS groups of the ketone and the catalyst, in the latter structure.[18] Furthermore, the β-substituent should discourage the 1,4-addition or polymerization side reactions that are probably responsible for the reduced yield observed in the reduction of **6a**. The CBS reductions of the β-TMS and β-*n*-Bu_3Sn enones (**6b** and **6c**) were outstanding as shown in Table 1. The use of dichloromethane as solvent provided uniformly better results than toluene.[19]

The choice of catalyst **4a**[15u] deserves comment. The catalyst bearing a bulky ((trimethylsilyl)methyl)boron substituent (**4a**) was used in the expectation that this would maximize the remote steric interactions present in complex **8b**. As anticipated, catalysts with smaller boron substituents, such as **4b** (*B*-4-*tert*-butylphenyl),[20] **4c** (*B*-*n*-butyl), and **4d** (*B*-methyl), resulted in lower enantioselectivity for the reduction of enone **6b** (Table 2).[21]

The removal of the olefinic substituent of compounds **7** was more difficult than originally foreseen. The cleavage of the TMS group of allylic alcohol **7b** was low yielding (≤15%) under a number of conditions (HI, benzene, 65 °C; HBF_4, acetonitrile, 55 °C; HF, acetonitrile, 23 °C; *p*-toluenesulfinic acid, acetoni-

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(15) For applications of the CBS reduction from this group see: (a) Corey, E. J.; Chen, C. P.; Parry, M. J. *Tetrahedron Lett.* **1988**, *29*, 2899 (PAF antagonists). (b) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201 (ginkgolides A and B). (c) Corey, E. J.; Su, W.-g. *Tetrahedron Lett.* **1988**, *29*, 3423. (d) Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111 (bilobalide). (e) Corey, E. J.; Jardine, P. D. S. *Tetrahedron Lett.* **1989**, *30*, 7297 (forskolin). (f) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207 (fluoxetine). (g) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275 (α-deutero alcohols). (h) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601 (isoproteranol). (i) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442 (denopamine). (j) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547 (chiral oxazaborolidines). (k) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906 (α-amino acids). (l) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025 (antheridic acid). (m) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431 (α-hydroxy acids). (n) Corey, E. J.; Yi, K. Y.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, *33*, 2319 (2,3-oxidosqualene). (o) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1993**, *34*, 5227 (terminal epoxides). (p) Corey, E. J.; Cimprich, K. A. *Tetrahedron Lett.* **1992**, *33*, 4099 (chiral thiols). (q) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835 (chiral controllers). (r) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153 (electronic effects). (s) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837 (cetirizine hydrochloride). (t) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675 (carbinoxamine). (u) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938 (propargylic alcohols). (v) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.*, in press (cicaprost ω-side chain).

(16) For an excellent discussion of the mechanism, see ref 14k.

(17) For the CBS reduction of acyclic enones, see: (a) Bach, J.; Berenguer, R.; Farras, J.; Garcia, J.; Meseguer, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1995**, *6*, 2683. (b) Mulzer, J.; Dupré, S.; Buschmann, J.; Luger, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1452. (c) References 13d,e, 14b,e and 15r.

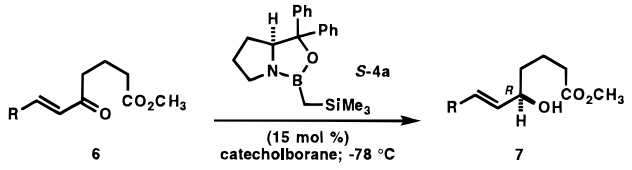
(18) For the use of remote steric interactions in the CBS reduction, see ref 15u.

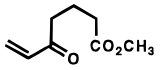
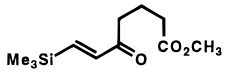
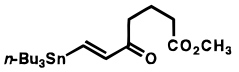
(19) In contrast, (*E*)-styryl methyl ketones gave rise to better enantioselectivities in toluene than in CH_2Cl_2; see ref 15r.

(20) Catalyst **4b** was developed by Mr. Christopher J. Helal of our group. A report on the applications of this catalyst is forthcoming.

(21) The same tendency was observed in the reduction of ketone **6c** (catecholborane, CH_2Cl_2, −78 °C) using the following oxazaborolidine catalysts (15 mol %): **4a** (90% ee, 94% yield), **4b** (79% ee, 57% yield), and **4c** (68% ee, 64% yield).

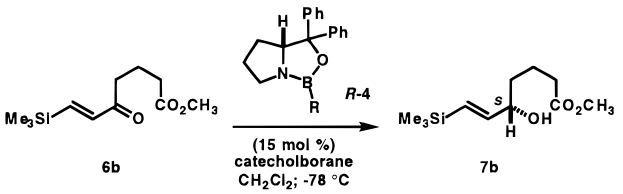
Table 1. Effect of the β-Substituent on the Reduction of Enones



Entry	Ketone	Solvent (ee, yield, time) toluene	CH_2Cl_2
a		70% ee 19% yield 3 h	76% ee 30% yield 3 h
b		78% ee[a] 85% yield 40 h	94% ee[a] 90% yield 3 h
c		75% ee 83% yield 72 h[b]	90% ee 94% yield 24 h

[a] Experiments were performed with catalyst **(*R*)-4a** to afford the (*S*)-product. [b] Reaction temperature: −78 to −40 °C.

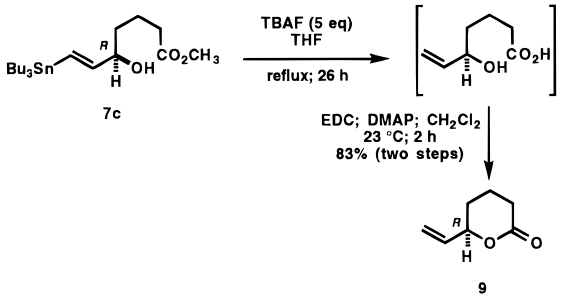
Table 2. Effect of the Catalyst on the Reduction of Enone **6b**



Catalyst	R- =	Enantioselectivity	Yield	Reaction time
4a	$(CH_3)_3Si-CH_2-$	94% ee	90%	3 h
4b	*t*-Bu-	93% ee[a]	78%	23 h
4c	*n*-Bu-	91% ee	92%	17 h
4d	Me-	81% ee	90%	2 h

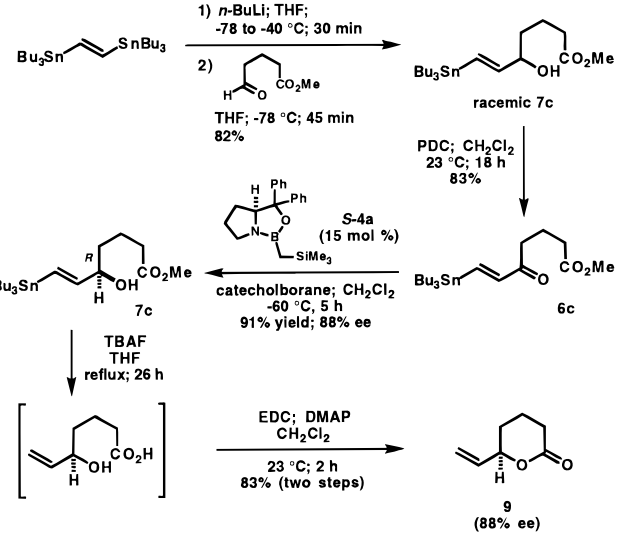
[a] Experiment was performed with catalyst **(*S*)-4a** to afford the (*R*)-product.

trile, reflux; *p*-toluenesulfonic acid, acetonitrile, reflux; and *n*-Bu_4NF, THF, reflux).[22] Consequently, we investigated the protodestannylation of alcohol **7c**. The removal of the *n*-Bu_3-Sn group of **7c** under mildly acidic conditions (silica gel, benzene, reflux, 6 h, Dean-Stark trap with 4 Å molecular sieves, 82%)[23] to afford lactone **9** was accompanied by partial racemization. In contrast, destannylation under basic conditions (*n*-



Bu_4NF, THF), followed by lactonization, provided **9** in 83% yield with no loss of optical purity. The absolute stereochemistry of **7c** was established by hydrogenation of **9** (H_2, Rh-C (5%), ether, 0−23 °C, 2 h, 69%) to afford (*S*)-δ-heptanolactone, followed by comparison of the specific rotation of the latter compound with that of an authentic sample.[24]

Scheme 2. Preparation of Lactone **9**



With optimized conditions for the CBS reduction in hand, the synthesis of key fragment **3** via lactone **9** was accomplished as follows. *trans*-Bis(tri-*n*-butylstannyl)ethylene[23,25] was monolithiated with *n*-butyllithium, and added over 5−10 min to methyl 5-oxopentanoate[26] in THF at −78 °C to afford racemic **7c** in 82% yield, as shown in Scheme 2.[23,25a] Oxidation of the allylic alcohol with pyridinium dichromate (PDC) provided enone **6c**.[27] The large-scale CBS reduction of this enone was best accomplished at −60 °C using freshly prepared catalyst (***S*)-4a**, which resulted in the formation of **7c** of 88% ee.[28] As described above, fluoride-induced destannylation of optically active **7c** produced the hydroxy acid shown, which without isolation was lactonized using 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride and 4-(dimethylamino)pyridine, to give **9** in 88% ee.

As indicated in Scheme 3, lactone **9** was deprotonated using lithium diisopropylamide, and alkylated with iodide **10**[12] in the presence of hexamethylphosphoramide to provide compound **11** in 51% yield along with recovered starting material (25%).[29] The Ireland−Claisen rearrangement of the corresponding silyl ketene acetal **12** proceeded smoothly upon heating in toluene to afford, after hydrolysis, carboxylic acid **13** in 94% yield from lactone **11**.[30]

Cyclohexenecarboxylic acid **13** was *enantiospecifically* converted into the corresponding cyclohexadiene **16** by the fol-

(22) HI: (a) Ostwald, R.; Chavant, P.-Y.; Stadtmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143. HBF_4: (b) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668. HF: (c) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. *p*-TsH: (d) Büchi, G.; Wüest, H. *Tetrahedron Lett.* **1977**, *49*, 4305. *p*-TsOH: (e) Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1999. *n*-Bu_4-NF: (f) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3257. For a review, see: (g) Fleming, I.; Dunogues, J.; Smithers, R. In *Organic Reactions*; Kende, A. S., Ed.; Wiley: New York, 1989; Vol. 37, Chapter 2.

(23) Wollenberg, R. H. Ph.D. Thesis, Harvard University, December 1976.

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(25) (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581. (b) Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221.

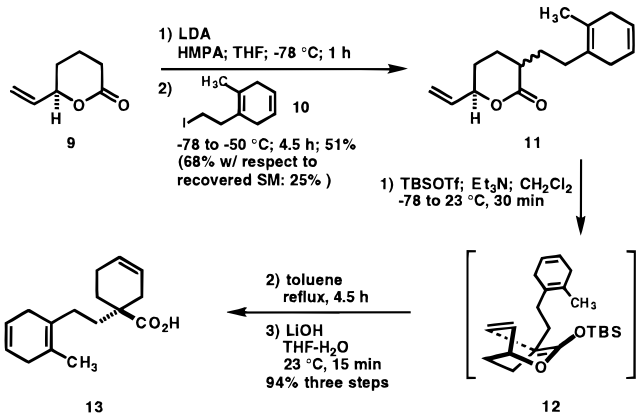
(26) Huckstep, M.; Taylor, R. J. K. *Synthesis* **1982**, 881.

(27) Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

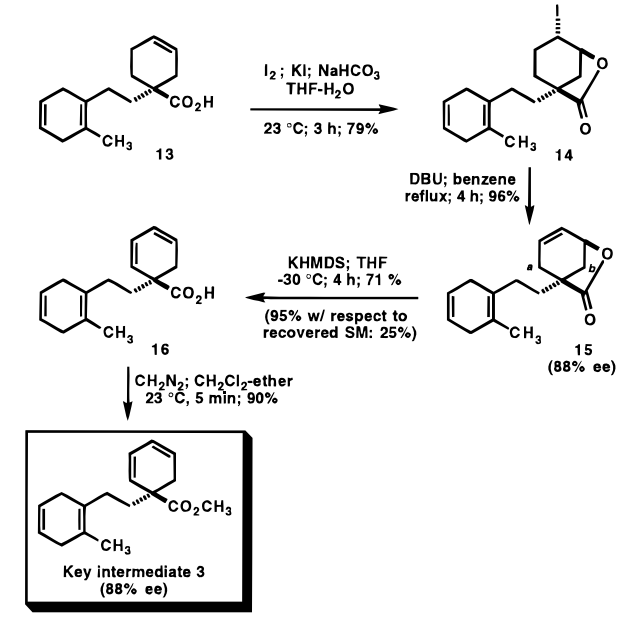
(28) Employment for large-scale experiments of catalyst that had been stored for more than one day gave rise to a product of low enantiomeric excess. Furthermore, the use of a reaction temperature of −78 °C at this scale resulted in a sluggish reduction rate.

(29) Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711.

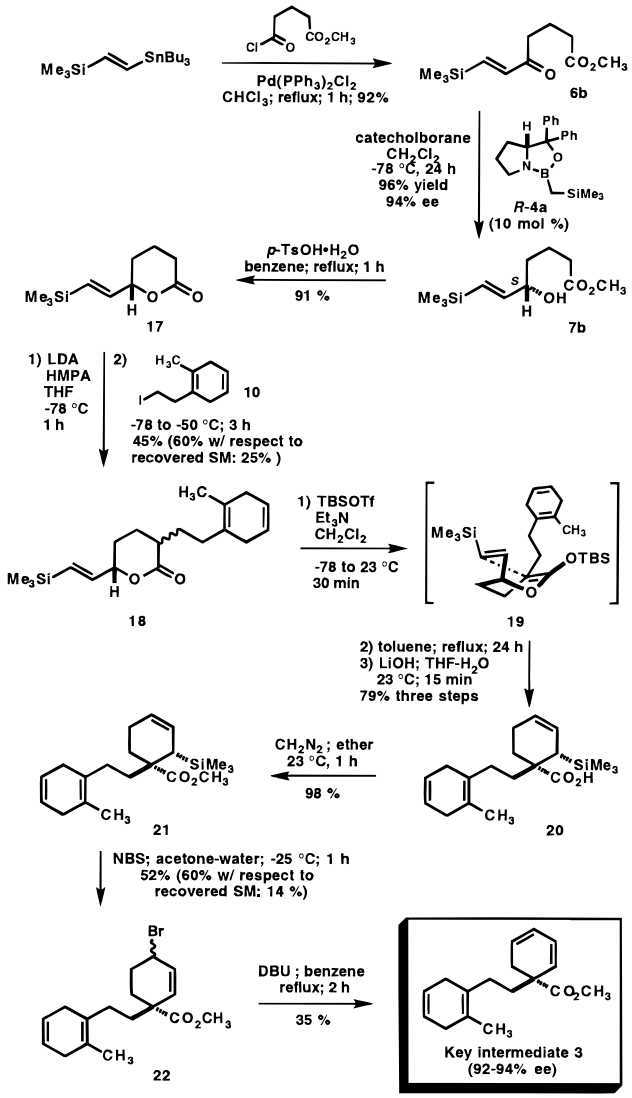
Scheme 3. Preparation of Acid **13**



Scheme 4. Preparation of Acid **13**



Scheme 5. An Alternative Route to Key Intermediate **3**



lowing sequence (Scheme 4): (1) iodolactonization in 79% yield, (2) elimination of the resulting iodide **14** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford **15** of 88% ee in 96% yield, and (3) position-selective elimination of lactone **15** using potassium hexamethyldisilazide in THF to provide acid **16** in 71% yield along with recovered starting material (25%). The enantiomeric excess of intermediate **15** (88% ee) attests to the complete chirality transfer that occurred via the Ireland−Claisen rearrangement. The elimination of lactone **15** was not driven to completion because this led to the concomitant isomerization of 1,3-diene **16** to the corresponding achiral 1,4-diene. The regioselectivity of the elimination is crucial; proton abstraction must occur exclusively from the allylic position *a* of **15**, and not at all from the less acidic position *b*, because competing deprotonation would result in racemization. The reaction is very selective as is evidenced by the 88% ee of the desired key intermediate **3**, prepared in 90% yield by reaction of acid **16** with diazomethane.

An alternative synthesis of compound **3**, which was developed using the allylic alcohol of higher optical purity **7b**, is shown in Scheme 5. 1-(Tri-*n*-butylstannyl)-2-(trimethylsilyl)ethylene[31] underwent efficient Stille coupling[32] with commercially available methyl 4-(chloroformyl)butanoate at reflux to afford ketone **6b** in 92% yield. As described above, the CBS reduction of this ketone using oxazaborolidine catalyst (***R***)-**4a** provided allylic alcohol **7b** of 94% ee in 96% yield; the absolute stereochemistry of **7b** was established by comparison of its specific rotation with that of an authentic sample.[33] Alcohol **7b** was cyclized under acidic conditions to give lactone **17**. Compound **17** was transformed to acid **20** by alkylation with **10**, followed by Ireland−Claisen rearrangement, as described for the compounds lacking the TMS group. The corresponding ester **21** was treated with *N*-bromosuccinimide in acetone−water at −25 °C to provide allylic bromide **22** in 60% yield (with respect to recovered starting material), which after elimination with DBU gave the desired key intermediate **3** of 92−94% ee. While this route to **3** is more direct than the stannyl route previously described, the last two steps provided only modest yields. It

(30) For references on the Ireland−Claisen rearrangement of lactonic silyl enolates, see: (a) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am .Chem. Soc.* **1980**, *102*, 6889. (b) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.*, **1980**, *102*, 6891. (c) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (d) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599. (e) Turos, E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231. (f) Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 9. (g) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332. For a recent review on the Ireland−Claisen rearrangement see: (h) Pereira, S.; Srebnik, M. *Aldrichim. Acta* **1993**, *26*, 17.

(31) Cunico, R. F.; Clayton, F. J. *J. Org. Chem.* **1976**, *41*, 1480.

(32) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.

(33) Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, *44*, 4073.

appears that the tetrasubstituted olefin in **21** competes for bromination with the allylic silane functionality, and this results in decreased yields. A number of experimental conditions were investigated for the elimination of bromide **22** (e.g., pentaisopropylguanidine in acetonitrile at reflux for 12 h, or $Pd(dba)_2$, $AgNO_3$, and dppp in acetonitrile at reflux for 6 h led mostly to decomposition), and while DBU provided the highest yield, the reaction was always plagued with competing decomposition pathways. The enantiospecificities of the Claisen rearrangement and the conversion of allylic silane **21** to diene **3** are evidenced by the high enantiomeric purity of the final product.

Conclusions

In this paper, we report the CBS reductions of β-trimethylsilyl and β-tri-*n*-butylstannyl acyclic enones, which give rise to higher enantioselectivities than those obtained from the reduction of unsubstituted acyclic enones. The enhanced enantioselectivities are a result of remote steric interactions between the distal trimethylsilyl or tri-*n*-butylstannyl groups on the enone β-position and the (trimethylsilyl)methyl group on the boron atom of catalyst **4a**, which strongly disfavor the minor reduction pathway. The tri-*n*-butylstannyl group can be removed from the allylic alcohol product with no loss of optical purity using tetra-*n*-butylammonium fluoride. These observations were applied to the enantioselective synthesis of a key intermediate in the preparation of the coffee bean-derived toxin atractyligenin. An Ireland−Claisen rearrangement of a lactonic silyl enolate was used for the complete transfer of chirality from the secondary alcohol generated by CBS reduction to the quaternary carbon stereocenter present in the key intermediate. The regioselective−enantiospecific elimination of lactone **15** to acid **16** is also a noteworthy step of the synthesis. The CBS reduction of enones and Ireland−Claisen rearrangement of lactonic silyl enolates sequence presented herein affords substituted cyclohexenes reminiscent of Diels−Alder adducts. The reliability and high enantioselectivity provided by the CBS reduction and the stereospecificity of the Claisen rearrangement should establish this sequence as a useful alternative to asymmetric Diels−Alder reactions.

Experimental Section

General Methods. All experiments involving moisture and/or air sensitive compounds were performed in oven- or flame-dried glassware equipped with rubber septa under a positive pressure of nitrogen or argon. When necessary, solvents and reagents were distilled prior to use and were transferred using a syringe or cannula. Reaction mixtures were magnetically stirred, unless otherwise noted. Thin layer chromatography was performed on Merck precoated silica gel F-254 plates (0.25 mm). Kugelrohr distillation temperatures are reported as oven temperatures. Flash column chromatography was performed on Baker 230−400 mesh silica gel. Proton NMR spectra were recorded in parts per million using the residual solvent signal as an internal standard: $CDCl_3$ (7.26 ppm) or C_6D_6 (7.15 ppm). Carbon NMR were recorded in parts per million relative to the solvent signal: $CDCl_3$ (77.07 ppm) or C_6D_6 (128.0 ppm). Mass spectra and high-resolution mass spectra (HRMS) were recorded on JEOL spectrometers and are reported in units of mass to charge (*m*/*e*). The Chiralcel and Chiralpak HLPC columns were obtained from Daicel Chemical Industries, Ltd., and the (*S*,*S*)-Whelk-O1 column was obtained from Regis Chemical Co.

(±)-Methyl 5-Hydroxy-7-(tri-*n*-butylstannyl)hept-6-enoate (Racemic 7c). A −78 °C solution of (*E*)-1,2-bis(tri-*n*-butylstannyl)-ethylene[23,25] (6.38 mL, 12.0 mmol) in THF (36 mL) was treated dropwise with *n*-butyllithium in hexanes (2.44 M, 5.41 mL, 13.2 mmol). The solution was allowed to slowly warm to −40 °C over 30 min, and was then cooled to −78 °C. The resulting solution was added via dry-ice-cooled cannula to a −78 °C solution of methyl 5-oxopentanoate[26] (2.97 mL, 24.0 mmol) in THF (72 mL), down the side of the flask over ca. 6 min. The reaction mixture was stirred for 45 min, quenched by addition of NH_4Cl (saturated aqueous solution) and ether, and allowed to warm to 23 °C. The layers were separated. The organic phase was washed twice with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 75:25) to afford 4.39 g (82% yield) of racemic **7c** as an oil. (For analytical data see **7c** below.)

Methyl 5-Oxo-7-(tri-*n*-butylstannyl)hept-6-enoate (6c). A solution of racemic stannyl alcohol **7c** (2.188 g, 4.89 mmol) in CH_2Cl_2 (52 mL) at 23 °C was treated in one portion with pyridinium dichromate (2.76, 7.34 mmol). The resulting dark mixture was stirred for 18 h, diluted with hexanes−ether (50:50), and filtered through a silica gel plug eluting with hexanes−ether (50:50). The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 85:15) to afford 1.817 g (83% yield) of product **6c** as an oil: R_f = 0.25 (hexanes−EtOAc, 90:10); FTIR (film) 2957, 2928, 2873, 2852, 1742, 1696, 1675, 1460, 1439, 1375, 1250, 1203, 1177, 998 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.60 (d, J = 19.7 Hz, 1H), 6.69 (d, J = 19.7 Hz, 1H), 3.29 (s, 3H), 2.35 (t, J = 7.1 Hz, 2H), 2.12 (t, J = 7.1 Hz, 2H), 1.91 (quintet, J = 7.1 Hz, 2H), 1.50 (m, 6H), 1.30 (sextuplet, J = 7.3 Hz, 6H), 0.99−0.85 (m, 15H); ^{13}C NMR (100 MHz, C_6D_6) δ 196.7, 173.0, 147.8, 146.3, 50.9, 37.9, 33.1, 29.3, 27.6, 19.5, 13.8, 9.8; CIMS (NH_3) 464 $[M + NH_4]^+$, 462 $[M + NH_4 - 2]^+$, 460 $[M + NH_4 - 4]^+$, 447 $[M + H]^+$, 428, 174, 157; HRMS calcd for $[C_{20}H_{38}O_3Sn + NH_4]^+$ 464.2187, found 464.2192.

(*S*)-1-Aza-2-bora-2-((trimethylsilyl)methyl)-3-oxa-4,4-diphenylbicyclo[3.3.0]octane ((*S*)-4a). A solution of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol[34] (0.507 g, 2.0 mmol) and ((trimethylsilyl)-methyl)boronic acid[15u] (0.317 g, 2.4 mmol) in toluene (20 mL) was heated at reflux through a Dean-Stark apparatus (side arm filled with 4 Å molecular sieves and toluene) for 14 h. Most of the toluene was then removed by distillation via the Dean-Stark side arm. The mixture was cooled to 23 °C. The Dean-Stark apparatus was rapidly replaced by a rubber septum. The flask was fitted with an additional rubber septum. The remaining toluene was removed *in vacuo* at 23 °C under inert conditions. The residue was dissolved in toluene (20 mL) to provide a 0.1 M solution of catalyst (***S*)-4a**. An aliquot of this solution was concentrated *in vacuo* at 23 °C under inert conditions; ^1H NMR analysis of this sample in dry $CDCl_3$ indicated that the catalyst formation was complete. The catalyst solution was cooled to −78 °C under a positive pressure of nitrogen. The nitrogen source was removed, and the flask was stored at −20 °C in a closed jar containing Drierite. Catalyst (***R*)-4a** was prepared similarly. Data for **4a**: ^1H NMR (400 MHz, dry $CDCl_3$) δ 7.52 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.17−7.35 (m, 6H), 4.28 (dd, J = 5.6, 10.0 Hz, 1H), 3.34 (m, 1H), 3.04 (m, 1H), 1.76 (m, 2H), 1.58 (m, 1H), 0.79 (m, 1H), 0.08 (s, 3H), 0.05 (s, 6H); for additional analytical data see ref 15u.

(*R*)-Methyl 5-Hydroxy-7-(tri-*n*-butylstannyl)hept-6-enoate (7c). Ketone **6c** (0.111 g, 0.25 mmol) was azeotropically dried twice with toluene (0.5 mL each) under inert conditions. The dry compound was treated with a solution of catalyst (***S*)-4a** in toluene (0.1 M, 0.380 mL, 0.038 mmol). The toluene was removed *in vacuo* under inert conditions, and replaced by CH_2Cl_2 (0.875 mL). The resulting solution was cooled to −78 °C and treated dropwise over 10 min with a solution of catecholborane (0.041 mL, 0.38 mmol) in CH_2Cl_2 (0.123 mL). The reaction mixture was stirred at −78 °C for 20 h, quenched by slow addition of MeOH (0.5 mL) down the side of the flask, warmed to 23 °C, and diluted with ether. The ethereal solution was washed repeatedly with a 2:1 mixture of NaOH (1 M aqueous)−$NaHCO_3$ (saturated aqueous solution) until the washings were colorless, washed once with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 75:25) to afford 0.105 g (94% yield) of desired product **7c** of 90% ee (determined by chiral HPLC of the corresponding benzoate ester).

The above procedure can also be used for larger scale work if the catalyst is prepared fresh, but for this scale it is more practical and reproducible to perform the reaction at −60 °C as follows: A solution of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol[34] (0.0633 g, 0.25 mmol) and ((trimethylsilyl)methyl)boronic acid[15u] (0.0396 g, 0.30 mmol) in toluene (5 mL) was heated at reflux through a Dean-Stark apparatus

(34) Kanth, J. V.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.

(side arm filled with 4 Å molecular sieves and toluene) for 14 h. Most of the toluene was then removed by distillation via the Dean-Stark side arm. The mixture was cooled to 23 °C. The Dean-Stark apparatus was rapidly replaced by a rubber septum. The remaining toluene was removed *in vacuo* at 23 °C under inert conditions. The residue was dissolved in CH_2Cl_2 (2.50 mL) to provide a 0.1 M solution of catalyst (***S*)-4a**. Ketone **6c** (0.334 g, 0.75 mmol) was azeotropically dried twice with toluene (1 mL each) under inert conditions. The dry compound was treated with the freshly prepared solution of catalyst in CH_2Cl_2 (0.1 M, 1.13 mL, 0.113 mmol) and CH_2Cl_2 (0.29 mL). The resulting homogeneous mixture was cooled to −60 °C and treated over ca. 11 min with a solution of catecholborane (0.120 mL, 1.13 mmol) in CH_2Cl_2 (0.72 mL) dropwise down the side of the flask. The reaction mixture was stirred at −60 °C for 5 h, quenched by slow addition of MeOH (1.0 mL) down the side of the flask, warmed to 23 °C, and diluted with ether. The ethereal solution was washed repeatedly with a 2:1 mixture of NaOH (1 M aqueous)−$NaHCO_3$ (saturated aqueous solution) until the washings were colorless, washed once with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 75:25) to afford 0.306 g (91% yield) of desired product **7c** of 88% ee (determined by chiral HPLC of the corresponding benzoate ester): R_f = 0.45 (hexanes−EtOAc, 70:30); $[\alpha]^{23}_D$ +0.1° (*c* 1.26, benzene); FTIR (film) 3441, 2957, 2925, 2870, 2851, 1741, 1458, 1374, 1337, 1285, 1243, 1175, 1073, 1045, 991 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (dd, J = 19.1, 0.9 Hz, 1H), 5.99 (dd, J = 19.1, 5.5 Hz, 1H), 4.07 (m, 1H), 3.67 (s, 3H), 2.35 (t, J = 7.4 Hz, 2H), 1.74−1.67 (m, 2H), 1.63 (br s, 1H), 1.59−1.53 (m, 2H), 1.52−1.45 (m, 6H), 1.30 (sextuplet, J = 7.3 Hz, 6H), 0.94−0.82 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 150.6, 128.1, 75.0, 51.5, 36.2, 33.9, 29.1, 27.3, 20.9, 13.7, 9.5; CIMS (NH_3) 466 $[M + NH_4]^+$, 464 $[M + NH_4 - 2]^+$, 462 $[M + NH_4 - 4]^+$, 431, 308 $[Bu_3SnNH_3]^+$, 306, 176, 174; HRMS calcd for $[C_{20}H_{40}O_3Sn{+}NH_4]^+$ 466.2343, found 466.2346; HPLC (chiral) of the corresponding benzoate ester (Whelk-O1 at 23 °C; λ = 254 nm; hexanes−2-propanol, 97.5:2.5) retention times 12.3 (major), 14.9 (minor) min at 1 mL/min flow rate.

(*R*)-6-Hepteno-5-lactone (9). Stannyl alcohol **7c** (0.459 g, 1.03 mmol) was treated with a solution of tetra-*n*-butylammonium fluoride in THF (1 M, 5.15 mL, 5.15 mmol). The resulting mixture was heated at reflux for 26 h, cooled to 23 °C, and treated with NaOH (1 M aqueous, 30 mL). The mixture was washed twice with ether (30 mL each). The aqueous layer was carefully acidified with HCl (4 M aqueous, 10 mL) and extracted three times with EtOAc (100 mL each). The combined organic extracts were washed once with brine (10 mL), dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. A solution of the residue in CH_2Cl_2 (13.5 mL) at 0 °C was treated with 4-(dimethylamino)pyridine (0.064 g, 0.52 mmol), followed by 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.238 g, 1.24 mmol). The mixture was stirred for 2 h at 23 °C, diluted with ether (ca. 55 mL), and filtered through a silica gel plug. The flask was rinsed repeatedly with CH_2Cl_2−ether (4:1). The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−ether, 30:70 to 20:80) to afford 0.108 g (83% yield) of product **9** of 88% ee (determined by chiral GC) as a fairly volatile oil: R_f = 0.29 (hexanes−ether, 30:70); $[\alpha]^{23}_D$ −61.3° (*c* 1.65, CH_2Cl_2); FTIR (film) 2956, 1733, 1366, 1344, 1239, 1194, 1168, 1110, 1040, 988, 931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.2, 10.6, 5.4 Hz, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 4.82 (m, 1H), 2.59 (m, 1H), 2.48 (m, 1H), 2.01−1.85 (m, 3H), 1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.1, 116.8, 80.2, 29.5, 27.8, 18.0; CIMS (NH_3) 144 $[M + NH_4]^+$, 127 $[M + H]^+$; HRMS calcd for $[C_7H_{10}O_2 + NH_4]^+$ 144.1025, found 144.1027; GC (chiral) (G-TA column at 100 °C (2 min), 1 °C/min ramp, 150 °C (30 min); FID; injector temp = detector temp = 250 °C) retention times 21.6 (major), 24.0 (minor) min at 20.0 psi of helium. The absolute stereochemistry was established by hydrogenation (H_2, Rh-C (5%), ether, 0−23 °C, 2 h, 69% yield) to afford (*S*)-δ-heptanolactone: $[\alpha]^{23}_D$ −51° (*c* 0.69, THF) (lit.[24] for the (*R*)-enantiomer $[\alpha]_D$ +55.0° (*c* 1.13, THF)).

(5*R*)-2-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-6-hepteno-5-lactone (11). A solution of diisopropylamine (0.084 mL, 0.60 mmol) in THF (5 mL) at 0 °C was treated dropwise with *n*-butyllithium in hexanes (2.5 M, 0.240 mL, 0.60 mmol). The solution was stirred for 15 min, treated with hexamethylphosphoramide (0.522 mL, 3.00 mmol), and cooled to −78 °C. The resulting homogeneous mixture was treated with a solution of lactone **9** (azeotropically dried with 0.25 mL of benzene) (0.063 g, 0.50 mmol) in THF (1 mL) over 30 min using a syringe pump, and stirred for an additional 30 min. The solution was then treated dropwise with iodide **10**[12] (0.167 mL, 1.00 mmol), and stirred for 5 min at −78 °C and 4.5 h at −50 °C. The reaction mixture was quenched by addition of NH_4Cl (saturated aqueous solution) and extracted with ether. The organic phase was washed once with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−ether, 80:20 to 60:40 to 20:80) to afford (in this order) recovered iodide **10**, dialkylated lactone (0.006 g, 3%), desired product **11** (0.063 g, 51% yield, 68% with respect to recovered starting material) as a ca. 1:1 mixture of diastereomers (determined by ^{1}H NMR), and recovered starting lactone **9** (0.016 g, 25%). Data for **11**: R_f = 0.40 (hexanes−EtOAc, 80:20); FTIR (film) 2926, 2871, 2815, 1736, 1249, 1181, 1115, 1066, 1016, 992, 934 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.67 (m, 2H), 5.33 (m, 1H), 5.21 (m, 1H), 4.83−4.75 (m, 1H), 2.60 (m, 4H), 2.41 (m, 1H), 2.14−1.92 (m, 5H), 1.63 (s, 3H), 1.70−1.47 (m, 3H); EIMS 246 $[M]^+$, 178, 119, 106; HRMS calcd for $[C_{16}H_{22}O_2]^+$ 246.1620, found 246.1623.

(*R*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-3-cyclohexenecarboxylic acid (13). A solution of lactone **11** (0.072 g, 0.292 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C was treated with Et_3N (0.122 mL, 0.876 mmol), followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.101 mL, 0.438 mmol). The reaction mixture was warmed to 23 °C over 30 min, and partitioned between pentane and ice-cold water. The organic phase was rapidly washed with ice-cold water, dried over K_2CO_3(anhyd), and concentrated *in vacuo* to provide silyl ketene acetal **12**. A solution of the residue in toluene (5.0 mL) was heated at reflux for 4.5 h, cooled to 23 °C, and concentrated *in vacuo*. A solution of the resulting oil in THF (3.0 mL) was treated with LiOH (1 M aqueous, 1.46 mL, 1.46 mmol) at 23 °C. The mixture was stirred for 15 min, acidified by addition of HCl (1 M, 1.8 mL) to ca. pH 1, and extracted with ether. The organic extract was washed twice with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc−AcOH, 95:5:0.5 to 90:10:0.5) to afford 0.068 g (94% yield) of desired product **13** as an oil: R_f = 0.40 (hexanes−EtOAc−AcOH, 80:20:1, on an AcOH treated plate); $[\alpha]^{23}_D$ +27° (*c* 1.4, $CHCl_3$); FTIR (film) 3065, 3027, 2920, 2875, 2845, 2815, 1696, 1455, 1440, 1296, 1244, 1203 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (m, 4H), 2.59 (m, 4H), 2.54 (m, 1H), 2.17−1.93 (m, 6H), 1.61 (s, 3H), 1.76−1.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 126.8, 126.4, 124.8, 124.7, 124.5, 124.1, 44.8, 36.4, 33.0, 32.6, 30.6, 29.5, 27.6, 22.7, 18.2; EIMS 246 $[M]^+$, 126, 121, 106; HRMS calcd for $[C_{16}H_{22}O_2]^+$ 246.1620, found 246.1627.

(1*S*,4*S*,5*S*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-4-iodo-6-oxa-7-oxobicyclo[3.2.1]octane (14). A solution of acid **13** (0.068 g, 0.276 mmol) in THF (0.6 mL) and water (0.6 mL) at 23 °C was slowly treated with $NaHCO_3$ (0.070 g, 0.828 mol). After the gas evolution had subsided, the mixture was treated with potassium iodide (0.060 g, 0.359 mol), followed by iodine (0.091 g, 0.359 mol). The resulting dark mixture was stirred in the dark for 3 h, quenched by addition of $Na_2S_2O_3$ (saturated aqueous solution) until the color disappeared, and extracted with ether. The ethereal extracts were washed twice with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 90:10) to afford 0.081 g (79% yield) of colorless product **14** which solidified: mp 78−88 °C; R_f = 0.31 (hexanes−EtOAc, 90:10); $[\alpha]^{23}_D$ −0.72° (*c* 2.76, $CHCl_3$); FTIR (film) 2920, 2872, 2840, 2814, 1773, 1445, 1358, 1336, 1317, 1209, 1197, 1177, 1162, 1091, 1047, 1015, 994, 961, 912, 855 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (m, 2H), 4.78 (dd, J = 6.0, 4.2 Hz, 1H), 4.49 (t, J = 4.5 Hz, 1H), 2.72 (d, J = 12.1 Hz, 1H), 2.61 (m, 4H), 2.43−2.30 (m, 2H), 2.15−2.05 (m, 2H), 1.92 (m, 1H), 1.84 (dd, J = 13.1, 5.5 Hz, 1H), 1.65 (s, 3H), 1.67−1.62 (m, 2H), 1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 126.3 (2C), 124.5, 124.4, 78.2, 46.2, 37.5, 32.9, 32.1, 30.5, 30.0, 29.3, 27.5, 23.7, 18.3; CIMS (NH_3) 390 $[M + NH_4]^+$; HRMS calcd for $[C_{16}H_{21}O_2I + NH_4]^+$ 390.0930, found 390.0930.

(1*S*,5*S*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-6-oxa-7-oxobicyclo[3.2.1]oct-3-ene (15). A solution of iodolactone **14** (0.078 g, 0.210 mmol) in benzene (1.0 mL) at 23 °C was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.047 mL, 0.315 mmol). The solution was heated at reflux for 4 h. The resulting heterogeneous mixture was allowed to cool to 23 °C, and partitioned between HCl (1 M aqueous) and ether. The ethereal layer were washed with brine, $NaHCO_3$ (saturated aqueous solution), and brine, dried over $MgSO_4$ (anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 85:15) to afford 0.049 g (96% yield) of the desired product **15** of 88% ee (determined by chiral HPLC) as a colorless solid: mp 60−63 °C (unrecrystallized); $R_f = 0.36$ (hexanes−EtOAc, 80:20); $[\alpha]^{23}_D$ −69.5° (*c* 0.755, $CHCl_3$); FTIR (film) 2916, 2873, 2815, 1769, 1427, 1381, 1308, 1265, 1130, 1104, 1053, 1016, 959, 947, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (m, 1H), 5.89 (m, 1H), 5.68 (m, 2H), 4.74 (t, $J = 5.4$ Hz, 1H), 2.61 (m, 4H), 2.43−2.30 (m, 3H), 2.16 (m, 1H), 2.02−1.94 (m, 2H), 1.76−1.67 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 131.3, 129.2, 126.5 (2C), 124.5, 124.4, 71.6, 45.5, 37.9, 35.3, 32.9, 32.6, 30.5, 27.3, 18.2; CIMS (NH_3) 262 $[M + NH_4]^+$, 245 $[M + H]^+$; HRMS calcd for $[C_{16}H_{20}O_2 + NH_4]^+$ 262.1807, found 262.1806; HPLC (chiral) (Chiralcel OD at 23 °C; $\lambda = 225$ nm; hexanes−2-propanol, 97.5:2.5) retention times 16.8 (major), 20.7 (minor) min at 1 mL/min flow rate.

(*R*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)cyclohexa-2,4-dienecarboxylic Acid (16). A solution of lactone **15** (0.052 g, 0.214 mmol) in THF (1 mL) at −78 °C was treated with a solution of potassium bis(trimethylsilyl)amide (0.047 g, 0.236 mmol) in THF (1 mL). The resulting solution was stirred at −30 °C for 4 h (at which point the conversion was estimated to be 80% by TLC), and quenched by addition of water. The mixture was partitioned between NaOH (0.1 M aqueous) and ether. The ethereal phase was washed twice with brine, dried with $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was filtered through a silica gel plug eluting with hexanes−EtOAc (80:20) to provide 0.013 g (25%) of recovered starting material. The basic aqueous phase was acidified to pH 0−1 with HCl (1 M aqueous) and extracted with ether. The organic extracts were washed twice with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was filtered through a silica gel plug eluting with hexanes−EtOAc (80:20) to afford 0.037 g (71% yield, 95% with respect to recovered starting material) of desired product **16** as a colorless solid: mp 65−69 °C (unrecrystallized); $R_f = 0.48$ (hexanes−EtOAc−AcOH, 80:20:1, on AcOH treated plates); $[\alpha]^{23}_D$ −80.3° (*c* 1.04, $CHCl_3$); FTIR (film) 3033, 2976, 2950, 2923, 2872, 2815, 1700, 1290, 1273, 1236 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (dd, $J = 9.6$, 5.1 Hz, 1H), 5.89 (m, 1H), 5.85 (d, $J = 9.6$ Hz, 1H), 5.78 (m, 1H), 5.66 (m, 2H), 2.77 (ddd, $J = 17.9$, 3.9, 2.3 Hz, 1H), 2.58 (m, 4H), 2.35 (ddd, $J = 17.9$, 4.7, 1.4 Hz, 1H), 2.03−1.94 (m, 2H), 1.83 (td, $J = 12.2$, 5.1 Hz, 1H), 1.70 (td, $J = 12.3$, 5.4 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 128.2, 126.7, 125.1, 124.6, 124.5, 124.4, 124.3, 123.2, 45.8, 35.3, 32.9, 30.6, 30.5, 27.9, 18.2; CIMS (NH_3) 262 $[M + NH_4]^+$, 134, 96; HRMS calcd for $[C_{16}H_{20}O_2 + NH_4]^+$ 262.1807, found 262.1798.

Methyl (*R*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)cyclohexa-2,4-dienecarboxylate (3). A solution of acid **16** (0.0280 g, 0.115 mmol) in CH_2Cl_2 (4 mL) at 23 °C was treated dropwise (over ca. 5 min) with a solution of CH_2N_2 in ether (ca. 0.45 M) until the solution remained yellow. The resulting mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 97.5:2.5) to afford 0.0267 g (90% yield) of desired product **3** of 88% ee (determined by chiral HPLC) as an oil: $R_f = 0.45$ (hexanes−EtOAc, 90:10); $[\alpha]^{23}_D$ −68.5° (*c* 1.02, $CHCl_3$); FTIR (film) 2950, 2815, 1733, 1432, 1224, 1199, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (dd, $J = 9.6$, 5.1 Hz, 1H), 5.87 (m, 1H), 5.84 (d, $J = 9.6$ Hz, 1H), 5.77 (m, 1H), 5.76 (m, 2H), 3.70 (s, 3H), 2.76 (ddd, $J = 17.8$, 3.9, 2.2 Hz, 1H), 2.57 (s, 4H), 2.33 (ddd, $J = 17.8$, 4.6, 1.5 Hz, 1H), 1.98−1.86 (m, 2H), 1.78 (td, $J = 12.3$, 5.1 Hz, 1H), 1.66 (td, $J = 12.6$, 5.5 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 128.8, 126.8, 125.2, 124.6, 124.4, 124.1, 124.0, 123.1, 52.0, 45.9, 35.5, 32.9, 30.8, 30.6, 28.0, 18.2; EIMS 258 $[M]^+$, 199 $[M - CO_2CH_3]^+$, 140, 137, 105; HRMS calcd for $[C_{17}H_{22}O_2]^+$ 258.1620, found 258.1614; HPLC (chiral) (Chiralcel OD at 23 °C; $\lambda = 254$ nm; hexanes−2-propanol, 99.9:0.1), retention times: 19.6 (minor), 22.4 min (major) at 1 mL/min flow rate.

Methyl 5-Oxo-7-(trimethylsilyl)hept-6-enoate (6b). A solution of 1-(tri-*n*-butylstannyl-2-(trimethylsilyl)ethylene[31] (7.65 mL, 20.0 mmol) and methyl 4-(chloroformyl)butanoate (Aldrich, 2.76 mL, 20.0 mmol) in $CHCl_3$ (20 mL) was treated at 23 °C with bis(triphenylphosphine)-palladium(II) chloride (0.070 g, 0.10 mmol). The solution was heated at reflux under a dry air atmosphere for 1 h. The resulting solution was cooled to 23 °C, diluted with ether, and shaken with potassium fluoride (half-saturated aqueous solution). The mixture was allowed to stand for 10 min and filtered. The solid was washed with ether. The organic layer of the filtrate was washed with potassium fluoride (half-saturated aqueous solution) and filtered. The filtrate was washed with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 85:15) to afford 4.18 g (92% yield) of desired product **6b** as a yellow oil: $R_f = 0.36$ (hexanes−EtOAc, 80:20); FTIR (film) 2956, 1739, 1698, 1679, 1437, 1251, 1206, 1175, 1150, 997, 865, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, $J = 19.3$ Hz, 1H), 6.46 (d, $J = 19.3$ Hz, 1H), 3.67 (s, 3H), 2.68 (t, $J = 7.2$ Hz, 2H), 2.37 (t, $J = 7.2$ Hz, 2H), 1.94 (quintet, $J = 7.2$ Hz, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 173.5, 146.7 142.0, 51.4, 38.0, 33.0, 19.0, −2.0; CIMS (NH_3) 246 $[M + NH_4]^+$, 229 $[M + H]^+$; HRMS calcd for $[C_{11}H_{20}O_3Si + NH_4]^+$ 246.1525, found 246.1534.

(*S*)-Methyl 5-Hydroxy-7-(trimethylsilyl)hept-6-enoate (7b). Ketoester **6b** (0.514 g, 2.25 mmol) was azeotropically dried twice with toluene (2 mL), treated with oxazaborolidine catalyst (***R*)-4a** (0.1 M in toluene, 2.25 mL, 0.225 mmol) at 23 °C, and concentrated *in vacuo* under inert conditions. The residue was dissolved in CH_2Cl_2 (8.10 mL). The resulting solution was cooled to −78 °C, and treated dropwise over 30 min with catecholborane (0.360 mL, 3.38 mmol) in CH_2Cl_2 (1.08 mL) via syringe pump directly into the solution. The reaction mixture was stirred at −78 °C for 24 h, quenched by slow addition of methanol (2 mL) down the side of the flask, warmed to 23 °C, and diluted with ether. The solution was washed with a 2:1 mixture of NaOH (1.0 M aqueous) and $NaHCO_3$ (saturated aqueous solution) until the washings were colorless, washed once with brine, dried over $MgSO_4$ (anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 70:30) to afford 0.500 g (96% yield) of desired product **7b** as a clear oil of 94% ee (determined by HPLC): $R_f = 0.22$ (CH_2Cl_2−EtOAc, 95:5); $[\alpha]^{22}_D$ +6.1° (*c* 0.80, $CHCl_3$); FTIR (film) 3448, 2955, 1741, 1621, 1438, 1420, 1365, 1308, 1248, 1201, 1175, 1101, 1065, 1042, 990, 867, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, $J = 18.7$, 5.3 Hz, 1H), 5.85 (dd, $J = 18.7$, 1.2 Hz, 1H), 4.09 (q, $J = 5.6$ Hz, 1H), 3.67 (s, 3H), 2.35 (t, $J = 7.3$ Hz, 2H), 1.8−1.5 (m, 4H), 0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 148.2, 129.5, 74.1, 51.6, 36.1, 33.8, 20.8, −1.3; CIMS (NH_3) 428 $[2M - CH_3OH]^+$, 248 $[M + NH_4]^+$, 213 $[M + H - H_2O]^+$; HRMS calcd for $[C_{11}H_{22}O_3Si + NH_4]^+$ 248.1682, found 248.1682; HPLC (chiral) (Regis Whelk-O1 at 23 °C; $\lambda = 250$ nm; hexanes−2-propanol, 97.5:2.5) retention times 12.3 (minor), 15.2 (major) min at 1 mL/min flow rate. The absolute stereochemistry was established by comparison of the optical rotation with that of an authentic sample: $[\alpha]^{25}_D$ +6.78° (*c* 1.15, $CHCl_3$).[33]

(*S*)-7-(Trimethylsilyl)-6-hepteno-5-lactone (17). A solution of allylic alcohol **7b** (1.50 g, 6.51 mmol) in benzene (65 mL) was treated with *p*-toluenesulfonic acid monohydrate (0.062 g, 0.326 mmol). The flask was fitted with a pressure-equalizing funnel containing 4 Å molecular sieves (25 mL), and above that a condenser. The reaction mixture was heated at reflux for 1 h, cooled to 23 °C, and quenched by addition of triethylamine (30 drops). The solution was passed through a small silica gel plug eluting with ether and concentrated *in vacuo*. The product was purified by flash chromatography (CH_2Cl_2) to afford 1.174 g (91% yield) of desired product **17** as a clear oil: $R_f = 0.50$ (CH_2Cl_2−EtOAc, 95:5); $[\alpha]^{20}_D$ +22.0° (*c* 1.06, $CHCl_3$); FTIR (film) 2956, 1739, 1245, 1087, 1041, 990, 867, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (dd, $J = 18.3$, 15.1 Hz, 2H), 4.80 (m, 1H), 2.56 (m, 1H), 2.49 (m, 1H), 2.01−1.83 (m, 3H), 1.65 (m, 1H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 142.7, 132.1, 81.6, 29.5, 27.7, 18.0, −1.6; CIMS (NH_3) 216 $[M + NH_4]^+$, 199 $[M + H]^+$; HRMS calcd for $[C_{10}H_{18}O_2Si + NH_4]^+$ 216.1420, found 216.1423.

(5*S*)-2-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-7-(trimethylsilyl)-6-hepteno-5-lactone (18). A solution of diisopropylamine (0.186, 1.33 mmol) in THF (11.0 mL) was treated with *n*-butyllithium (2.5 M in hexanes, 0.532 mL, 1.33 mmol) at 0 °C, stirred for 15 min, and treated with hexamethylphosphoramide (1.16 mL, 6.66 mmol). The resulting solution was cooled to −78 °C and treated over 30 min (via syringe pump) with lactone **17** (dried azeotropically with toluene, 2 × 1 mL) (0.220 g, 1.11 mmol) in THF (1.5 mL). The reaction mixture was stirred for 30 min, and treated dropwise with iodide **10**[12] (0.168 mL, 1.01 mmol). The solution was warmed to −50 °C, stirred for 3 h, then cooled to −78 °C, and quenched by addition of NH_4Cl (saturated aqueous solution). The mixture was warmed to 23 °C, and partitioned between ether and water. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes eluted excess **10**; hexanes−EtOAc, 95:5, eluted the product; hexanes−EtOAc, 70:30 eluted the remaining starting material **17**) to afford 0.055 g (25% yield) of starting lactone **17**, and 0.158 g (45% yield, 60% with respect to recovered starting material) of desired product **18** as a ca. 1:1 mixture of diastereomers (determined by ^{1}H NMR): R_f = 0.45, 0.39 (hexanes−EtOAc, 80:20); FTIR (film) 2954, 2871, 1736, 1459, 1371, 1248, 1215, 1178, 1095, 1071, 989, 864, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (m, 2H), 5.68 (m, 2H), 4.78 (m, 1H), 2.61 (m, 4H), 2.43 (m, 1H), 2.14−1.93 (m, 6H), 1.75 (m, 1H), 1.65 (s, 3H), 1.6−1.4 (m, 1H), 0.07 (s, 9H); CIMS (NH_3) 336 $[M + NH_4]^+$, 319 $[M + H]^+$; HRMS calcd for $[C_{19}H_{30}O_2Si + NH_4]^+$ 336.2359, found 336.2357.

(1*R*,2*S*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-2-(trimethylsilyl)-3-cyclohexenecarboxylic Acid (20). A solution of lactone **18** (0.327 g, 1.03 mmol) in CH_2Cl_2 (5 mL) at −78 °C was treated with triethylamine (0.431 mL, 3.09 mmol), followed by *tert*-butyldimethylsilyl triflate (0.355 mL, 1.55 mmol). The resulting solution was warmed to 23 °C over 30 min, and partitioned between pentane and ice-cold water. The organic layer was washed with ice-cold water, dried over K_2CO_3(anhyd), and concentrated *in vacuo* to provide silyl ketene acetal **19**. A solution of the residue in toluene (15 mL) was heated at reflux for 24 h. The solution was cooled to 23 °C and concentrated *in vacuo*. A solution of the residue in THF (10 mL) was treated with lithium hydroxide (1 M aqueous, 2.1 mL, 2.1 mmol). The reaction mixture was stirred at 23 °C for 15 min and treated with pH 4 buffer solution (30 mL), ether, and HCl (1 M aqueous, 2.1 mL, 2.1 mmol). The organic phase was separated. The aqueous layer was extracted again with ether. The combined organic extracts were washed three times with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 90:10) to afford 0.259 g (79% yield) of desired product **20** as a colorless solid: mp 88−92 °C (not recrystallized); R_f = 0.38 (hexanes−EtOAc, 80:20); $[\alpha]^{20}_D$ +199° (*c* 0.640, $CHCl_3$); FTIR (film) 2955, 2875, 1695, 1292, 1265, 1249, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70−5.53 (m, 4H), 2.59 (br s, 4H), 2.14−1.64 (m, 9H), 1.61 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 127.0, 126.7, 124.8, 124.5, 123.9. 122.9, 46.1, 37.6, 34.2, 33.0, 30.7, 27.9, 23.3, 22.0, 18.2, −1.0; CIMS (NH_3) 336 $[M + NH_4]^+$; HRMS calcd for $[C_{19}H_{30}O_2 + NH_4]^+$ 336.2359, found 336.2353.

Methyl (1*R*,2*S*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-2-(trimethylsilyl)-3-cyclohexenecarboxylate (21). A solution of acid **20** (0.049 g, 0.154 mmol) in ether (3 mL) was treated at 23 °C with diazomethane (1.5 mL, 0.45 M in ether, 0.675 mmol) in three separate portions (waiting 30 min between each) until the yellow color persisted. The solution was quenched by addition of glacial acetic acid (1 drop). The reaction mixture was partitioned between ether and $NaHCO_3$ (saturated aqueous solution). The organic layer was washed with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo* to afford 0.050 g (98% yield) of desired product **21** as a colorless solid: mp 32−34 °C (not recrystallized); R_f = 0.51 (hexanes−EtOAc, 90:10); $[\alpha]^{23}_D$ +198° (*c* 1.20, $CHCl_3$); FTIR (film) 3025, 2952, 2923, 2916, 2874, 2839, 2815, 1731, 1249, 1189, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69−5.58 (m, 3H), 5.50 (m, 1H), 3.68 (s, 3H), 2.57 (s, 4H), 2.08−1.82 (m, 6H), 1.72 (m, 3H), 1.59 (s, 3H), −0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 127.0, 126.8, 124.7, 124.5, 123.7, 122.8, 51.3, 46.1, 37.5, 34.3, 32.9, 30.6, 27.9, 23.7, 22.1, 18.1−1.2; CIMS (NH_3) 350 $[M + NH_4]^+$, 333 $[M + H]^+$; HRMS calcd for $[C_{20}H_{32}O_2Si + NH_4]^+$ 350.2515, found 350.2512.

Methyl (1*R*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)-4-bromo-2-cyclohexenecarboxylate (22). A solution of ester **21** (0.0312 g, 0.0938 mmol) in acetone−water (4:1 mixture, 3.0 mL) at −25 °C was treated dropwise with *N*-bromosuccinimide (0.0701 g/mL solution in acetone, 0.298 mL, 0.1173 mmol). The resulting solution was stirred at −25 °C in the dark for 1 h. The reaction mixture was quenched by addition of Na_2SO_3 (saturated aqueous solution) and partitioned between water and ether. The organic layer was washed with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 95:5) to afford 0.0044 g (14% yield) of starting material **21** and 0.0165 g (52% yield, 60% with respect to recovered starting material) of **22** as a ca. 1:1 mixture of diastereomers (determined by ^{1}H NMR): R_f = 0.45, 0.37 (hexanes−EtOAc, 90:10); FTIR (film) 2950, 2926, 2871, 2814, 1732, 1445, 1435, 1267, 1227, 1201, 1171, 1130, 1057, 988, 806 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04−5.95 (m, 1H), 5.89 (d, J = 10.2 Hz, 1/2H), 5.78 (d, J = 9.8 Hz, 1/2H), 5.67 (m, 2H), 4.77 (m, 1/2H), 4.72 (m, 1/2H), 3.73 (s, 3/2H), 3.68 (s, 3/2H), 2.58 (m, 4H), 2.62−2.35 (m, 8H), 1.61 (s, 3/2H), 1.58 (s, 3/2H); CIMS (NH_3) 358 $[M + NH_4 + 2]^+$, 356 $[M + NH_4]^+$; HRMS calcd for $[C_{17}H_{23}O_2Br + NH_4]^+$ 356.1225, found 356.1216.

Methyl (*R*)-1-(2-(2-Methyl-1,4-cyclohexadienyl)ethyl)cyclohexa-2,4-dienecarboxylate (3). A solution of allylic bromide **22** (0.0057 g, 0.0168 mmol) in benzene (0.5 mL) was treated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.025 mL, 0.168 mmol) and heated at reflux for 2 h. The reaction mixture was cooled to 23 °C, diluted with ether, washed with brine, dried over $MgSO_4$(anhyd), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes−EtOAc, 95:5) to afford 0.0015 g (35% yield) of desired product **3** of 92−94% ee (determined by HPLC): $[\alpha]^{23}_D$ −71.4° (*c* 1.34, $CHCl_3$); for additional analytical data see **3** above.

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