Enantioselective Synthesis and Photoracemization Studies of (+)-2-Cyclopropyl-7,8-dimethoxy-2*H*-chromene-5-carboxylic Acid Methyl Ester, an Advanced Intermediate of a Dihydrofolate Reductase Inhibitor

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Several new inhibitors of dihydrofolate reductase (DHFR) have recently progressed into clinical development due to their potent anticancer and antibiotic properties.[1,2] For the treatment of bacterial diseases, DHFR inhibitors such as trimethoprim are often applied in combination with a sulfonamide (Bactrim, Septra). Representative clinical applications include the treatment of urinary tract infections, bronchial infections, and pneumonia.[2] Chromene **1** was recently reported to have submicromolar activities against pathogenic microorganisms such as *Staphylococcus aureus* and *Pseudomonas carinii* (Figure 1).[3] Since only racemic **1** was evaluated for biological activity and the reported synthetic strategy was limited to the preparation of racemic products, we embarked on an enantioselective synthesis of this interesting lead structure.

Chromenes have been obtained by the cyclization of allylic ethers using Grubbs' ruthenium catalyst.[4] An attractive aspect of this methodology is the use of a chiral ether of type **3** for the installation of the stereocenter at C(2) of chromene **2** (Scheme 1).[5] Allyl ether **3** could be obtained from a Mitsunobu displacement with phenol **4**, and the vinyl substituent appeared to be readily derived by an organometallic coupling of a halogenated derivative of **5**. In this paper, we report the successful realization of this strategy, albeit with less than the desired high enantioselectivity due to an unexpectedly facile chromene photoracemization process.

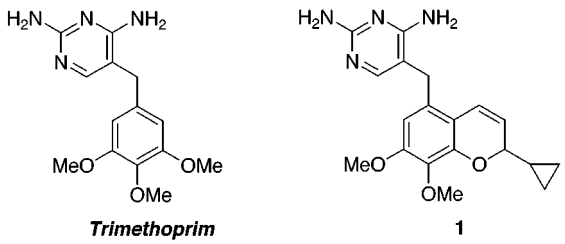
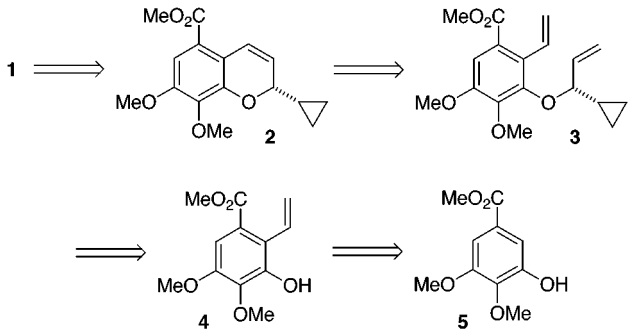
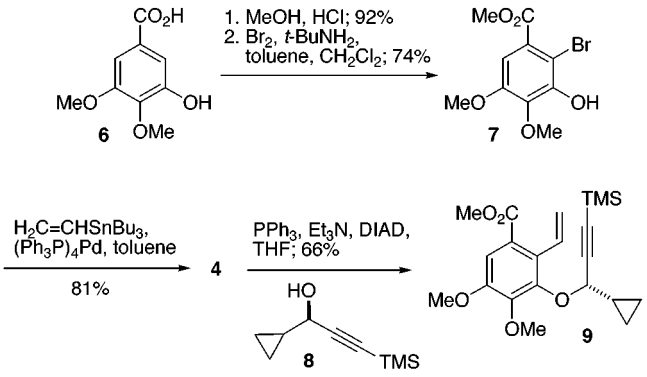


Figure 1.

Scheme 1



Scheme 2



Results and Discussion

The polysubstituted *o*-bromophenol **7** was synthesized in two steps from commercially available 3-hydroxy-4,5-dimethoxybenzoic acid (**6**) according to Tanaka's protocol (Scheme 2).[6] Stille-coupling of **7** with tributylvinyltin provided styrene **4** in 81% yield. Subsequent Mitsunobu reaction[7] with carbinol (*R*)-**8** in the presence of triethylamine[8] provided the allylic ether **9** in 66% yield. The propargyl alcohol **8** was prepared by Friedel−Crafts acylation[9] of bis(trimethylsilyl)acetylene with cyclopropanecarbonyl chloride followed by asymmetric reduction

(1) Balasubramanian, B. N.; Kadow, J. F.; Kramer, R. A.; Vyas, D. M. *Annu. Rep. Med. Chem.* **1998**, *33*, 151.

(2) McCormack, J. J. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Taylor, J. B., Eds.; Pergamon: Oxford 1990; Vol. 2, Chapter 7.2, p 271.

(3) Masciadri, R. U.S. Patent 5,773,446; Hoffmann-La Roche, June 30, 1998.

(4) (a) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488. (b) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864. (c) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343. (d) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340.

(5) For the use of kinetic resolution or chromatographic separation of chiral chromenes, see: (a) Vander Velde, S. L.; Jacobsen, E. N. *J. Org. Chem.* **1995**, *60*, 5380. (b) Loncartomaskovic, L.; Mintas, M.; Trotsch, T.; Mannschreck, A. *Enantiomer* **1997**, *2*, 459. Chiral chromene was also obtained from dehydrogenation of chromane and cyclization of an α,β-unsaturated sulfoxide: (c) Stocker, A.; Netscher, T.; Rüttimann, A.; Müller, R. K.; Schneider, H.; Todaro, L. J.; Derungs, G.; Woggon, W.-D. *Helv. Chim. Acta* **1994**, *77*, 1721. (d) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097.

(6) Tanaka, M.; Ikeya, Y.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron* **1995**, *51*, 11703.

(7) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127.

(8) Richter, L. S.; Gadek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705.

(9) (a) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45. (b) Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280.

(10) (a) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214. (b) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938.

(11) The enantiomeric excess was determined by integration of the 500 MHz ^{1}H NMR spectrum of the (*R*)-acetylmandelic acid ester derivative of **8**. A plot of the optical rotation of carbinol **8** ($c \approx 1$, $CDCl_3$) vs the %de of the (*R*)-AMA ester yielded the following relationship: % ee = $-1.9129[\alpha]_D - 3.1769$ ($R = 0.99$). (*R*)-AMA-Cl was prepared in two steps from mandelic acid by treatment with acetyl chloride (neat) then acid chloride formation using oxalyl chloride in CH_2Cl_2 in the presence of catalytic DMF: Thayer, F. K. *Organic Syntheses*; Gilman, H., Ed.; Wiley: New York, 1932; Coll. Vol. 1, p 12.

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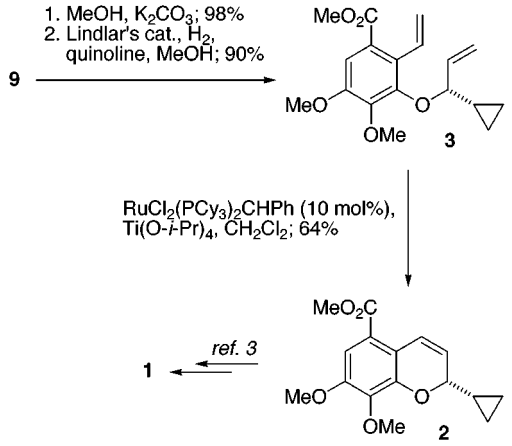
Scheme 3



using Corey's (*R*)-oxazaborolidine catalyst.[10] In the presence of 50 mol % of the chiral catalyst and 2.5 equiv of BH_3·THF complex, **8** was obtained in 68% ee.[11] The enantiomeric excess was strongly dependent on catalyst loadings. It could be increased to a maximum of 87% ee when one full equivalent of (*R*)-oxazaborolidine was used. The absolute stereochemistry of propargyl alcohol **8** was determined by degradation via ozonolysis to known 2-cyclopropyl-2-hydroxyacetic acid.[12,13]

Removal of the trimethylsilyl group in **9** with potassium carbonate in methanol followed by catalytic hydrogenation using Lindlar's catalyst in the presence of quinoline led to the diene **3** in 88% yield (Scheme 3). The ring-closing metathesis reaction of diene **3** proved to be more problematic than anticipated. In contrast to less-substituted substrates,[4] the more-hindered **3** required longer reaction times and higher temperatures as well as higher catalyst loadings. Since we suspected that the presence of the ester functionality ortho to the vinyl group on **3** could engage in undesired chelate formation with a ruthenium metallocycle intermediate, we followed Fürstner's protocol and administered $Ti(O\text{-}i\text{-}Pr)_4$ to compete with chelation.[14] The optimized procedure involved the addition of a CH_2Cl_2 solution of 10 mol % of the catalyst to a solution of diene **3** heated at reflux in the presence of $Ti(O\text{-}i\text{-}Pr)_4$. Chromene **2** was also quite labile in the presence of metal impurities, and for workup the reaction solution was passed through neutral alumina before removal of the solvent to avoid significant decomposition. Since racemic **2** has been converted into diaminopyrimidine **1**,[3] this sequence constitutes a formal asymmetric synthesis of this potent dihydrofolate reductase inhibitor. The absolute configuration of **2** was independently confirmed by circular dichroism spectroscopy.[15]

Chiral HPLC analysis (Chiralcel OD with 7% EtOAc in hexanes as eluant) of a sample of **2** revealed an enantiomeric excess of 59%. Indeed, in all preparations we found a small but relevant decrease in the optical purity of our substrate in the conversion of **8** to **2**. Moreover, exposure of chromene **2** to ambient light on a benchtop led to a rapid decrease in the optical activity. Half-lives for racemization of **2** ranged from 513 h (hood light) to 57.2 h (standard room light) to 16.5 h (desk light, Figure 2). In contrast, a sample of **2** kept in the dark did not show any detectable racemization over a period of 27 days.

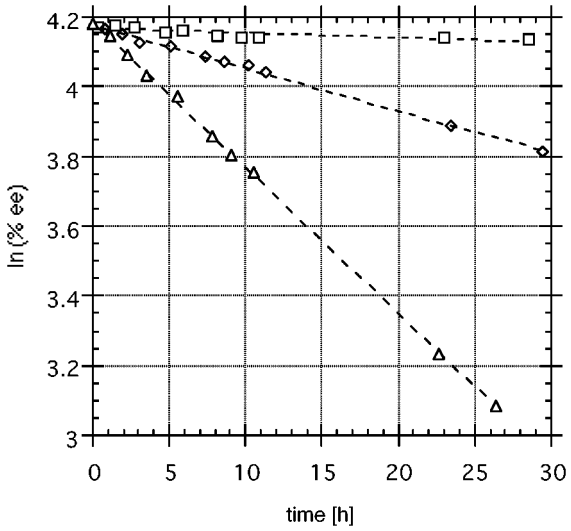


Figure 2. Plot of the logarithm of the % ee of a solution of **2** in hexanes as a function of time and light source (□ dim hood light; ◇ standard lab room light; △ bright desk light) at room-temperature behind Pyrex.

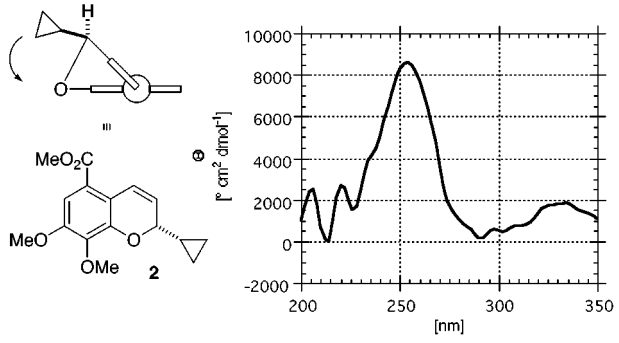
The photoracemization of chromene (2*H*-1-benzopyran) derivatives is not well-known although the photochromism of structurally closely related compounds has been used in the design of materials exhibiting variable optical transmission.[16,17] The barrier ($\Delta G^{\ddagger}$) for the thermal racemization of benzopyrans with extended chromophores has been determined as 100−130 kJ/mol.[17] The mechanism for racemization can be envisioned as a

(12) (a) Silbert, L. S.; Foglia, T. A. *Anal. Chem.* **1985**, *57*, 1404. (b) Cannon, J. G.; Darko, L. L. *J. Org. Chem.* **1964**, *29*, 3419. (c) Bur, D.; Luyten, M. A.; Wynn, H.; Provencher, L. R.; Jones, J. B.; Gold, M.; Friesen, J. D.; Clarke, A. R.; Holbrook, J. J. *Can. J. Chem.* **1989**, *67*, 1065.

(13) The absolute stereochemistry of the product of the CBS reduction of alkynyl ketones is somewhat controversial. Our assignment agrees with the results obtained by Parker et al.[10a]

(14) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.

(15) (a) Ishibashi, M.; Ohizumi, Y.; Cheng, J.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1988**, *53*, 2855. (b) Kikuchi, T.; Mori, Y.; Yokoi, T.; Nakazawa, S.; Kuroda, H.; Masada, Y.; Kitamura, K.; Kuriyama, K. *Chem. Pharm. Bull.* **1983**, *31*, 106. The absolute configuration of **2** was deduced on the basis of Kikuchi's method. The CD of **2** exhibited a positive Cotton effect around 254 nm (MeOH, $[\Theta]_{254}$ +8600) due to the styrene chromophore, indicative of a left-handed helix. The cyclopropyl side chain of **2** adopts a pseudoequatorial position and thus the absolute configuration of **2** is *S*.



(16) Van Gemert, B. In *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Plenum: New York 1999; Vol. 1, Chapter 3, p 111.

(17) Harie, G.; Samat, A.; Guglielmetti, R.; Van Parys, I.; Saeyens, W.; De Keukeleire, D.; Lorenz, K.; Mannschreck, A. *Helv. Chim. Acta* **1997**, *80*, 1122.

(18) See, for example: Loncar, L.; Otocan, K.; Mintas, M.; Trötsch, T.; Mannschreck, A. *Croat. Chem. Acta* **1993**, *66*, 209.

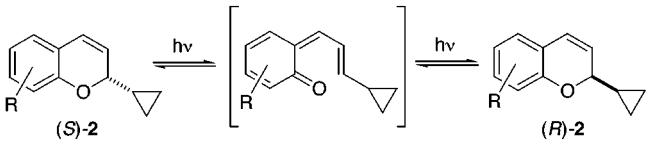


Figure 3.

formal retro-Claisen rearrangement (Figure 3).[18] 2*H*-1-Benzopyrans are generally considerably less photochromic than the corresponding naphthopyrans, and their UV absorptions are at lower wavelengths.[16] The surprisingly facile photoracemization of colorless chromene **2** at room temperature in Pyrex flasks is likely due to the presence of both electron-donating and electron-withdrawing substitutents at the benzene ring and serves as a reminder that substituent effects have a considerable influence over the photochromic properties of these heterocycles.[16] It is also noteworthy to point out that several chromene-containing natural products have been isolated as racemates or in variable degrees of optical purity, which could be a consequence of spontaneous photoracemization.[19]

In conclusion, Stille-coupling followed by Mitsunobu etherification and ring-closing metathesis provides a versatile entry to chiral chromenes. In a formal asymmetric synthesis of the potent dihydrofolate reductase inhibitor **1**, the enantioenriched building block (*S*)-**2** was thus obtained in seven steps and in 21% overall yield from benzoate **6**. A caveat in the preparation and pharmaceutical use of chromenes of type **2** is their surprisingly facile photoracemization at the stereocenter next to the chromene oxygen. The half-lives for racemization of a solution of **2** in a Pyrex flask can be as short as 16 h. To the best of our knowledge, this study represents the first kinetic analysis of chromene photoracemization.

Experimental Section

General Methods. All air- or moisture-sensitive reactions were performed under an atmosphere of N_2 and all glassware was dried in an oven at 170 °C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone and LAH, respectively. Dry CH_2Cl_2 and toluene were obtained by distillation from CaH_2. Unless otherwise stated, solvents or reagents were used without further purification. NMR spectra were recorded at either 300 MHz/75 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ at 21 °C unless stated otherwise. Chemical shifts (δ) are reported in parts per million and the residual solvent peak or TMS was used as an internal standard. 4,5-Dimethoxy-3-hydroxybenzoic acid was obtained from Lipomed and the (*R*)-CBS catalyst ((*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (1 M in toluene)) was obtained from Aldrich; all other chemicals were readily available from commercial sources. Chiral HPLC analyses were performed on a Chiralcel OD column from Chiral Technologies, eluting with 7% ethyl acetate in hexanes at a flow rate of 1 mL min^{-1} with detection at 280 nm.

4,5-Dimethoxy-3-hydroxybenzoic Acid Methyl Ester. Hydrogen chloride gas was bubbled for 15 min into an ice-cold methanolic (90 mL) solution of 4,5-dimethoxy-3-hydroxybenzoic acid (**6**, 8.59 g; 43.3 mmol). The reaction flask was allowed to warm to room temperature. After 13 h most of the solvent was removed on a rotary evaporator, and toluene was added and removed to obtain crude product that was purified on SiO_2 (hexanes:EtOAc, 5:2) to yield colorless crystalline 4,5-dimethoxy-3-hydroxybenzoic acid methyl ester (8.49 g; 92%): mp 73.5−74.5 °C; R_f = 0.63 (hexanes:EtOAc,1:1); ^1H NMR δ 7.31 (d, 1 H, J = 1.7 Hz), 7.20 (d, 1 H, J = 2.0 Hz), 5.81 (s, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H); ^{13}C NMR δ 166.9, 152.2, 149.2, 139.6, 125.8, 110.1, 105.8, 61.2, 56.2, 52.4; MS (EI) *m*/*z* 212 (M^+, 100), 197 (61), 181 (54); HRMS calcd for $C_{10}H_{12}O_5$: 212.0685, found 212.0675.

2-Bromo-4,5-dimethoxy-3-hydroxybenzoic Acid Methyl Ester (7). Bromine (3.3 mL; 64.1 mmol) was added dropwise over 10 min to a cold (−78 °C) solution of *tert*-butylamine (13.4 mL; 128 mmol) in freshly distilled toluene (275 mL). After 15 min a solution of 4,5-dimethoxy-3-hydroxybenzoic acid methyl ester (11.64 g; 54.9 mmol) in freshly distilled CH_2Cl_2 (50 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to 0 °C over 1 h, stirred at this temperature for 1.5 h, allowed to warm to room temperature over 1 h, and kept at this temperature for 6 h. After addition of EtOAc, the solution was washed with 1 M HCl, water, and satd NaCl and then dried ($MgSO_4$), filtered, and concentrated. The resulting crude brown-green oil was purified on SiO_2 (hexanes:EtOAc, 2:1) to yield **7** as an off-white microcrystalline solid (11.75 g; 74%). This compound could be recrystallized to transparent, large crystals by slow evaporation of a CH_2Cl_2 solution: mp 110.4−112.8 °C; R_f = 0.38 (hexanes:EtOAc, 2:1); IR (KBr) 3377, 1716 cm^{-1}; ^1H NMR δ 7.05 (s, 1 H), 6.23 (s, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 3 H); ^{13}C NMR δ 166.5, 151.2, 147.6, 138.9, 127.0, 107.2, 101.5, 61.4, 56.4, 52.7; MS (EI) *m*/*z* 292 ($[M + 2]^+$, 97), 290 (M^+, 100), 277 (25), 275 (28); HRMS calcd for $C_{10}H_{11}BrO_5$: 289.9790, found 289.9802.

4,5-Dimethoxy-3-hydroxy-2-vinyl-benzoic Acid Methyl Ester (4). Tetrakis(triphenylphosphine)palladium(0) (1.57 g; 1.36 mmol) was added to a degassed solution of bromide **7** (3.958 g; 13.6 mmol) and tributylvinyltin (4.92 g; 15.1 mmol) in freshly distilled toluene (70 mL). The mixture was again degassed and heated at 90 °C (bath temperature) for 14.5 h and at 110 °C for 21.8 h. After removal of the solvent, the residue was chromatographed on SiO_2 (hexanes:EtOAc, 5:2) and the resulting 2.8 g of a light orange viscous liquid was triturated with hexanes and stored in a freezer overnight to yield **4** as a pale orange solid (2.643 g; 81%): mp 51.0−52.5 °C; R_f = 0.40 (hexanes:EtOAc, 5:2); IR (KBr) 3422, 1830, 1701 cm^{-1}; ^1H NMR δ 7.00 (dd, 1 H, J = 11.7, 17.9 Hz), 6.98 (s, 1 H), 6.26 (s, 1 H), 5.77 (dd, 1 H, J = 1.9, 17.9 Hz), 5.53 (dd, 1 H, J = 1.9, 11.7 Hz), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.88 (s, 3 H); ^{13}C NMR δ 168.1, 150.4, 147.8, 138.2, 130.8, 125.6, 119.3, 119.1, 105.6, 61.0, 55.9, 52.3; MS (EI) *m*/*z* 238 (M^+, 100), 207 (49); HRMS calcd for $C_{12}H_{14}O_5$: 238.0841, found 238.0832.

1-Cyclopropyl-3-(trimethylsilyl)propyn-1-one. A solution of bis(trimethylsilyl)acetylene (5.1119 g; 30.0 mmol) and cyclopropanecarbonyl chloride (3.1332 g; 30.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 20 min to an ice-cold slurry of $AlCl_3$ (4.00 g; 30.0 mmol) in CH_2Cl_2 (100 mL). After 2.5 h at 0 °C, the reaction mixture was treated with 1 M HCl (100 mL) and stirred at 0 °C for 10 min. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with water and saturated NaCl solution, dried (Na_2SO_4), and filtered. The solution was concentrated and chromatographed on SiO_2 (pentane:ether, 20:1). Pure 1-cyclopropyl-3-(trimethylsilyl)propyn-1-one was obtained after Kugelrohr distillation (29 mmHg/105 ± 5 °C) as a clear, colorless liquid (4.02 g; 81%): R_f = 0.38 (pentane:ether, 20:1); IR (neat) 2149, 1662 cm^{-1}; ^1H NMR δ 2.11−2.02 (m, 1 H), 1.34−1.15 (m, 2 H), 1.15−0.95 (m, 2 H), 0.24 (s, 9 H); ^{13}C NMR δ 188.2, 100.3, 97.6, 24.4, 11.2, −0.7; MS (EI) *m*/*z* 166 (M^+, 40), 151 (100); HRMS calcd for $C_9H_{14}OSi$: 166.0814, found 166.0811.

(*R*)-1-Cyclopropyl-3-(trimethylsilyl)prop-2-yn-1-ol (8). A solution of (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*][1,3,2]oxazaborole (1 M in toluene; 1.50 mL; 1.50 mmol) was cooled to −40 °C and BH_3·THF (1 M in THF; 6.2 mL; 6.2 mmol) was added via syringe, with the solution allowed to run down the side of a flask in order to cool.[20] A solution of 1-cyclopropyl-3-(trimethylsilyl)propyn-1-one (0.30 mM in THF; 8.3 mL; 2.5 mmol) that had been dried with activated 4 Å

(19) (a) Venkateswarlu, Y.; Faulkner, D. J.; Steiner, J. L. R.; Corcoran, E.; Clardy, J. *J. Org. Chem.* **1991**, *56*, 6271. (b) Jaipetch, T.; Kanghae, S.; Pancharoen, O.; Patrick, V. A.; Reutrakul, V.; Tuntiwachwuttikul, P.; White, A. H. *Aust. J. Chem.* **1982**, *35*, 351. (c) Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1993**, *58*, 6565.

(20) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1997**, *38*, 7511.

molecular sieves was likewise added down the side of the flask via syringe pump over 80 min. After 12.3 h, the reaction was quenched with dry methanol (2 mL) and, when bubbles ceased to form, most of the solvent was removed on a rotary evaporator. Ether was added, and the mixture was washed with water. The aqueous layer was extracted with pentane and the combined organic layers were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. The material was chromatographed on SiO_2 (pentane:ether, 4:1) to give **8** as a pale yellow liquid (264.0 mg; 63%) in 68% ee based on (*R*)-AMA ester analysis: R_f = 0.40 (pentane:ether, 4:1); $[\alpha]^{19}_D$ −37.2 (*c* 1.0, $CDCl_3$); IR (neat) 3354, 2174 cm^{-1}; ^1H NMR δ 4.25 (t, 1 H, *J* = 6.3 Hz), 1.87 (d, 1 H, *J* = 6.4 Hz), 1.3−1.15 (m, 1 H), 0.62−0.38 (m, 4 H), 0.17 (s, 9 H); ^{13}C NMR δ 104.2, 89.7, 66.0, 16.8, 3.2, 1.5, −0.1; MS (CI, isobutane) *m*/*z* 184 ($[M + CH_4]^+$, 15), 167 ($[M - H]^+$, 43), 151 (92).

(*S*)-3-(1-Cyclopropyl-3-(trimethylsilyl)prop-2-ynyloxy)-4,5-dimethoxy-2-vinylbenzoic Acid Methyl Ester (9). A solution of diisopropyl azodicarboxylate (400 μL; 1.93 mmol) in THF (9 mL) was added dropwise over 20 min to an ice-cold solution of phenol **4** (467.5 mg; 1.96 mmol), carbinol **8** (274.2 mg; 1.63 mmol), Et_3N (45 μL, 0.32 mmol), and Ph_3P (519.1 mg; 1.96 mmol) in THF (31 mL). The ice bath was removed and the reaction stirred at room temperature for 22 h. The solvent was removed, and the product was partially purified on basic alumina (Brockman I, 80 g, CH_2Cl_2) followed by chromatography on SiO_2 (CH_2Cl_2) to yield **9** as a yellow liquid (420.5 mg; 66%): R_f = 0.44 (CH_2Cl_2), 0.35 (hexanes:EtOAc, 6:1); $[\alpha]^{18}_D$ +9.5 (*c* 1.16, CH_2Cl_2); IR (neat) 2176, 1725 cm^{-1}; ^1H NMR δ 7.07 (s, 1 H), 6.98 (dd, 1 H, *J* = 11.5, 17.7 Hz), 5.51 (dd, 1 H, *J* = 1.6, 17.6 Hz), 5.41 (dd, 1 H, *J* = 1.9, 11.5 Hz), 4.77 (d, 1 H, *J* = 6.9 Hz), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 1.42−1.32 (m, 1 H), 0.64−0.50 (m, 3 H), 0.5−0.4 (m, 1H), 0.07 (s, 9 H); ^{13}C NMR δ 168.8, 151.7, 149.1, 145.4, 131.6, 128.1, 125.7, 119.1, 109.0, 101.7, 91.7, 76.5, 60.9, 56.1, 52.2, 15.1, 4.0, 2.0, −0.4; MS (EI) *m*/*z* 388 (M^+, 13), 329 (55); HRMS calcd for $C_{21}H_{28}O_5Si$: 388.1706, found 388.1695.

(*S*)-3-(1-Cyclopropylprop-2-ynyloxy)-4,5-dimethoxy-2-vinylbenzoic Acid Methyl Ester. Potassium carbonate (817.6 mg) was added to a methanolic (25 mL) solution of TMS-alkyne **9** (408.9 mg; 1.05 mmol). After 50 min most of the solvent was removed and ether was added. The mixture was washed with water, and the aqueous layers were re-extracted with CH_2Cl_2. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Pure (*S*)-3-(1-cyclopropylprop-2-ynyloxy)-4,5-dimethoxy-2-vinylbenzoic acid methyl ester was obtained after chromatography on SiO_2 (CH_2Cl_2) as a yellow liquid (326.1 mg; 98%): R_f = 0.28 (4:1 hexanes:EtOAc); $[\alpha]^{19}_D$ +19.3 (*c* 1.14, CH_2Cl_2); IR (neat) 3287, 2116, 1723 cm^{-1}; ^1H NMR δ 7.10 (s, 1 H), 6.98 (dd, 1 H, *J* = 11.5, 17.8 Hz), 5.55 (dd, 1 H, *J* = 1.8, 17.8 Hz), 5.44 (dd, 1 H, *J* = 1.8, 11.5 Hz), 4.75 (dd, 1 H, *J* = 2.1, 7.2 Hz), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 2.37 (d, 1 H, *J* = 2.2 Hz), 1.46−1.33 (m, 1 H), 0.64−0.40 (m, 4 H); ^{13}C NMR δ 168.5, 151.7, 148.7, 145.3, 131.3, 127.7, 125.6, 119.3, 109.1, 80.2, 75.6, 74.6, 60.9, 55.9, 52.1, 15.2, 4.1, 1.8; MS (EI) *m*/*z* 316 (M^+, 11), 301 (13), 285 (15), 257 (100); HRMS calcd for $C_{18}H_{20}O_5$: 316.1311, found 316.1312.

(*R*)-3-(1-Cyclopropylallyloxy)-4,5-dimethoxy-2-vinylbenzoic Acid Methyl Ester (3). Lindlar's catalyst (5% Pd on $CaCO_3$, poisoned with lead; 11.8 mg) was added to a solution of (*S*)-3-(1-cyclopropyl-prop-2-ynyloxy)-4,5-dimethoxy-2-vinylbenzoic acid methyl ester (296.3 mg; 937 μmol) and quinoline (968.1 mg; 7.50 mmol) in methanol (45 mL). The reaction was alternately exposed to reduced pressure (water aspirator) and hydrogen gas for four times and finally left under hydrogen. After 4.0 h the suspension was filtered, and the solvent was removed. Pure **3** (267.2 mg; 90%) was obtained as a yellow, viscous liquid after chromatography on SiO_2 (CH_2Cl_2:*i*-PrOH, 200:1): $[\alpha]^{18}_D$ +15.7 (*c* 1.17, CH_2Cl_2); R_f = 0.36 (hexanes:EtOAc, 4:1); IR (neat) 1724 cm^{-1}; ^1H NMR δ 7.06 (s, 1 H), 6.93 (dd, 1 H, *J* = 11.5, 17.7 Hz), 6.0−5.88 (m, 1 H), 5.55 (1 H, dd, *J* = 1.9, 17.8 Hz), 5.42 (dd, 1 H, *J* = 1.8, 11.5 Hz), 5.14−5.00 (m, 2 H), 4.02 (t, 1 H, *J* = 8.0 Hz), 3.88 (s, 6 H), 3.85 (s, 3 H), 1.2−1.1 (m, 1 H), 0.57−0.42 (m, 2 H), 0.32−0.21 (m, 1 H), 0.21−0.11 (m, 1 H); ^{13}C NMR δ 168.7, 151.7, 149.5, 145.4, 136.9, 131.6, 127.8, 125.6, 119.1, 117.1, 108.5, 88.1, 60.8, 56.0, 52.2, 15.3, 4.3, 1.6; MS (EI) *m*/*z* 318 (M^+, 9), 286 (6); HRMS calcd for $C_{18}H_{22}O_5$: 318.1467, found 318.1481.

(*S*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-chromene-5-carboxylic Acid Methyl Ester (2). A solution of diene **3** (22.2 mg; 69.7 μmol) in freshly distilled CH_2Cl_2 (10 mL) was added to Ti(O^iPr)$_4$ (8.4 mg; 29 μmol). This solution was heated at reflux under nitrogen for 1.3 h followed by addition of a solution of $RuCl_2(CHPh)(PCy_3)_2$ (5.7 mg; 6.9 μmol) in freshly distilled CH_2Cl_2 (2 mL). The whole apparatus was wrapped in aluminum foil to exclude light. After 5 d at reflux, the product was partially purified by passing the reaction solution through neutral alumina (8 g, activity I), followed by washing with CH_2Cl_2 until a yellow material had passed through then eluting the product with CH_2Cl_2:CH_3OH (200:1). Pure chromene **2** was obtained in 59% ee (chiral HPLC) as an off-white solid (13.0 mg; 64%) after chromatography on SiO_2 (hexanes:EtOAc, 11:2): mp 55.9−60.7 °C; R_f = 0.36 (7:2 hexanes:EtOAc); $[\alpha]^{19}_D$ + 43.7 (*c* 1.23, $CDCl_3$); IR (KBr) 1713 cm^{-1}; ^1H NMR δ 7.33 (dd, 1 H, *J* = 1.4, 10.2 Hz), 7.09 (s, 1 H), 5.84 (dd, 1 H, *J* = 3.8, 10.3 Hz), 4.24 (ddd, 1 H, *J* = 1.5, 3.8, 8.3 Hz), 3.96 (s, 3 H), 3.89 (s, 6 H), 1.32−1.22 (m, 1 H), 0.65−0.28 (m, 4 H); ^{13}C NMR δ 167.2, 152.1, 147.4, 141.0, 124.4, 122.4, 120.9, 118.4, 106.5, 78.8, 61.1, 56.1, 52.1, 15.1, 3.0, 1.6; MS (EI) *m*/*z* 290 (M^+, 100), 275 (91), 249 (96); HRMS calcd for $C_{16}H_{18}O_5$: 290.1154, found 290.1149.

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

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