Total synthesis of the eupomatilones. J Org Chem

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · DECEMBER 2007

Impact Factor: 4.72 · DOI: 10.1021/jo701415m · Source: PubMed

3 AUTHORS, INCLUDING:

Soumya Mitra
The Ohio State University
5 PUBLICATIONS **233** CITATIONS

SEE PROFILE

JOC*Article*

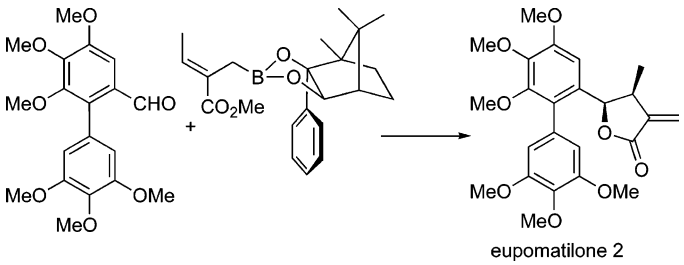
Total Synthesis of the Eupomatilones

Soumya Mitra, Srinivas Reddy Gurrala, and Robert S. Coleman*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

coleman@chemistry.ohio-state.edu

Received July 10, 2007



Full details of the total syntheses of five members of the eupomatilone family of lignans are reported.

Introduction

Eupomatilones 1−7 (Figure 1) were isolated by Carroll and Taylor in 1991 from the Australian shrub *Eupomatia bennettii*, and were found to co-occur with a structurally diverse set of related lignan natural products.[1] Howarth defined lignan natural products as cinnamic acid dimers, connected via the β-carbons.[2] The aromatic rings are normally oxygenated and oftentimes highly modified. This family of plant natural products is distributed throughout the producing plants, including the roots, stems, leaves, fruit, and seeds.

In the eupomatilone family of lignans, the dimeric β-cinnamic acid carbon skeleton has undergone an unprecedented rearrangement that involves cleavage of a carbon−aryl bond. Carroll and Taylor proposed that the spirocyclohexadienone skeleton of eupodienone precursor **1** undergoes hemiketal formation to afford **2**, which fragments to lactone **3** (Figure 2).[3] All six carbons of the side chains of the cinnamic acid precursors end up attached to one of the aromatic rings. The eupomatilones equilibrate about the biaryl axis, which is stereogenic for eupomatilones 5, 6, and 7. Two isomers are observed by both ^{1}H and ^{13}C NMR for eupomatilones 5, 6, and 7. The hydrogens on the trimethoxyphenyl ring of eupomatilone 4 are diastereotopic and slowly interconverting. The atropdiastereomers are inseparable, and show a coalescence temperature between 97 and 102 °C.[2]

The α-methylene-γ-lactone found in eupomatilones 1, 2, and 5 readily forms covalent bonds to cellular proteins via Michael addition of thiol nucleophiles.[4] This produces antigenic compounds within the cell, which are a cause of chronic actinic dermatitis (CAD). The moiety is also reported to form [2+2] photoadducts with the DNA base thymine in the presence of sunlight, and hence its photochemical role is strongly implicated in CAD. The α-methylene-γ-lactone moiety has also been shown to target the I$\kappa\beta$ kinase (IKK) in addition to the transcription factor regulator nuclear factor-kappaB (NF-κB), signifying their potential role in the cellular signaling process.[5] The α-methylene lactone is presumably the biologically relevant functionality of these natural products.[6−8]

Herein, we will discuss two conceptually different strategies, one of which is asymmetric, for the construction of the lactone ring that is attached to the highly oxygenated biaryl system. It is to be noted that the carbon that is incorporated as the carbonyl of the lactone ring (Figure 3) for eupomatilones 4 and 6 is the allylic carbon, adjacent to indium, which subsequently undergoes a late stage oxygenation by hydroboration−oxidation reaction. In the case of eupomatilones 1, 2, and 5, the lactone carbonyl is directly incorporated from the existing carbomethoxy group of the chiral crotylboronate reagent. The *exo*-methylene group is formed from the allylic carbon of the boronate (Figure 3).

In our preliminary account of work on this family of natural products, we detailed the total synthesis of eupomatilone 4 and

(1) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1615.
(2) Ayers, D. C.; Loike, J. D. *Lignans*: *Chemical, Biological and Clinical Properties*, University Press: Cambridge, UK, 1990.
(3) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705.
(4) Patel, B. B.; Waddell, T. G.; Pagni, R. M. *Fitoterapia* **2001**, *72*, 511.
(5) Huang, W.-C.; Chan, S.-T.; Yang, T.-L.; Tzeng, C.-C.; Chen, C.-C. *Carcinogenesis* **2004**, *25*, 1925.
(6) Cassady, J. M.; Suffness, M. *Anticancer Agents Based on Natural Product Models*; Acedemic: New York, 1980; Vol. 7, p 201.
(7) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem* **1971**, *14*, 1147.
(8) Kupchan, S. M.; Fessler, D. C.; Eakin, M. A.; Giacobbe, T. J. *Science* **1970**, *168*, 376.

10.1021/jo701415m CCC: $37.00
Published on Web 10/11/2007

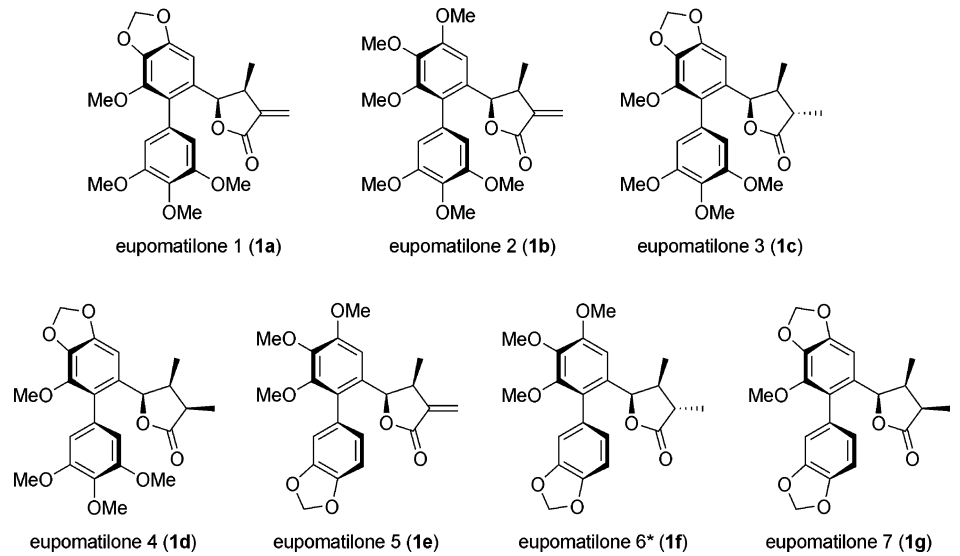


FIGURE 1. Structures of the eupomatilones.

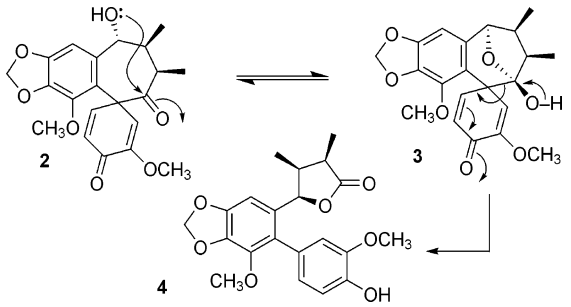


FIGURE 2. Rearrangement of the dimeric lignan skeleton.[3]

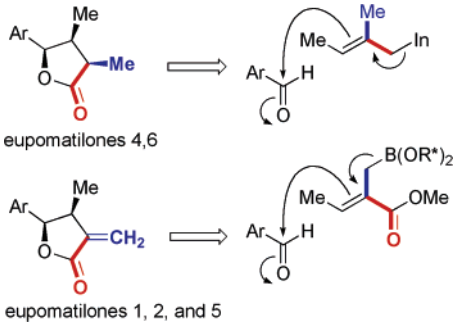


FIGURE 3. Lactone formation strategies.

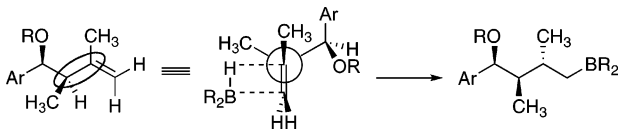


FIGURE 4. Diastereoselective hydroboration.

the purported structure of eupomatilone 6 by a stereochemically unambiguous route. In reality, the original structure reported for eupomatilone 6 was incorrect, and we had synthesized 3-*epi*-eupomatilone 6.[9] Consequently, we revised the structure of the natural product to possess a *trans* relationship of the C3 and C4 methyl groups (cf. Figure 1).[10] There have been reports of

(9) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012.

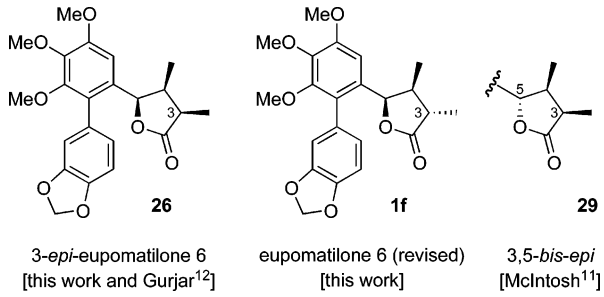


FIGURE 5. Epimers and correct structure of eupomatilone 6.

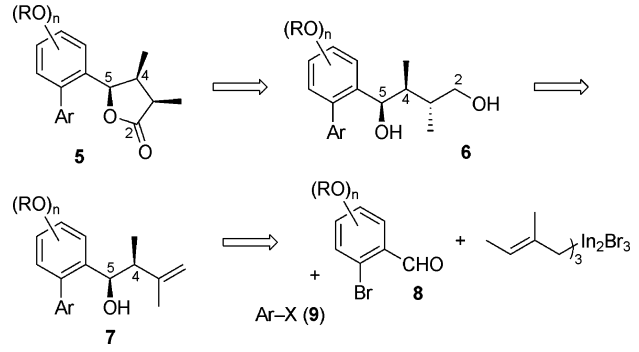
synthetic approaches to eupomatilone 6, by McIntosh and co-workers,[11] who reported the synthesis of a bis-epimeric version of eupomatilone 6, and by Gurjar and co-workers, who also reported the total synthesis of 3-*epi*-eupomatilone 6.[12] Hall and co-workers have later reported the synthesis of eupomatilone 6 and its three unnatural diastereomers by acid catalyzed allylboration.[13] We now report full details of the total synthesis of eupomatilones 1, 2, 4, 5, and 6.

Results and Discussion

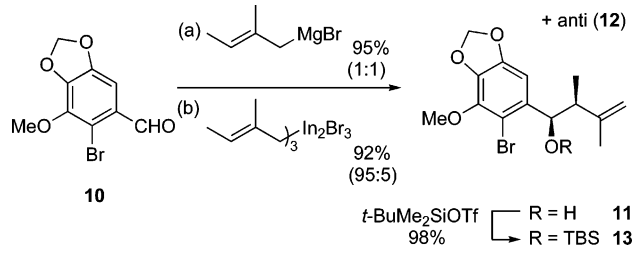
The initial synthetic plan for the synthesis of eupomatilones bearing a *cis*-1,2-dimethyl-substitution pattern (eupomatilones 4 and 7, and what was assumed to be eupomatilone 6, as in generic structure **5**, Scheme 1) was based on the use of an indium-based crotylation addition reaction that had been developed as part of another study[14] (Scheme 1). The combination of aryl aldehyde **8** and the (*E*)-2-methyl-2-butenylindium reagent would install the 1-hydroxy-3-butenyl side chain of **7**, thereby introducing two of the three stereogenic elements of the targets at C4 and C5 (eupomatilone numbering). The biaryl bond of **7** would be formed either by Suzuki−Miyaura coupling

(10) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025.
(11) (a) Hutchison, J. M.; Hong, S.-P.; McIntosh, M. C. *J. Org. Chem.* **2004**, *69*, 4185. (b) Hong, S.-P.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19.
(12) Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317.
(13) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808.
(14) Coleman, R. S.; Gurrala, S.; Mitra, S.; Raao, A. *J. Org. Chem.* **2005**, *70*, 8932.

SCHEME 1. First Generation Retrosynthetic Analysis



SCHEME 2. Crotylation with Indium Reagent



of the bromide of **8** with the corresponding arylboronic acid **9** (X = $B(OH)_2$) or by using the Lipshutz oxidative cuprate biaryl coupling with **9** (X = Br). Hydroboration of the alkene of **7** would oxidize the terminal carbon of the butenyl chain and introduce the third stereogenic center at C3 via $A^{1,3}$-controlled diastereofacial selectivity. Final C2 alcohol to carboxylic acid oxidation of **6** with concomitant lactone formation would provide the targeted natural products (**5**)

Initially, various methods were examined for crotylation. Addition of (*E*)-2-methyl-2-buten-1-ylmagnesium bromide to aldehyde **10** (THF, −78 °C, 1.5 h) provided a 1:1 mixture of *syn* and *anti* adducts **11** and **12** in 95% yield (Scheme 2). This reaction could be effected in an asymmetric fashion via the corresponding diisopinocampheylborane reagent, albeit with no diastereoselectivity due to equilibration of the Grignard precursor.[14] The undesired *anti* adduct **12** could be converted to the desired *syn* adduct **11** by Mitsunobu inversion with *p*-nitrobenzoic acid[15] (Ph_3P, DIAD, THF, 0−25 °C) and hydrolysis (K_2CO_3, MeOH, 25 °C), which resulted in an overall yield for conversion of **10** to **11** of 73%. Most effectively with respect to diastereoselection, **11** could be produced in racemic form as a 95:5 *syn*/*anti* mixture in 92% yield by addition of the corresponding indium reagent[16] to aldehyde **10**. The alcohol of **11** was protected as the *tert*-butyldimethylsilyl ether (*t*-$BuMe_2$SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 20 min) to afford **13**.

In this system, we implemented the methodology of Lipshutz for biaryl coupling,[17] which involves low-temperature formation of a mixed biarylcuprate followed by oxidation of this species to form a carbon−carbon biaryl bond. This reaction is essentially insensitive to steric or electronic features of the aromatic systems compared to palladium-mediated processes and worked well in this system. We have employed this reaction in a stereocontrolled synthesis of the natural products calphostin A and phleichrome[18] and several members of the dibenzocyclooctadiene lignan family.[14]

In the present case (Scheme 3), aryl bromide **13** was converted to the aryllithium reagent **14** (*t*-BuLi, MeTHF, −78 °C), and subsequently to the lower order cyanocuprate **15** (CuCN, MeTHF, −40 °C). Aryl bromide **16** was similarly converted to aryllithium **17** (*t*-BuLi, MeTHF, −78 °C), which was added to cyanocuprate **15** (−125 °C, 30 min) to form a biarylcuprate species. Treatment with oxygen (−125 °C, 3 h) affected conversion to the biaryl system **18**, in modest yield.

Hydroboration of **18** (9-BBN, THF, 0−25 °C, 12 h) followed by oxidation (NaOH, H_2O_2, 0−25 °C, 3 h) afforded the corresponding primary alcohol in essentially quantitative yield, with complete control of diastereoselectivity (Scheme 3). Deprotection of the silyl ether (*n*-Bu_4NF, THF, 25 °C, 3 h) afforded diol **19**. Selective oxidation of the primary alcohol of **19** (TEMPO, NCS, *n*-Bu_4NI, CH_2Cl_2/1:1 0.05 M K_2CO_3/0.5 M $NaHCO_3$, 25 °C, 1 h)[19] was accompanied by lactonization, and afforded eupomatilone 4 (**1d**) in 92% yield for the two-step sequence. Eupomatilone 4 was synthesized in eight steps from known **16** and **10**, in 33% overall yield. The ^{1}H NMR spectrum of synthetic eupomatilone 4 was identical with that reported for the natural product.

The origin of the diastereoselection in the hydroboration of **18** is due to $A^{1,3}$ strain in the transition state (Figure 4). In the lowest energy conformation (MM3) about the sp^2−sp^3 bond, the allylic hydrogen is eclipsed with the alkene, thereby minimizing $A^{1,3}$ strain. The least sterically congested approach by 9-BBN is from the side of the allylic methyl group, giving the new stereogenic center wherein the methyl groups are *anti*. This model has precedent in several related contexts.[20]

Total synthesis of what we believed to be eupomatilone 6 (bearing the *cis*-dimethyl-substitution pattern) proceeded from aryl bromides **20**[21] and commercially available **23** (Scheme 4). Cuprate coupling of the corresponding aryllithium reagents **21** and **24** under previously described conditions afforded biphenyl **25**. Following reaction conditions used in the total synthesis of eupomatilone 4, hydroboration/oxidation of the alkene of **25** afforded the corresponding primary alcohol (42% for two steps). Fluoride-mediated desilylation and selective oxidation of the primary alcohol afforded γ-lactone **26**, supposedly eupomatilone 6. However, there were slight discrepancies in the ^{1}H NMR spectrum of synthetic **26** compared to the data published for eupomatilone 6,[3] present in the chemical shifts of and coupling constants between C3-H and C4-H. Our spectral data matched exactly that obtained by Gurjar and co-workers[12] in their synthesis of this putative structure of eupomatilone 6.

We had inadvertently synthesized the correct structure of eupomatilone 6 during prior studies on the oxidation/lactone

(15) (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(16) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.

(17) (a) Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161. (b) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276. (c) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815. (d) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567.

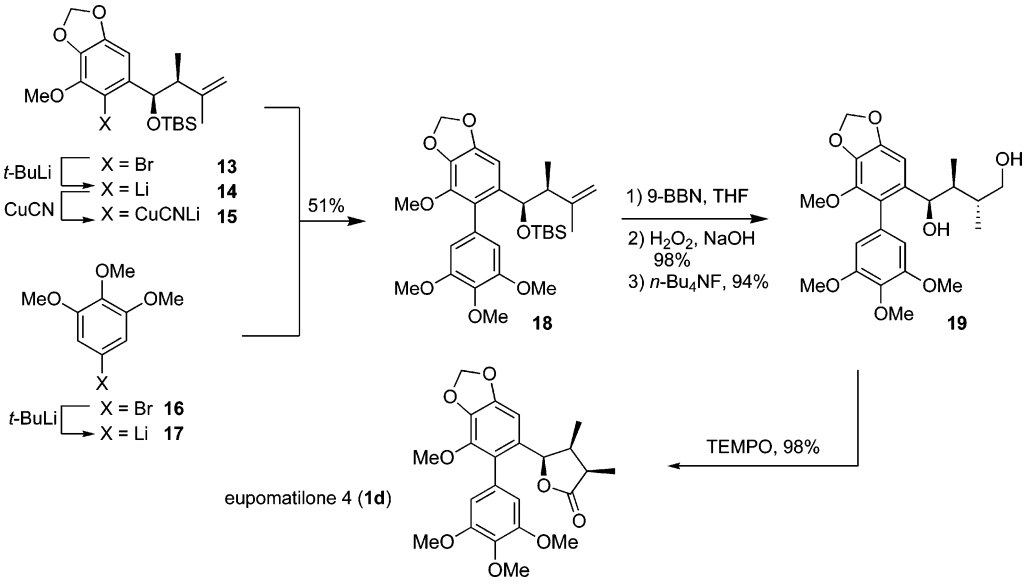
(18) (a) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1994**, *116*, 8795. (b) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995**, *117*, 10889.

(19) (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452. (b) Kamal, A.; Sandbhor, M.; Shaik, A. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1575.

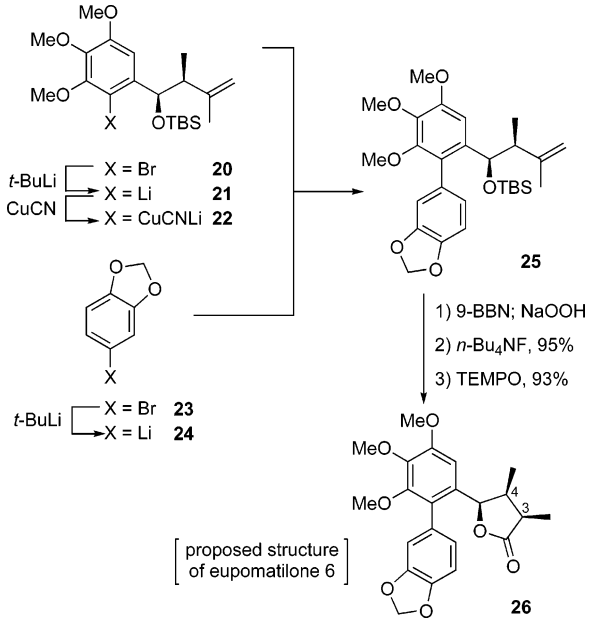
(20) (a) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1984**, 629. (b) Coutts, L. D.; Cywin, C. L.; Kallmerten, J. *Synlett* **1993**, 696. (c) Bernsmann, H.; Fröhlich, R.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 4347. (d) Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983. (e) Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129.

(21) Prepared from 2-bromo-3,4,5-trimethoxybenzaldehyde (cf.: Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533) as described for the preparation of **13**.

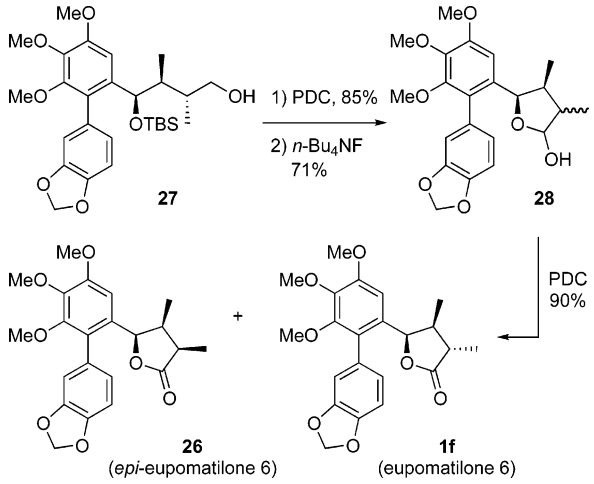
SCHEME 3. Cuprate Coupling, Hydroboration, and Eupomatilone 4 Total Synthesis



SCHEME 4. Synthesis of the Putative Structure of Eupomatilone 6



SCHEME 5. Eupomatilone 6 Total Synthesis



formation sequence (Scheme 5). Oxidation of alcohol **27** with pyridinium dichromate (CH_2Cl_2, 25 °C, 3 h, 85%) afforded the corresponding aldehyde, which cyclized to lactol **28** after fluoride-mediated deprotection of the silyl ether (THF, 25 °C, 6 h). Compound **28** was produced as a mixture of diastereomers, which were formed presumably by epimerization of the intermediate aldehyde under basic silyl deprotection reaction conditions, and which originally led to the abandonment of this oxidation protocol. Lactol to lactone oxidation (CH_2Cl_2, 25 °C, 2 h, 90%) afforded a 1:3 mixture of **26** and its epimer **1f**, which could be separated—with difficulty—by preparative TLC. The ^{1}H NMR spectrum of pure **1f** proved identical with that published for eupomatilone 6.[3]

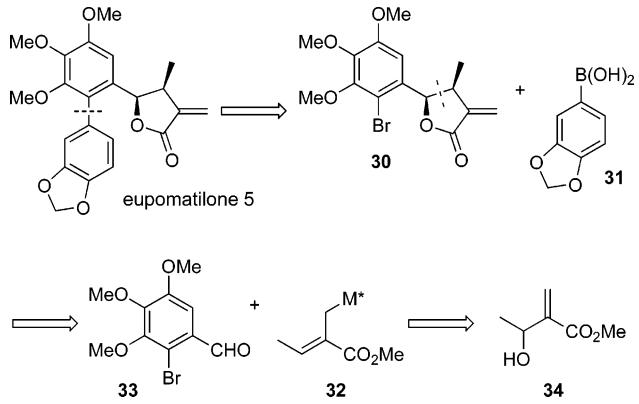
Thus, our synthesis of **26** (Scheme 4) produced 3-*epi*-eupomatilone 6, whereas the structure of the natural product must possess a *trans* relationship of the C3 and C4 methyl groups, as in **1f** (Figure 5). This result changed the work of McIntosh and co-workers,[11] whose reported synthesis of 5-*epi*-eupomatilone 6 was now a synthesis of 3,5-bis-*epi*-eupomatilone 6 (**29**).

Our approach to the synthesis of eupomatilones 1, 2, and 5 relied on the development of an asymmetric crotylboration strategy to directly assemble the α-methylene-γ-lactone moiety with *syn*-stereochemistry at the C4 and C5 positions of the lactone ring. Several crotylation strategies were explored to construct the required α-methylene-γ-lactone moiety in an asymmetric fashion.

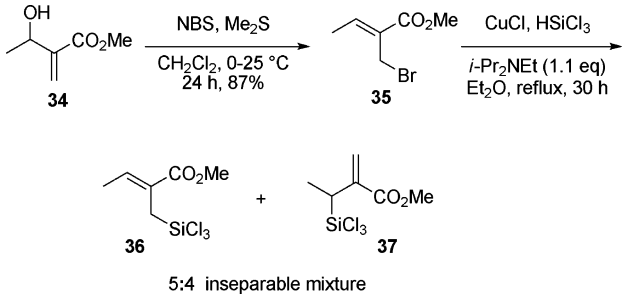
There has been one report of a synthetic approach leading to eupomatilones 2 and 5 by Kabalka,[22] and Buchwald reported an asymmetric approach to eupomatilone 3.[23] Herein, we report the first asymmetric total synthesis of eupomatilones 2 and 5. An attempt at the asymmetric total synthesis of eupomatilone 1 will be discussed separately. A convergent synthetic strategy was developed (Scheme 6) that was based on a Suzuki—Miyaura cross coupling of **30** and **31** and an asymmetric carbomethoxy-crotylation reaction protocol to directly install the α-methylene-

(22) Kabalka, G. W.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 7325.
(23) Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6177.

SCHEME 6. Retrosynthetic Analysis of Eupomatilone 5



SCHEME 7. Attempt with Leighton's Chiral Diamine Route

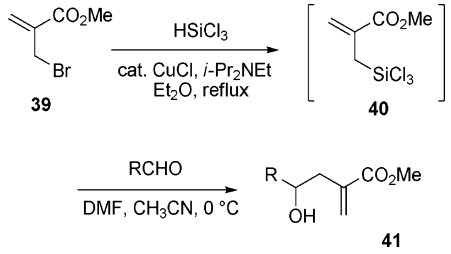


γ-lactone moiety onto the aldehyde **33**. 1,3-Allylic rearrangement of **34** would afford the carbomethoxycrotyl reagent **32** in an efficient and stereocontrolled manner. A major challenge with this strategy was how to make **32** stable and chiral, and how to provide effective enantioselection in the addition to electron-rich aryl aldehydes.

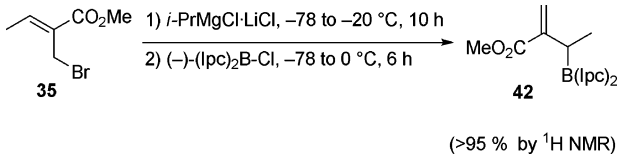
The initial attempt to synthesize a chiral carbomethoxycrotyl reagent targeted silane **32**, using Leighton's chiral diamine strategy.[24,25] We had successfully applied this strategy in the asymmetric total synthesis of dibenzocyclooctadiene lignans.[26] The allyl alcohol **34** (Scheme 7) was synthesized in good yield (85%) from acetaldehyde and methyl acrylate **38** with use of DABCO (100 mol %),[27] which was converted to the allylic bromide **35** by using NBS.[28,29] However, in this case, we observed a 5:4 inseparable regioisomeric mixture of the carbomethoxycrotyl trichlorosilanes **36** and **37** upon reaction of trichlorosilane with allylic bromide **35**, as observed by ^{1}H NMR (Scheme 7), presumably formed via an allylic rearrangement under the reaction conditions that required copper chloride as a catalyst. Purification of the trichlorosilanes, using distillation under reduced pressure, proved to be extremely difficult and required a distillation temperature $\geq$200 °C, only to afford the mixture of the trichlorosilanes. All attempts to preferentially crystallize one of the regioisomers with Leighton's chiral diamine strategy were also an exercise in futility.

Carbomethoxycrotyl organosilicon reagents have been successfully used for asymmetric crotylations by Kobayashi[30] and

SCHEME 8. Organosilicon Promoted Reaction with Aldehydes[30]



SCHEME 9. Attempt with Brown's Chlorodiisopinocampheyl Borane Route



Itoh.[31] These workers used an unsubstituted allyl bromide **39** (Scheme 8), to form an alkylidene carbomethoxycrotyl trichlorosilane intermediate **40**, which was used in the construction of an α-methylene-γ-lactone moiety. Problems of allylic transposition observed in our work were nullified in their approach due to the absence of the β-methyl substitution with respect to the carbomethoxy group in **39**. We faced a similar problem in earlier work on dibenzocyclooctadiene lignan total syntheses; at the time, there were no reports of crotyl metal reagents that bore substituents that made them dissymmetric with respect to allylic transposition.[14]

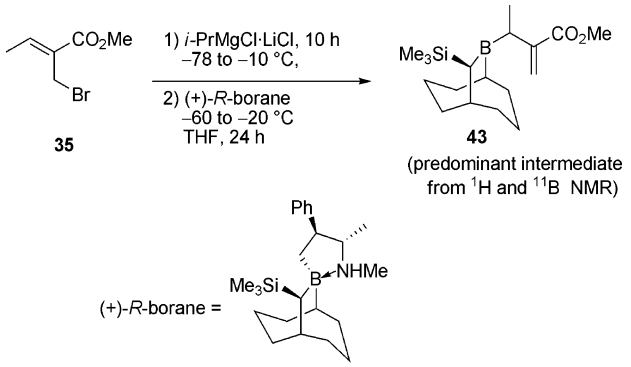
The unsuccessful attempts with organosilicon chemistry directed our attention into organoboron chemistry. In our asymmetric total synthesis of dibenzocyclooctadiene lignans,[26] we had made a nonstereodefined tiglyl Grignard reagent (from tiglyl bromide) at low temperature. After transmetallation from magnesium to boron by treatment with (−)-(Ipc)$_2$BCl, to form Brown's diisopinocampheylborane reagent,[32] the resulting crotylborane provided high levels of enantioselection in the addition to aryl aldehydes, but no diastereoselection. We again examined Brown's chlorodiisopinocampheyl borane strategy in our quest for making a chiral carbomethoxycrotyl reagent.

The allylic bromide **35** (Scheme 9) was treated with Knochel's reagent *i*-PrMgCl·LiCl[33,34] at −78 °C, and was gradually warmed to −20 °C to form the Grignard reagent. (−)-(Ipc)$_2$BCl was added at −78 °C to form the desired diisopinocampheylcrotylborane reagent. Analysis of the crude reaction mixture by ^{1}H and ^{11}B NMR revealed almost exclusive (>95%) formation of the undesired 1,3-allylically rearranged carbomethoxycrotylborane species **42**.

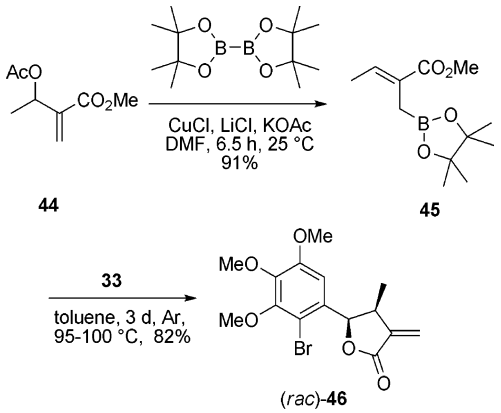
Inspired by contributions of Soderquist,[35,36] we attempted to synthesize the chiral (*E*)-carbomethoxycrotyl reagent **32.** The carbomethoxy allylic bromide **35** (Scheme 10) was treated with *i*-PrMgCl·LiCl under Knochel's conditions,[33,34] followed by

(24) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.
(25) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375.
(26) Coleman, R. S.; Gurrala, S. R.; Mitra, S.; Raao, A. *J. Org. Chem.* **2005**, *70*, 8932.
(27) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.
(28) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333.
(29) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213.
(30) Kobayashi, S.; Yasuda, M.; Nishio, K. *Synlett* **1996**, 153.
(31) Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267.
(32) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.
(33) Liu, C.-Y.; Ren, H.; Knochel, P. *Org. Lett.* **2006**, *8*, 617.
(34) Sapountzis, I.; Dohle, W.; Knochel, P. *Chem. Commun.* **2001**, 2068.
(35) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044.
(36) Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397.

SCHEME 10. Attempt with Soderquist's Route



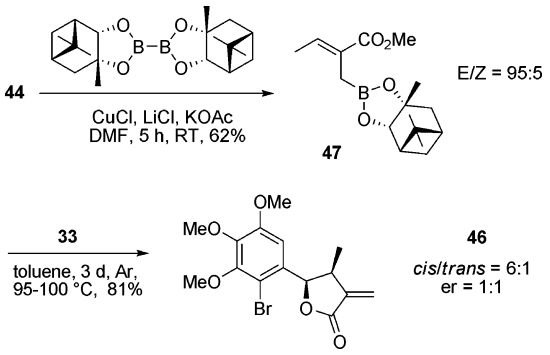
SCHEME 11. Synthesis of α-Methylene-γ-lactones with Achiral Crotylboronate



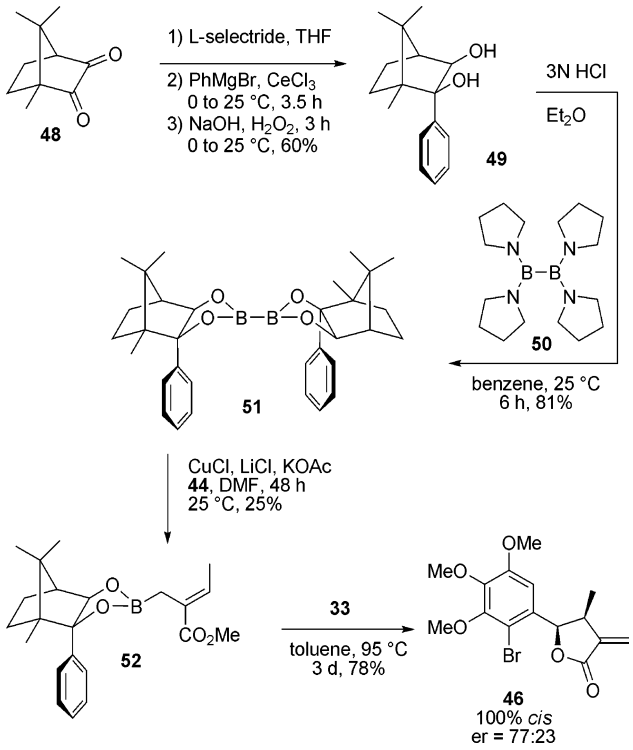
addition of Soderquist's air-stable crystalline pseudoephedrine borinic ester complexes of 10-trimethylsilyl-9-borabicyclo[3.3.2]-decane. Unfortunately, the intermediate **43** obtained in this case was almost exclusively the undesired 1,3-allylic rearranged carbomethoxycrotylborane, which was confirmed by ^{1}H and ^{11}B NMR analysis of the crude reaction mixture.

The previously unsuccessful attempts with allylic bromides led us to examine allylic acetates,[37] to generate **44** from **34**, and use diboranes to generate boryl−copper species as intermediates, as reported by Miyaura[38,39] and Ramachandran.[40] The boryl−copper species is reportedly nucleophilic and undergoes an allylic rearrangement via the acetate **44** to stereoselectively generate **45** (*E*/*Z* ratio = 95:5) (Scheme 11). Compound **45** was further subjected to thermal crotylboration conditions under argon in toluene for 3 days at 95−100 °C with 3,4,5-trimethoxybromobenzaldehyde **33** to obtain **46**, the top half of eupomatilone 5, in good yield (82%). Synthesis of the carbomethoxycrotyl reagent **32** by an alternate strategy (achiral version with boron) has also been reported by Hall and Kennedy[41] by tandem carbocupration of alkynoate esters followed by electrophilic trapping with halomethyl boronates at low temperature with HMPA as an additive. Hall and co-workers have also reported **46** was synthesized under Lewis acid-catalyzed conditions[13] in their synthesis of eupomatilone 6.

SCHEME 12. Synthesis of α-Methylene-γ-lactones with a Chiral Carbomethoxycrotyl Boronate



SCHEME 13. Asymmetric Crotylboration of Monoaryl Aldehydes with the New Diborane Reagent 51



On the basis of the success of the thermal crotylboration reaction[41,42] with 3,4,5-trimethoxybromobenzaldehyde **33**, attempts were directed toward developing a chiral carbomethoxycrotyl boronate for the asymmetric version of this reaction. Bis[(±)-pinanediolato]diboron was examined (Scheme 12) to obtain the chiral crotylboronate **47** in an *E*/*Z* ratio of 95:5. A one-pot thermal crotylboration was attempted with the aldehyde **33**, which afforded **46** as a *cis*/*trans* mixture (6:1), although surprisingly with no enantioselection (er = 1:1).

On the basis of the above result it was realized that to enhance the enantioselectivity in the thermal crotylborations, a more effective chiral carbomethoxycrotyl boronate was required, where we can efficiently direct the approach of the aldehyde in the transition state. Villiéras and co-workers[43] and Hoffmann

(37) Cha, J. H.; Pae, A. N.; Choi, K.; Cho, Y. S.; Yun, H.-C.; Lee, J.; Koh, H. Y.; Lee, E. *Biotechnol. Lett.* **2002**, *24*, 1695.
(38) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982.
(39) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47.
(40) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481.
(41) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898.
(42) Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Chem. Commun.* **2005**, 1988.
(43) Chataigner, I.; Lebreton, J.; Zammattio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719.

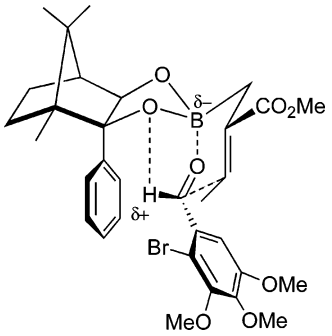


FIGURE 6. A model for the stereoinduction based on a proposal by Villieras et al.[43]

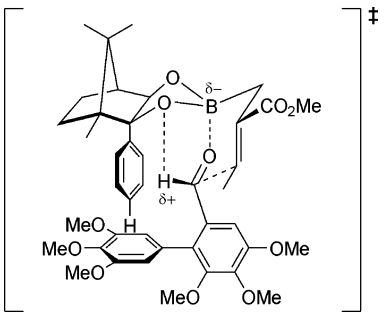
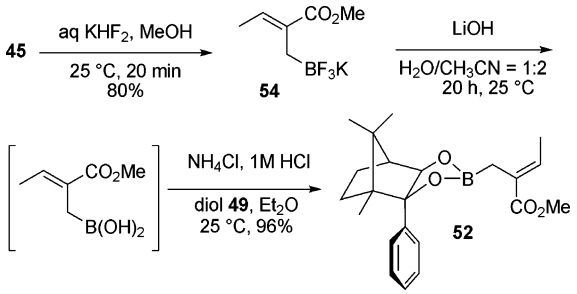


FIGURE 7. Enhanced stability in the transition state due to edge-to-face CH−π interaction.

and Herold[44] reported one such boronic ester auxiliary, which was used by Hall and co-workers[45] in their study of enantioselective additions with dual auxiliary allylboronates. Hence, efforts were directed toward the synthesis of a new diborane reagent **51** with the boronic ester auxiliary (Scheme 13). (+)-(*R*)-Camphorquinone was reduced with L-selectride[46] followed by addition of the phenylcerium reagent generated in situ to obtain the diol **49** in 60% yield. Diol **49** was subjected to treatment with tetra(pyrrolidino)diborane **50** in benzene with freshly prepared 3 M HCl in ether[47] and was allowed to stir for 6 h at room temperature. Air stable colorless crystals of the diborane reagent **51** were obtained, which were recrystallized from hexane. This reagent was subjected to Miyaura's boryl−copper protocol to obtain the desired chiral carbomethoxycrotyl boronate **52**, although in low yield (25%). The low yield of **52** can be attributed to the fact that the oxidative insertion of copper into the boron−boron bond during the formation of the boryl copper intermediate is sterically hindered owing to the steric bulk of the phenyl groups and the quaternary methyl groups in the transition state. However, crotylation of this reagent with aldehyde **33** resulted in a completely *cis*-selective reaction with a modest enantiomeric ratio of 77:23 (reverse phase HPLC, Chiralpak AD-RH, *i*-PrOH−H_2O 1:1, flow rate = 0.35 mL/min, λ = 254 nm, injection volume = 20 μL) to afford **46**. The diborane reagent was found to be fairly insoluble in DMF and would only dissolve gradually on gently heating the DMF mixture. A 1:1 THF/DMF mixture was made in an attempt to solubilize the diborane reagent, but that resulted in a complete

SCHEME 14. Generation of the Crotylboronate via Trifluoroborate and Trans-Esterification Route



shutdown of the reaction. This observation corroborated the fact that boryl−copper reactions are known to occur only in highly polar solvents.[38,39]

The justification for a better stereoinduction via this auxiliary (Figure 6) is adapted from the model proposed by Villiéras and co-workers.[43] The aldehyde **33** is directed from one face of the phenyl group, the orientation of which is likely governed by stereoelectronics and steric hindrance in the system.

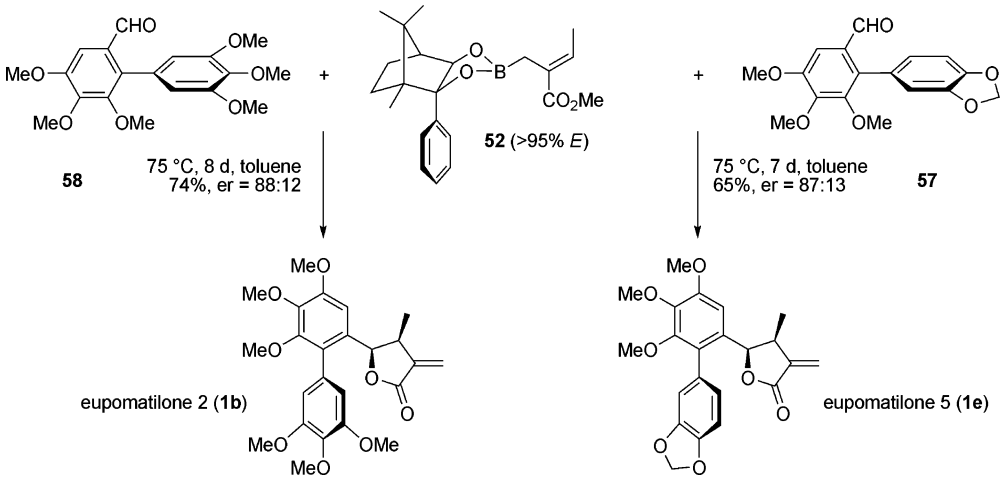
The transition state is also stabilized due to a possible attractive interaction between the acidic aldehyde proton and the coplanar oxygen attached to the electron-rich boron. In addition to this, the boron-centered anomeric effect (n → s* interactions) between the axial lone pairs of the ring oxygen of the 6-membered cyclic transition state and the C−H single bond of the B−O═CH−R system is also proposed to play some role in the stereoinduction.

The poor yield of **52**, however, led us to modify the route (Scheme 14) and increase the efficiency of the process by applying the chemistry of Molander[48] and Hutton.[49] The pinacolylboronate **45** was converted to its corresponding trifluoroborate salt **54**, which was recrystallized from hot acetone and ether to afford **54** in ≥95:5 *E*/*Z* diastereomeric ratio. This compound was subjected to hydrolysis with LiOH (1:2 H_2O/CH_3CN, 20 h) and was trans-esterified in situ with a catalytic amount of 1 N HCl and solid NH_4Cl, with dropwise addition of diol **49** in ether, to afford close to 70% overall yield of **52** in three steps starting from the acetate **44**.

The enantiomeric ratio of the product after the crotylation with aldehyde **33** was found to be a modest 77:23 at 95 °C. Lowering of the reaction temperature to 65 °C led to a slight increase in the ratio to 83:17, implicating that the reaction temperature had only a small effect on the difference of energies of the transition states. The reaction rate was found to be extremely slow at 65 °C (65% yield brsm, after 16 days). Addition of $Sc(OTf)_3$ as a Lewis acid to enhance the reaction rate in the crotylboration reaction did not have any effect in our system.[50] Hence, our focus was shifted to increasing the differences in energies of the diastereomeric transition states by possible introduction of other noncovalent stabilizing factors. It was envisioned that an "edge-to-face" CH−π interaction[51] could perhaps make the transition state more stable and compact, and enhance the enantioselectivity of the reaction. This was based on extrapolation of the model proposed by Chataigner[40] and co-workers as depicted below (Figure 7). Edge-to-face

(44) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375.
(45) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412.
(46) Lachance, H.; St-Onge, M.; Hall, D. G. *J. Org. Chem.* **2005**, *70*, 4180.
(47) Ali, H. A.; Goldberg, I.; Srebnik, M. *Eur. J. Inorg. Chem.* **2002**, 73.
(48) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
(49) Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899.
(50) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586.
(51) Matsushima, A; Fujita, T.; Nose, T.; Shimohigashi, Y. *J. Biochem.* (*Tokyo*) **2000**, *128* (2), 225.

SCHEME 15. Asymmetric Thermal Crotylboration of Biaryl Aldehydes



aromatic interactions and CH−π interactions[52] have been invoked previously in stabilizing certain protein folding motifs in literature.[53]

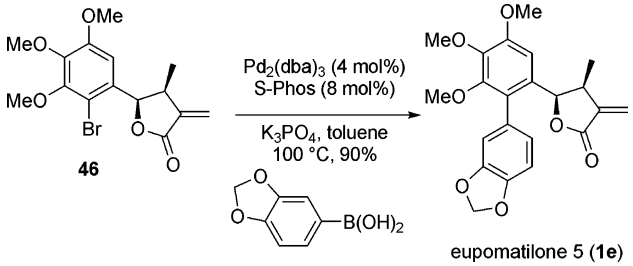
Having this preconceived notion in mind, the asymmetric thermal crotylboration was attempted on electron-rich biaryl aldehydes that were direct precursors to eupomatilones 2 and 5, which afforded good enantioselectivity (88:12 and 87:13 enantiomeric ratios, respectively) for the natural products (Scheme 15). The ^{1}H NMR spectrum of synthetic eupomatilones 2 and 5 were identical with that reported for the natural product. This level of enantioselection was the maximum observed in this work.

Optimization of the Suzuki−Miyaura Biaryl Cross-Coupling Reaction. After optimization of the crotylation reaction, the focus was on optimizing the Suzuki−Miyaura biaryl cross-coupling reaction. Several variations of Suzuki conditions were attempted on two electron-rich boronic acids **55** and **56** with aryl bromide **33**, the results of which are given in Table 1.

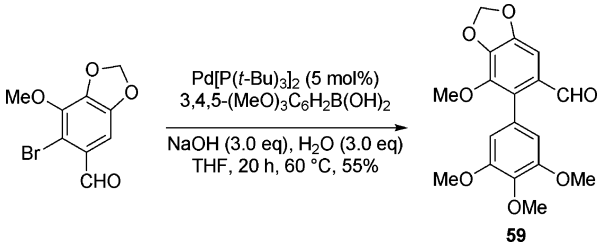
Buchwald conditions[54,23] (entries 7 and 8) were found to work best for our system. On the basis of the above optimization we examined Suzuki conditions on **46** in a sealed tube that was preflushed with argon. All the reaction materials were weighed in a glovebox before the reaction vessel was sealed and heated for 22 h at 95 °C. The reaction mixture was then passed through a short pad of Celite and chromatographic purification afforded eupomatilone 5 (**1e**) in excellent yield (90%) with an enantiomeric ratio of 83:17 (Scheme 16).

After successful application of our asymmetric biaryl crotylboration strategy to the synthesis of eupomatilones 2 and 5, we thought of extending it to the asymmetric synthesis of eupomatilone 1. Buchwald's Suzuki−Miyaura conditions[54,23] were found to be ineffective for synthesizing this biaryl subunit **59** with a methylenedioxy group (Scheme 17). We subsequently tried Itami, Yoshido conditions[55] using bis(tri-*tert*-butylphosphine)palladium (which proved to be successful in the total synthesis of strobilurin B by Coleman and Lu[56]) in our system, and it worked fine affording **59**, with no impurities, in a decent isolated yield (55%).

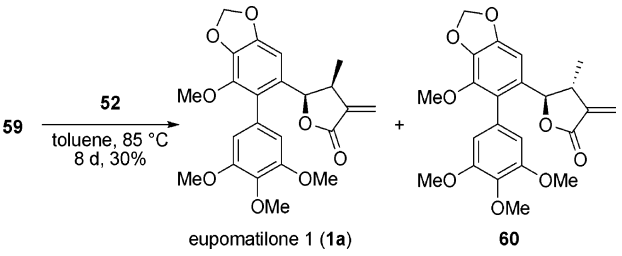
SCHEME 16. Suzuki−Miyaura Biaryl Cross Coupling with Buchwald Conditions[54]



SCHEME 17. Suzuki−Miyaura Coupling with Itami, Yoshido Conditions[55]



SCHEME 18. Synthesis of Eupomatilone 1



Quite interestingly, when this methylenedioxy biaryl aldehyde **59** was subjected to standard thermal carbomethoxycrotylboration conditions with reagent **52**, the reaction was extremely sluggish and afforded eupomatilone 1 (**1e**) (30%) after heating at 80−85 °C for 8 days, albeit with poor diastereoselectivity, as an inseparable mixture of cis (**1a**) and trans (**60**) isomers

(52) Kim, E.-i.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc*. **1998**, *120*, 11192.

(53) (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (b) Burley, S. K.; Petsko, G. A. *Adv. Protein Chem*. **1988**, *39*, 125. (c) Burley, S. K.; Petsko, G. A. *Trends Biotechnol.* **1989**, *7*, 354.

(54) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(55) Itami, K.; Kamei, T.; Yoshida, J.-I. *J. Am. Chem. Soc*. **2003**, *125*, 14670.

(56) Coleman, R. S.; Lu, X. *Chem. Commun*. **2006**, 423.

TABLE 1. Optimization of the Suzuki−Miyaura Cross Coupling Reaction

no.	equiv of **55** or **56**	equiv of Aryl-Br	Suzuki−Miyaura coupling conditions	yield (%)
1	1.4 (**55**)	1.0	$Pd(OAc)_2$ (1 mol %), DABCO (2 mol %), K_2CO_3 (3.0 equiv), acetone, 90 °C, 10 h	
2	1.2 (**55**)	1.0	$Pd(OAc)_2$ (1 mol %), DABCO (2 mol %), K_2CO_3 (3.0 equiv), NMP, 80 °C, 22 h	50
3	1.0 (**55**)	2.0	$Pd[(PPh)_3]_4$ (5 mol %), 85 °C, 21 h toluene/ethanol/2 M Na_2CO_3 (3:2:1.5)	41
4	1.2 (**55**)	1.0	$Pd[(PPh)_3]_4$ (3 mol %), Cs_2CO_3 (1.5 equiv), DMF, 80 °C, 18 h	59
5	1.2 (**56**)	1.0	$Pd[(PPh)_3]_4$ (8 mol %), PPh_3 (10 mol %), Cs_2CO_3 (1.5 equiv), DMF, 75 °C, 15 h	76
6	1.2 (**56**)	1.0	$Pd[(PPh)_3]_4$ (8 mol %), PPh_3 (12 mol %), Cs_2CO_3 (2.0 equiv), DMF, 75 °C, 24 h	81
7	2.0 (**56**)	1.0	$Pd_2(dba)_3$ (4 mol %), S-Phos (8 mol %), K_3PO_4 (3.0 equiv), toluene, 95 °C, 6 h	82
8	2.0 (**55**)	1.0	$Pd_2(dba)_3$ (4 mol %), S-Phos (8 mol %), K_3PO_4 (3.0 equiv), toluene, 100 °C, 6 h	90

(3:1, Scheme 18). HPLC analysis showed that the er was 94:6 for the natural cis isomer **1a**, and 8:1 for the unnatural trans isomer **60**. On the basis of our assumption of possible leakage from the transition state at temperatures above 80 °C, the thermal crotylboration was examined at 60 °C for 18 days in toluene, with no improvement in diastereoselection. This indicated that temperature does not play any significant role in the transition state in this case. The role of electronic effect, if any, of the methylenedioxy group in the enantioselectivity of the thermal crotylboration reactions needs further scrutiny.

Conclusion

In conclusion, we have demonstrated a successful strategy for the synthesis of members of the eupomatilone family. The total synthesis of eupomatilones 4 and 6 rectified the previous incorrect stereochemical assignments. The asymmetric total synthesis of eupomatilones 2 and 5 was completed in five linear steps in close to 55% overall yield. The key to the success of the sequence was a highly efficient Suzuki−Miyaura biaryl cross-coupling reaction and an efficient asymmetric carbomethoxycrotylboration reaction. The edge-to-face effect observed in the aryl−aryl interaction exemplified the importance of weak noncovalent electrostatic components in stabilizing transition states. In the process of developing a chiral carbomethoxycrotylboration reagent, a new air-stable diborane reagent was prepared. Although its solubility in DMF posed a problem, other solvent systems need to be examined to achieve optimized conditions for the asymmetric crotylboration reaction with this reagent. The optimized conditions for the Suzuki−Miyaura biaryl cross-coupling reaction would be useful for the synthesis of other electron-rich biaryl coupling partners.

Experimental Section

5-((1*S,2*R**)-1-Hydroxy-2,3-dimethyl-3-butenyl)-6-bromo-7-methoxy benzo[*d*][1,3]dioxole (11).** A solution of (*E*)-2-methyl-2-butene-1-ylmagnesium bromide in THF (0.3 M, 21 mL, 6.3 mmol) was added dropwise by syringe over 20 min to a solution of **8** (1.5 g, 5.8 mmol) in THF at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The volatiles were removed and the residue was dissolved in EtOAc (100 mL) and washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (silica, 10% EtOAc/hexane) to afford a 1:1 mixture of *syn*/*anti* isomers (1.8 g, 95%). *Syn* isomer (**11**): ^{1}H NMR ($CDCl_3$, 500 MHz) 6.85 (s 1H), 5.97 (s, 2H), 5.10 (d, 1H, J = 3.4 Hz), 4.95 (app t, 1H, J = 1.4 Hz), 4.88 (s, 1H), 4.03 (s, 3H), 2.69 (qd, 1H, J = 3.4, 7.0 Hz), 1.95 (br s, 1H), 1.92 (s, 3H), 0.87 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.5, 148.0, 140.0, 136.4, 135.0, 111.7, 106.4, 102.9, 101.6, 72.6, 60.1, 43.9, 22.2, 11.4; IR (neat) ν_{max} 3442, 3054, 2986, 1642, 1474, 1421, 1264, 1080, 1046, 895 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{14}H_{17}BrO_4Na$ 351.0202, found 351.0208. *Anti* isomer (**12**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.76 (s, 1H), 5.98 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 4.6 Hz), 5.04 (dd, 1H, J = 9.1, 2.5 Hz), 4.97 (app t, 1H, J = 1.8 Hz), 4.96 (s, 1H), 4.03 (s, 3H), 2.47 (qd, 1H, J = 8.0, 7.1 Hz), 2.23 (d, 1H, J = 2.5 Hz), 1.79 (s, 3H), 0.91 (d, 3H J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.1, 147.2, 139.7, 137.0, 136.2, 1140., 109.0, 102.3, 101.7, 74.0, 60.2, 50.4, 19.0, 15.5; IR (neat) ν_{max} 3448, 2969, 1642, 1474, 1402, 1272, 1210, 1082, 1048, 959, 895 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{14}H_{17}BrO_4Na$ 351.0202, found 351.0214.

Biaryl 18. A solution of **13** (0.20 g, 0.45 mmol) in MeTHF (15 mL) was treated with *t*-BuLi (2.3 M, 0.39 mL, 0.90 mmol) at −78 °C under argon. After 30 min, the aryllithium was transferred via cannula to a flask containing CuCN (40.0 mg, 0.45 mmol) in MeTHF (15 mL) at −78 °C under argon. The heterogeneous mixture was allowed to warm to −40 °C over 1 h and was stirred until it became homogeneous. The resulting solution was cooled to −125 °C. In a separate flask, a solution of 1,2,3-trimethoxy-5-bromobenzene (**16**, 0.11 g, 0.45 mmol) in MeTHF (15 mL) was treated with *t*-BuLi (2.3 M, 0.39 mL 0.90 mmol) at −78 °C for 15 min. This aryllithium was transferred via cannula dropwise to the previously prepared arylcuprate at −125 °C over 30 min, and the resulting mixture was allowed to stir for 10 min at this temperature. Oxygen was bubbled through the reaction mixture via a fine-fritted gas dispersion tube at −125 °C for 2 h, as the solution turned from red to brown. The oxygen was removed in vacuo, and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (20 mL) at this temperature. The reaction mixture was allowed to warm to 25 °C, diluted with EtOAc (50 mL), and washed with water and saturated aqueous NH_4Cl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (5% EtOAc/hexane) to afford **18** (0.12 g, 51%) as a syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (s, 1H), 6.41 (d, 1H, J = 1.7 Hz), 6.40 (d, 1H, J = 1.7 Hz), 5.98 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 14.6 Hz), 4.74 (d, 1H, J = 1.9 Hz), 4.67 (s, 1H), 4.53 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 1.95 (q, 1H, J = 6.9 Hz), 1.20 (s, 3H), 0.89 (d, 3H, J = 6.8 Hz), 0.88 (s, 9H), −0.09 (s, 3H), −0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2 (2 C), 147.9, 147.3, 140.5, 137.8, 137.2, 135.3, 132.0, 125.5, 111.1, 108.9, 106.5, 102.5, 100.9, 71.5, 60.9, 60.0, 56.2, 56.0, 46.3, 25.9, 21.8, 18.3, 10.4, −4.5, −5.0; IR (neat) ν_{max} 2933, 2855, 1615, 1583, 1552, 1499, 1472, 1422, 1409, 1236, 1128, 1080, 1048, 1009, 887, 834, 774 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{42}O_7SiNa$ 553.2592, found 553.2583.

Diol 19. A solution of **17** (0.10 g, 0.19 mmol) in THF (2 mL) was cooled to 0 °C, and a solution of 9-BBN in THF (0.5 M, 0.68 mL, 0.34 mmol) was added dropwise by syringe over 30 min at this temperature. The reaction mixture was allowed to warm to 25 °C over 3 h, then was stirred at this temperature for 6 h. The resulting mixture was cooled to 0 °C, and aqueous NaOH (45 mg, 1.13 mmol), aqueous 30% H_2O_2 (0.13 mL, 1.13 mmol), and EtOH (0.4 mL) were added dropwise, then the reaction mixture was allowed to warm to 25 °C. After 3 h at this temperature, the volatiles were removed, and the residue was diluted with EtOAc (25 mL) and washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was

purified by flash chromatography (30% EtOAc/hexane) to afford the corresponding primary alcohol (0.10 g, 98%) as a syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.82 (s, 1H), 6.40 (d, 1H, J = 1.7 Hz), 6.36 (d, 1H, J = 1.7 Hz), 5.97 (ABq, 2H, J = 1.4 Hz, $\Delta\nu$ = 14.6 Hz), 4.78 (d, 1H, J = 1.5 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.42 (ABX, 2H, J_{AB} = 10.7 Hz, J_{AX} = 4.0 Hz, J_{BX} = 5.9 Hz, $\Delta\nu$ = 57.7 Hz), 1.57−1.38 (m, 1H), 1.31−1.26 (m, 2H), 0.92 (s, 9H), 0.81 (d, 3H, J = 6.9 Hz), 0.47 (d, 3H, J = 6.9 Hz), −0.08 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.2, 153.1, 147.8, 140.6, 137.8, 137.3, 135.3, 132.0, 125.6, 108.9, 106.5, 102.8, 100.9, 71.5, 66.1, 60.9, 60.0, 56.2, 56.1, 42.4, 37.6, 26.0, 18.2, 14.9, 9.1, −3.9, −4.7; IR (neat) ν_{max} 3436, 2931, 1618, 1583, 1508, 1472, 1423, 1409, 1306, 1234, 1127, 1080, 1047, 834, 773, 736 cm^{-1}; HRMS (ESI, *m*/*z* calcd for $C_{29}H_{44}O_8SiNa$ 571.2697, found 571.2722.

A solution of *n*-Bu_4NF (12 mg, 0.04 mmol) in THF (2 mL) was added to a solution of the above primary alcohol (25 mg, 0.04 mmol) in THF at 25 °C and the reaction mixture was stirred for 2 h at this temperature. The volatiles were removed and the residue was dissolved in EtOAc (10 mL), and then washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (40% EtOAc/hexane) to afford the diol **19** (18 mg, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.91 (s, 1H), 6.44 (d, 1H, J = 1.7 Hz), 6.36 (d, 1H, J = 1.7 Hz), 5.97 (s, 2H), 4.69 (d, 1H, J = 2.2 Hz), 3.89 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.35 (ABX, 2H, J_{AB} = 10.9 Hz, J_{AX} = 9.1 Hz, J_{BX} = 4.7 Hz, $\Delta\nu$ = 29.8 Hz), 2.92 (br s, 1H), 1.64−1.59 (m, 2H), 1.49−1.46 (m, 1H), 0.79 (d, 3H, J = 7.2 Hz), 0.66 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.1, 152.9, 148.3, 140.9, 137.2, 137.0, 135.7, 132.0, 126.4, 108.3, 106.9, 101.3, 101.1, 73.7, 64.2, 60.9, 60.1, 56.2, 56.1, 43.7, 39.9, 16.9, 5.7; IR (neat) ν_{max} 3354, 2962, 1617, 1583, 1507, 1469, 1409, 1305, 1271, 1236, 1169, 1126, 1080, 1050, 1008, 972, 930, 844, 736 cm^{-1}; HRMS (ESI), *m*/*z* calcd for $C_{23}H_{30}O_8Na$ 457.1832, found 457.1824.

Eupomatilone 4 (1d). A solution of diol **19** (12 mg, 0.03 mmol), TEMPO (1.0 mg), and *n*-Bu_4NI (15 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) and 2 mL of 0.5 M aqueous $NaHCO_3$ and 0.05 M K_2CO_3 (1:1) was vigorously stirred at room temperature for 5 min. *N*-Chlorosuccinimide (10 mg, 0.08 mmol) was added and the reaction mixture was stirred for 1 h at this temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (30% EtOAc/hexane) to afford eupomatilone 4 (**1d**, 11.8 mg, 98%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.76 (s, 1H), 6.43 (d, 1H, J = 1.7 Hz), 6.30 (d, 1H, J = 1.7 Hz), 6.00 (s, 2H), 5.28 (d, 1H, J = 5.0 Hz), 3.93 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 2.71 (app quintet, 1H, J = 7.3 Hz), 2.18 (qd, 1H, J = 7.3, 5.2 Hz), 1.11 (d, 3H, J = 7.3 Hz), 0.59 (d, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.5, 153.3, 153.1, 148.8, 141.0, 137.3, 136.3, 131.2, 129.0, 126.2, 107.7, 106.3, 101.3, 101.1, 80.4, 60.9, 60.0, 56.3, 56.2, 40.6, 39.1, 9.9, 9.8; IR (neat) ν_{max} 2972, 2940, 2837, 1773, 1618, 1582, 1505, 1477, 1425, 1410, 1378, 1338, 1310, 1278, 1239, 1172, 1126, 1093, 1061, 1022, 975, 929, 839, 733 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}O_8Na$ 453.1519, found 453.1519.

1-((1*S,2*R**)-1-(*tert*-Butyldimethylsilyl)oxy-2,3-dimethyl-3-butenyl)-2-bromo-3,4,5-trimethoxybenzene (20).** Following the procedure for the preparation of **11**, to a solution of (*E*)-2-methyl-2-butene-1-ylmagnesium bromide in THF (0.3 M, 28 mL, 8.5 mmol) was added *o*-bromotrimethoxybenzaldehyde (1.91 g, 7.7 mmol) to afford *syn* and *anti* isomers (1:1) (2.4 g, 90%) as a syrup. *Syn* isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.97 (s, 1H), 5.12 (app t, 1H, J = 2.4 Hz), 4.98 (s, 1H), 4.89 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.75−2.70 (m, 1H), 1.99 (d, 1H, J = 2.1 Hz), 1.95 (s, 3H), 0.90 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.5, 150.5, 148.1, 142.1, 136.9, 111.7, 107.9, 107.2, 72.4, 61.1, 61.0, 56.1, 43.8, 22.3, 11.3; IR (neat) ν_{max} 3472, 2969, 2937, 1642, 1568, 1481, 1448, 1426, 1394, 1324, 1194, 1162, 1105, 1037, 1009, 893, 817, 738 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}BrO_4Na$ 367.0521, found 367.0512. *Anti* isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (s, 1H), 5.05 (d, 1H, J = 9.1 Hz), 4.99 (s, 2H), 3.89 (s, 9H), 2.50 (qd, 1H, J = 7.1, 9.0 Hz), 2.27 (br s, 1H), 1.80 (s, 3H), 0.92 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.2, 150.3, 147.2, 142.6, 137.4, 113.7, 110.5, 106.6, 73.7, 61.1, 61.0, 56.2, 50.5, 18.8, 15.6; IR (neat) ν_{max} 3421, 2966, 2941, 1642, 1482, 1394, 1324, 1238, 1195, 1162, 1104, 1011, 886, 824 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}BrO_4Na$ 367.0521, found 367.0553.

Following the procedure for the preparation of **13**, 2,6-lutidine (0.3 mL, 2.6 mmol) and $BuMe_2SiOTf$ (0.44 mL, 1.9 mmol) were added to a solution of the preceding *syn* isomer (0.6 g, 1.7 mmol) to afford **20**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (s, 1H), 5.07 (d, 1H, J= 3.1 Hz), 4.82 (s, 1H), 4.77 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.40−2.35 (m, 1H), 1.86 (s, 3H), 0.97 (d, 3H, J = 6.9 Hz), 0.89 (s, 9H), 0.03 (s, 3H), −0.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 152.1, 150.0, 147.2, 141.8, 139.2, 111.8, 108.0, 107.9, 74.7, 61.1, 61.0, 56.0, 45.7, 25.9, 22.2, 18.2, 12.0, −4.8, −5.2; IR (neat) ν_{max} 3053, 2985, 2856, 1480, 1422, 1395, 1324, 1265, 1195, 1162, 1106, 1039, 1010, 895, 737, 704 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{35}BrO_4SiNa$ 481.1386, found 481.1360.

3-*epi*-Eupomatilone 6 (26). Following the previously described procedure for the preparation of the eupomatilone 4 diol **19**, a solution of *n*-Bu_4NF (18 mg, 0.07 mmol) in THF (2 mL) was added to a solution of alcohol (30 mg, 0.06 mmol) to afford the corresponding diol (22 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.99 (s, 2H), 6.87 (d, 1H, J = 7.6 Hz), 6.86 (d, 1H, J = 7.9 Hz), 6.72 (d, 2H, J = 1.5 Hz), 6.70 (d, 1H, J = 1.5 Hz), 6.68 (br s, 3H), 6.62 (dd, 1H, J = 7.9, 1.5 Hz), 6.02 (d, 2H, J = 1.3 Hz), 6.00 (br s, 2H), 4.81 (d, 1H, J = 2.0 Hz), 4.74 (d, 1H, J = 2.0 Hz), 3.93 (s, 6H), 3.90 (s, 3H), 3.89 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.42 (td, 1H, J = 2.1, 10.9 Hz), 3.35 (dd, 1H, J = 4.5, 10.9 Hz), 2.32 (br, 2H), 1.67−1.60 (m, 2H), 1.55−1.50 (m, 2H), 1.30−1.22 (m, 2H), 0.81 (d, 3H, J = 7.3 Hz), 0.79 (d, 3H, J = 7.3 Hz), 0.69 (d, 6H, J = 7.1 Hz); IR (neat) ν_{max} 3355, 2935, 1597, 1571, 1479, 1401, 1321, 1267, 1230, 1125, 1081, 1038, 935, 810, 737 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}O_7SiNa$ 427.1733, found 427.1734.

Following the procedure for the preparation of eupomatilone 4, *N*-chlorosuccinimide (10 mg) was added to a solution of the preceding diol (15 mg, 0.04 mmol), TEMPO (1.0 mg), and *n*-Bu_4NI (19 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) and 2 mL of 0.5 M aqueous $NaHCO_3$ and 0.05 M K_2CO_3 (1:1) to afford **26** (two atropisomers) (14 mg, 93%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (d, 1H, J = 7.9 Hz), 6.87 (d, 1H, J = 7.9 Hz), 6.83 (s, 1H), 6.82 (s, 1H), 6.73 (d, 1H, J = 1.4 Hz), 6.70 (dd, 1H, J = 1.4, 7.9 Hz), 6.62 (d, 1H, J = 1.4 Hz), 6.57 (dd, 1H, J = 1.4, 7.9 Hz), 6.05 (dd, 2H, J = 1.1, 4.3 Hz), 6.03 (m, 2H), 5.40 (d, 1H, J = 4.9 Hz), 5.32 (d, 1H, J = 4.9 Hz), 3.91 (s, 6H), 3.90 (s, 6H), 3.66 (s, 3H), 3.65 (s, 3H), 2.74 (app sextet, 2H, J = 7.0 Hz), 2.20−2.10 (m, 2H), 1.12 (d, 6H, J = 7.3 Hz), 0.56 (d, 3H, J = 7.3 Hz), 0.54 (d, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.7, 152.9, 151.5, 147.7, 147.6, 147.0, 146.9, 141.6, 130.2, 129.2, 129.1, 126.3, 126.2, 123.5, 122.4, 110.6, 109.6, 108.5, 108.2, 105.0, 104.9, 101.2, 101.1, 80.6, 80.5, 61.2, 61.1, 60.8, 56.2, 40.7, 38.9, 38.6, 29.7, 9.9, 9.8, 9.7; IR (neat) ν_{max} 2972, 2938, 1775, 1598, 1482, 1458, 1436, 1402, 1360, 1340, 1323, 1273, 1226, 1173, 1127, 1092, 1057, 1038, 1006, 970, 934, 910, 859, 810, 734 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_7Na$ 423.1420, found 423.1416.

Eupomatilone 6 (1f). Pyridinium dichromate (15 mg, 0.07 mmol) was added to a solution of alcohol **27** (30 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) at 25 °C. The reaction mixture was stirred at this temperature for 2 h, diluted with Et_2O (15 mL), and washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated to afford corresponding aldehyde (25 mg, 85%), which was used without further purification.

The preceding aldehyde was treated with *n*-Bu_4NF (25 mg, 0.1 mmol) in THF (1 mL) at 25 °C and the reaction mixture was stirred at this temperature for 1 h, and then diluted with EtOAc (10 mL) and washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was passed through a bed of silica to afford corresponding lactol **28** (13 mg, 71%), which was used without further purification.

Pyridinium dichromate (1.5 mg, 0.07 mmol) was added to a solution of lactol **28** (14 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) at 25 °C and the reaction mixture was stirred at this temperature for 2 h, diluted with Et_2O (10 mL), and washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated to afford a mixture of **26** and **1f** (1:3) (10 mg, 90%). An analytically pure sample of **1f** was obtained by preparative TLC (20% EtOAc/hexane; multiple developments) as a mixture of interconverting atropdiastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (d, 1H, J = 7.9 Hz), 6.87 (d, 1H, J = 7.9 Hz), 6.73 (d, 1H, J = 1.5 Hz), 6.70 (dd, 1H, J = 1.6, 7.9 Hz), 6.68 (s, 1H), 6.67 (s, 1H), 6.66 (d, 1H, J = 1.5 Hz), 6.59 (dd, 1H, J = 1.6, 7.9 Hz), 6.03 (ABq, 2H, J = 1.3 Hz, $\Delta\nu$ = 8.7 Hz), 5.65 (d, 1H, J = 6.9 Hz), 5.54 (d, 1H, J = 6.9 Hz), 3.91 (s, 6H), 3.89 (s, 6H), 3.65 (s, 3H), 3.64 (s, 3H), 2.37 (sextet, 2H, J = 7.2 Hz), 2.05−1.96 (m, 2H), 2.20 (d, 3H, J = 7.4 Hz), 1.19 (d, 3H, J = 7.4 Hz), 0.73 (d, 3H, J = 7.1 Hz), 0.70 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.8, 153.0, 151.8, 148.0, 147.8, 147.1, 147.0., 142.0, 130.5, 129.3, 129.2, 127.4, 127.3, 124.0, 122.9, 111.2, 110.1, 108.5, 108.3, 105.0, 104.9, 101.4, 101.3, 80.1, 80.0, 61.3, 61.2, 61.0, 56.3, 42.9, 42.7, 41.7, 41.4, 15.7, 15.5, 15.1, 15.0; IR (neat) ν_{max} 2972, 2931, 1774, 1599, 1482, 1458, 1440, 1406, 1325, 1225, 1154, 1173, 1127, 1038, 1004, 971, 933, 810, 733 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_7Na$ 423.1420, found 423.1383.

(*E*)-Methyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-methyl)but-2-enoate (45). A flame-dried round-bottomed flask was charged with CuCl (257.4 mg, 2.60 mmol) and LiCl (110.2 mg, 2.60 mmol). DMF (3 mL) was added and the mixture was stirred for 30 min at 25 °C under argon. A solution of bis-pinacolatodiboron (660 mg, 2.60 mmol) in DMF (2 mL) was cannulated into the reaction mixture, which was stirred for 5 min. Dried KOAc (255.2 mg, 2.60 mmol) was added to the reaction mixture in one portion, and the reaction mixture turned blackish-brown. A solution of acetate **44** in DMF (1 mL) was added dropwise. The reaction mixture was stirred for 6.5 h at 25 °C during which the color of the reaction mixture turned blue. The reaction mixture was quenched by the addition of water (4 mL). The mixture was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was quickly purified by flash chromatography (silica, 10% ether/hexane) to afford **45** as a colorless oil (437 mg, 91%) that was found to be a 93:7 *E*/*Z* mixture by ^{1}H NMR. The major *Z* diastereomer was characterized: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.83 (tq, 1H, J = 7.5, 1.0 Hz), 3.71 (s, 3H), 1.86 (s, 2H), 1.78 (d, 3H, J = 7.0 Hz), 1.24 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 135.7, 130.0, 83.3, 83.2, 51.6, 24.9, 24.7 (4C), 14.5; IR (thin film) ν_{max} 2979, 2950, 1712, 1650, 1436, 1354, 1324, 1271, 1195, 1163, 1146, 1124, 1051, 968, 884, 847, 756, 675, 542 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{21}BO_4Na$ 263.1431, found 263.1426.

(4*S*,5*S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)dihydro-4-methyl-3-methylenefuran-2(3*H*)-one (46). A solution of trimethoxybromoaldehyde **33** (212 mg, 0.77 mmol) in toluene (2 mL) was added to a solution of carbomethoxycrotyl boronate **52** (318 mg, 0.86 mmol) in toluene (3 mL) under argon. The reaction vessel was sealed with Teflon and the reaction mixture was warmed at 95 °C for 72 h. The reaction mixture was quenched by the addition of water (2 mL). The mixture was diluted with ether (5 mL) and the aqueous layer was re-extracted with ether (2 × 5 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica, 10% Et_2O/hexane) to afford **46** as a colorless syrup (240 mg, 78%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (s, 1H), 6.35 (d, 1H, J = 2.5 Hz), 5.85 (d, 1H, J = 7.5 Hz), 5.68 (d, 1H, J = 2.0 Hz), 3.92 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.70 (m, 1H), 0.80 (d, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 153.1, 150.8, 142.7, 140.5, 131.4, 122.9, 107.4, 106.0, 80.9, 61.1, 56.3, 37.3, 16.9; IR (thin film) ν_{max} 2926, 2853, 1772, 1570, 1484, 1452, 1397, 1360, 1324, 1267, 1244, 1148, 1108, 1004, 972, 813 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}BrO_5Na$ 379.0157, found 379.0161; er 77:23 (HPLC, chiralpak AD-RH column, *i*-PrOH−H_2O 1:1, flow rate = 0.35 mL/min, λ = 254 nm, injection volume = 20 μL).

(*E*)-*iso*-Pinanecamphenyl Crotylboronate (47). An oven-dried round-bottomed flask was charged with CuCl (143.5 mg, 1.45 mmol) and LiCl (61.5 mg, 1.45 mmol). DMF (3 mL) was added and the mixture was stirred for 1 h at 25 °C under argon when the solution became brownish-yellow. A solution of bis((±)-pinanediolato)diboron (465 mg, 1.30 mmol) in DMF (5 mL) was added via cannula to the reaction mixture over 5 min. Dry KOAc (140 mg, 1.45 mmol) was added to the reaction mixture in one portion, and the reaction mixture turned blackish-brown. A solution of allyl acetate **44** (178 mg, 1.03 mmol) in DMF (2 mL) was added dropwise. The reaction mixture was stirred for 5 h at 25 °C, during which time the color of the reaction mixture gradually faded to light pink and finally turned blue. The reaction mixture was quenched by the addition of water (4 mL). The mixture was extracted with ether (2 × 10 mL) and the aqueous layer was re-extracted with ether (2 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was quickly purified by flash chromatography (silica, 5% EtOAc/hexane) to afford boronate **47** (95:5 = *E*/*Z*) as a colorless oil (180 mg, 86% brsm): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 (q, 1H, J = 7.0 Hz), 4.27 (dd, 1H, J = 9.0, 2.0 Hz), 3.72 (s, 3H), 2.32 (m, 1H), 2.21 (m, 1H), 2.05 (t, J = 5.7 Hz, 1H), 1.82 (m, 1H), 1.90 (m, 3H), 1.79 (d, J = 7 Hz, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.22 (d, J = 10.9 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 135.7, 130.1, 85.7, 77.9, 51.6, 51.3, 39.5, 38.2, 35.5, 29.7, 28.6, 27.1, 26.3, 24.0, 14.5; ^{11}B NMR ($CDCl_3$, 80 MHz) δ 32.06; IR (thin film) ν_{max} 2922, 1712, 1649, 1440, 1380, 1344, 1279, 1191, 1160, 1123, 1028, 755 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{25}O_4BNa$ 315.1744, found 315.1736.

Diboron Reagent 51. A solution of tetra(pyrrolidino)diborane (**50**, 61.3 mg, 0.20 mmol) in freshly distilled benzene (0.5 mL) was added to a vigorously stirred solution of diol **49** (100 mg, 0.41 mmol) in benzene (0.2 mL) at 25 °C. A solution of 3 M HCl in ether (0.5 mL) was added to the resulting mixture. After 6 h of vigorous stirring, the reaction mixture was filtered and benzene was removed under vacuum to afford the crude product as a yellow oil that was purified by flash chromatography (silica, 10% Et_2O/hexane) to obtain the desired diborane reagent **51** (82 mg, 78%) as colorless crystals, which were found to be air-stable for several days: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (s, 1H), 7.41 (s, 1H), 7.31−7.22 (m, 3H), 4.72 (s, 1H), 2.21 (d, 1H, J = 5 Hz), 1.83 (m, 1H), 1.27 (s, 3H), 1.20−1.14 (m, 2H), 1.03−0.95 (m, 1H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.5, 127.4, 127.2, 126.7, 96.0, 88.4, 52.2, 50.5, 48.8, 29.6, 24.9, 23.7, 20.7, 9.5; ^{11}B NMR ($CDCl_3$, 80 MHz) δ 31.90; IR (film) ν_{max} 2958, 1485, 1445, 1369, 1265, 1244, 1145, 992, 956, 749, 703 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{40}B_2O_4Na$ 533.3010, found 533.2998.

Carbomethoxycrotyl Potassium Trifluoroborate Salt 54. An aqueous solution of KHF_2 (4.5 M, 1.7 mL) was added dropwise under nitrogen to a solution of carbomethoxy pinacolylcrotylboronate **45** (520 mg, 2.17 mmol) in MeOH (10 mL). The reaction mixture was stirred for 25 min at 25 °C then concentrated in vacuo, and the residue was dissolved in hot acetone. The reaction mixture was filtered and the filtrate was concentrated and recrystallized from a minimum volume of hot acetone and a few drops of ether several times to obtain the required (*E*)-diastereomer of the potassium trifluoroborate salt **54** (380 mg, 80%) as a colorless needle-like crystalline solid: ^{1}H NMR (acetone-d_6, 400 MHz) δ 6.40 (q, 1H,

J = 6.8 Hz), 3.59 (s, 3H), 1.69 (d, 3H, J = 6.8 Hz), 1.38 (br s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.9, 137.1, 128.9, 51.2, 14.5; ^{11}B NMR (acetone-d_6, 80 MHz) δ 4.07 (q, J = 60 Hz); IR (film) ν_{max} 2947, 2916, 1698, 1438, 1283, 1239, 1200, 1125, 1056, 1020, 935, 765 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_6H_9BF_3O_2K$ 258.9919, found 258.9918.

Carbomethoxycrotyl Boronate 52. Trifluoroborate **54** (226 mg, 1.03 mmol) was dissolved in a mixture of acetonitrile and water (9 mL, 2:1), and LiOH (74 mg, 3.09 mmol) was added in one portion. The reaction mixture was stirred for 20 h at 25 °C. Solid NH_4Cl (70 mg, 1.31 mmol) was added to the reaction mixture followed by diol **49** (266 mg, 1.08 mmol) and a solution of 1 N HCl (0.05 mL) was added dropwise by syringe. After vigorous stirring for 4 h, the reaction mixture was separated, the aqueous layer was extracted with ether (3 × 10 mL), and the combined organic extracts were washed with water (3 × 10 mL) and saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (silica, 10% Et_2O/hexane) afforded boronate **52** (367 mg, 97%) as a colorless oil (≥95% (*E*)-isomer by NMR): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 2H), 7.33 (m, 3H), 6.82 (q, 1H, J = 7.2 Hz), 4.73 (s, 1H), 3.41 (s, 3H), 2.14 (d, 1H, J = 5.2 Hz), 1.88 (d, 2H, J = 2.0 Hz), 1.83 (m, 1H), 1.72 (d, 3H, J = 7.2 Hz), 1.57 (s, 1H), 1.23 (s, 3H), 1.18 (m, 2H), 1.05 (m, 1H), 0.94 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 141.8, 135.8, 129.6, 127.4, 127.2, 126.7, 95.7, 88.9, 88.4, 52.0, 51.3, 50.2, 48.8, 29.6, 24.9, 24.7, 23.6, 20.8, 14.5, 9.4, 9.3; ^{11}B NMR ($CDCl_3$, 80 MHz) δ 34.23; IR (film) ν_{max} 3448, 2956, 2365, 1718, 1648, 1341, 1270, 1156, 1012 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}BO_4Na$ 391.2057, found 391.2051.

2-(Benzo[*d*][1,3]dioxol-6-yl)-3,4,5-trimethoxybenzaldehyde (57). 2-Bromo-3,4,5-trimethoxybenzaldehyde (**33**) (200 mg, 0.73 mmol), 3,4-(methylenedioxy)phenylboronic acid (**55**, 241.3 mg, 1.45 mmol), $Pd_2(dba)_3$ (26.6 mg, 0.03 mmol), S-Phos (23.8 mg, 0.06 mmol), and anhydrous K_3PO_4 (462.8 mg, 2.18 mmol) were added to an oven-dried conical vial in a glovebox. The vial was taken out of the glovebox and flushed with argon. Toluene (3 mL) was added and the conical vial was sealed with a Teflon cap and heated at 100 °C for 6 h. After cooling to 25 °C, the reaction mixture was passed through a short pad of Celite (ether wash, 20 mL). Concentration of the filtrate and purification of the residue by flash chromatography (silica, 5−10% EtOAc/hexane) afforded **57** (216 mg, 90%): ^{1}H NMR ($CDCl_3$, 500 MHz) 9.70 (s, 1H), 7.34 (s, 1H), 6.89 (d, 1H, J = 7.88 Hz), 6.85 (s, 1H), 6.74 (d, 1H, J = 7.84 Hz), 6.05 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.3, 153.1, 151.2, 147.6, 147.5, 134.0, 130.0, 126.3, 124.8, 111.3, 107.9, 105.2, 101.3, 61.1 (2C), 56.1, 29.7; IR (film) ν_{max} 2937, 1681, 1587, 1504, 1480, 1461, 1438, 1390, 1325, 1288, 1235, 1197, 1159, 1129, 1083, 1039, 1005, 929, 860, 810, 757 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}O_6Na$ 339.0845, found 339.0845.

2-(3,4,5-Trimethoxyphenyl)-3,4,5-trimethoxybenzaldehyde (58). 2-Bromo-3,4,5-trimethoxybenzaldehyde (**33**) (100 mg, 0.36 mmol), 3,4,5-trimethoxyphenylboronic acid (**56**, 154.4 mg, 0.73 mmol), finely powdered K_3PO_4 (231.8 mg, 1.09 mmol), $Pd_2(dba)_3$ (14 mg, 0.015 mmol), and S-Phos (11.9 mg, 0.03 mmol) were added to an oven-dried conical vial in a glovebox. The vial was taken out of the glovebox and flushed with argon. Toluene (3 mL) was added and the conical vial was sealed with a Teflon screw-cap and heated at 100 °C for 8 h. After cooling to 25 °C, the reaction mixture was passed through a short pad of Celite (ether wash, 20 mL). The filtrate was evaporated and the residue was purified by flash chromatography (silica, 10% EtOAc/hexane) to afford **58** (108 mg, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.69 (s, 1H), 7.35 (s, 1H), 6.54 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 3.86 (s, 6H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.3, 153.2, 152.8, 151.1, 147.6, 137.8, 134.3, 129.8, 128.3, 108.4, 105.1, 61.3, 61.1, 61.0, 60.4, 56.3, 56.2, 21.0, 14.2; IR (film) ν_{max} 2940, 1682, 1584, 1482, 1464, 1401, 1316, 1252, 1238, 1196, 1127, 1102, 1007, 929 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}O_7Na$ 385.1263, found 385.1263.

7-Methoxy-6-(3,4,5-trimethoxyphenyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (59). $Pd[P(t\text{-}Bu)_3]_2$ (10 mg, 0.019 mmol) and 6-bromo-7-methoxybenzo[*d*][1,3]dioxole-5-carbaldehyde (100 mg, 0.386 mmol) were added to an oven-dried conical vial in a glovebox. The vial was taken out of the glovebox and flushed with argon. THF (2 mL) was added to the mixture, which was then stirred for about 8 min. 3,4,5-Trimethoxyphenylboronic acid (164 mg, 0.772 mmol) in THF (2 mL) was added by cannula to the reaction mixture (THF wash, 1 mL). Finely powdered NaOH (46.3 mg, 1.16 mmol) was quickly added to the reaction mixture in one portion followed by dropwise addition of *d*-H_2O (22 μL, 1.16 mmol) by a microsyringe. The reaction mixture was heated at 60 °C for 22 h. It was then quenched by the addition of water (10 mL) and diluted with ether (10 mL). The aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were collected, washed with saturated aqueous NaCl (2 × 10 mL), and dried (Na_2SO_4). Concentration of the filtrate and purification of the residue by flash chromatography (silica, 5% to 10% EtOAc/hexane) afforded **59** (73 mg, 55%) as a colorless crystalline solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.56 (s, 1H), 7.21 (s, 1H), 6.49 (s, 2H), 6.01 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 3.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.8, 153.4, 152.8, 149.1, 142.2, 140.7, 137.8, 135.4, 129.9, 128.3, 108.4, 104.7, 102.2, 101.0, 60.9, 60.2, 56.3, 56.2; IR (film) ν_{max} 2936, 1679, 1606, 1582, 1509, 1462, 1411, 1362, 1285, 1243, 1126 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{18}O_7Na$ 369.0950, found 369.0947.

Eupomatilone 2 (1b). A solution of **58** (36.3 mg, 0.10 mmol) in toluene (1 mL) was added to a solution of the carbomethoxycrotyl boronate **52** (39 mg, 0.106 mmol) in toluene (1 mL) via a syringe. The reaction vessel was flushed with Argon, then sealed with Teflon and heated at 75 °C for 9 days. The reaction mixture was quenched by the addition of water (2 mL). The aqueous layer was washed with ether (2 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (silica, 10−50% Et_2O/hexane) afforded eupomatilone 2 (**1b**, 34 mg, 74%) as a colorless syrup, in an 88:12 enantiomeric ratio (chiralpak AD-RH, *i*-PrOH/H_2O = 50:50, flowrate = 0.35 mL/min, injection volume = 20 μL, λ = 254 nm); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (s, 1H), 6.46 (d, 1H, J = 1.5 Hz), 6.37 (d, 1H, J = 2.0 Hz), 6.26 (d, 1H, J = 2.5 Hz), 5.55 (d, 1H, J = 2.0 Hz), 5.52 (d, 1H, J = 7.0 Hz), 3.92 (s, 6H), 3.89 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.70 (s, 3H), 2.88 (app tp, 1H, J = 7.5, 2.0 Hz), 0.87 (dd, 3H, J = 4.0, 2.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 153.3, 153.1, 153.0, 151.3, 141.9, 140.9, 137.3, 131.1, 129.9, 127.7, 122.2, 107.4, 106.4, 104.9, 79.3, 61.4, 61.0, 60.9, 56.3, 56.2, 56.1, 38.3, 16.9; IR (film) ν_{max} 2965, 2935, 2836, 1767, 1583, 1489, 1463, 1404, 1363, 1313, 1247, 1127, 1103, 1002, 974 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{28}O_8Na$ 467.1682, found 467.1675.

Eupomatilone 5 (1e): Method A. Suzuki−Miyaura. Aryl bromide **46** (17 mg, 0.048 mmol), 3,4-(methylenedioxy)phenylboronic acid (20.4 mg, 0.096 mmol), $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol), S-Phos (1.6 mg, 0.004 mmol), and finely powdered K_3PO_4 (30.6 mg, 0.144 mmol) were added to an oven-dried round-bottomed flask in a glovebox. The reaction vessel was taken out of the glovebox and flushed with argon. Toluene (2 mL) was added, and the reaction mixture was warmed at 95 °C for 22 h. The reaction mixture was cooled to 25 °C and passed through a short pad of Celite, then the filtrate was diluted with ether (5 mL), washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (silica, 10−20% Et_2O/hexane) afforded eupomatilone 5 (**1e**, 18 mg, 95%) as a colorless oil: 83:17 enantiomeric ratio (chiralpak AD-RH, *i*-PrOH/H_2O = 50:50, flowrate = 0.35 mL/min, injection volume = 20 μL, λ = 254 nm).

Method B. Crotylboration. An oven-dried round-bottomed flask (5 mL) was charged with carbomethoxycrotyl boronate **52** (30.2 mg, 0.082 mmol) in toluene (1.0 mL) under argon. A solution of biaryl aldehyde **57** (23.4 mg, 0.074 mmol) in toluene (0.75 mL) was added via a syringe. The reaction mixture was vigorously stirred at 75 °C for 7 days and then quenched by the addition of water (2 mL) and diluted with ether (5 mL). The water layer was extracted with ether (2 × 5 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica, 10−20% Et_2O/hexane) to afford eupomatilone 5 (**1e**, 17 mg, 65%) as a colorless oil: 87:13 enantiomeric ratio (chiralpak AD-RH, *i*-PrOH/H_2O = 50:50, flow rate = 0.35 mL/min, injection volume = 20 μL, λ = 254 nm); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (d, 2H, J = 8 Hz), 6.73 (dd, 2H, J = 5.6, 1.6 Hz), 6.69 (s, 2H), 6.65 (d, 1H, J = 1.2 Hz), 6.60 (dd, 1H, J = 8.0, 1.2 Hz), 6.24 (d, 2H, J = 2 Hz), 6.03 (ABq, 4H, J = 1.0 Hz, $\Delta\nu$ = 8.7 Hz), 5.54 (d, 3H, J = 7.2 Hz), 5.45 (d, 1H, J = 7.2 Hz), 3.91 (s, 6H), 3.88 (s, 6H), 3.66 (s, 3H), 3.65 (s, 3H), 2.87 (dq, 2H, J = 5.0, 2.5 Hz), 0.83 (d, 3H, J = 7.6 Hz), 0.80 (d, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 152.9, 151.5, 147.7, 147.1, 141.9, 141.2, 130.1, 129.0, 127.2, 123.4, 122.8, 122.0, 110.6, 110.0, 108.6, 108.2, 104.8, 101.2, 79.4, 61.2, 60.9, 56.2, 38.4, 38.2, 17.3, 17.1; IR (film) ν_{max} 2929, 2853, 2253, 1766, 1598, 1482, 1459, 1403, 1362, 1325, 1266, 1236, 1196, 1156, 1128, 1089, 1038, 1002, 971, 936, 912, 811, 733 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{22}O_7Na$ 421.1263, found 421.1265.

Eupomatilone 1. An oven-dried round-bottomed flask (5 mL) was charged with carbomethoxycrotyl boronate **52** (27 mg, 0.073 mmol) in toluene (0.5 mL) under argon. A solution of biaryl aldehyde **59** (23 mg, 0.067 mmol) in toluene (1 mL) was added via a syringe. The resulting reaction mixture was vigorously stirred at 85 °C for 8 days. It was quenched by the addition of water (1 mL) and diluted with ether (5 mL). The water layer was extracted with ether (2 × 2 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by chromatography (silica, 10−40% ether/hexane) to afford eupomatilone 1 (**1a**) (9.2 mg, 32%) as a colorless oil: 3.3:1 inseparable diastereomeric *cis*:*trans* mixture **1a** and **60**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (s, 1H), 6.44 (d, 1H, J = 2.0 Hz), 6.33 (d, 1H, J = 2.0 Hz), 6.25 (d, 1H, J = 2.8 Hz), 6.00 (s, 2 H), 5.53 (d, 1H, J = 2.4 Hz), 5.44 (d, 1H, J = 7.6 Hz), 3.91 (s, 3H), 3.856 (s, 3H), 3.852 (s, 3H), 3.846 (s, 3H), 2.93 (m, 1H), 0.88 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 153.3, 153.0, 148.8, 140.7, 137.3, 136.6, 131.0, 128.9, 127.4, 121.9, 107.7, 106.7, 101.4, 100.8, 79.3, 60.9, 60.0, 56.2, 56.1, 29.7, 22.7, 14.1; IR (thin film) ν_{max} 2922, 2851, 2361, 2340, 1764, 1581, 1464, 1410, 1237, 1127, 1089, 1055, 974 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C23H_{24}O_8Na$ 451.1369, found 451.1366; enantiomeric ratio, er 94:6 for the *cis*-isomer, er 8:1 for *trans* isomer [Chiralpak-AD-RH column; λ = 254 nm; flow rate = 0.25 mL/min; injection volume = 20 μL; *i*-PrOH:H_2O = 50:50].

Acknowledgment. This work was supported by a grant from the National Cancer Institute (NIH R01 CA91904). S.M. thanks Dr. Dennis Bong (Ohio State University) for helpful discussions.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701415M