Asymmetric Synthesis and Stereochemical Assignment of RS-97613, a Potent Immunosuppressive and Antiinflammatory Agent†

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Introduction

As part of a medicinal chemistry program directed toward the design and synthesis of analogues of the immunosuppressive agent mycophenolic acid (**1**), we discovered RS-97613 as an entity worthy of further study (Figure 1).[1] In order to advance this compound we required a synthesis capable of providing multigram quantities. The initial synthesis was tedious, involving a separation of the compound from the less active diastereomer and thus could provide only milligram amounts at best. This paper describes an efficient preparative scale synthesis of nonracemic RS-97613 along with information gathered to assign both absolute and relative stereochemistry of the compound.[2]

Results and Discussion

The synthesis began with a side-chain degradation of mycophenolic acid **1** (Scheme 1). After Fischer esterification to provide compound **2**, the phenol was protected as the *tert*-butyldimethylsilyl ether **3**.[3] Compound **3** was then subjected to excess ozone in methylene chloride/methanol to provide aldehyde **4** after thiourea reduction of the intermediate methoxy hydroperoxide.[4] At that stage, oxidation using sodium periodate and catalytic ruthenium trichloride in ethyl acetate/water afforded the acid **5**.[5] Initial coupling of a cyclopentenylzinc reagent with the acid chloride derived from **5** used an organometallic prepared from cyclopentenyl bromide. Following reports in the literature, preparation of this bromide is capricious at best and hazardous at worst.[6] We were fortunate to discover that commercially available cyclopentenyl chloride may readily be used for our purposes.[7] Lithiation of this chloride was followed by transmetalation with anhydrous zinc chloride to provide a reagent that reacted smoothly with the acid chloride under palladium catalysis to provide enone **6**.[8]

At that stage, asymmetry was introduced using a modification of the method of Corey (CBS reduction, Scheme 2).[9] The use of borane·dimethyl sulfide

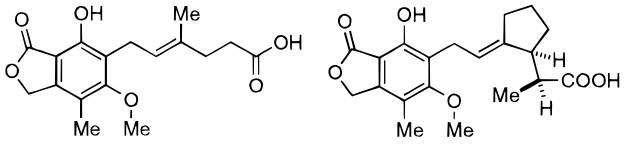
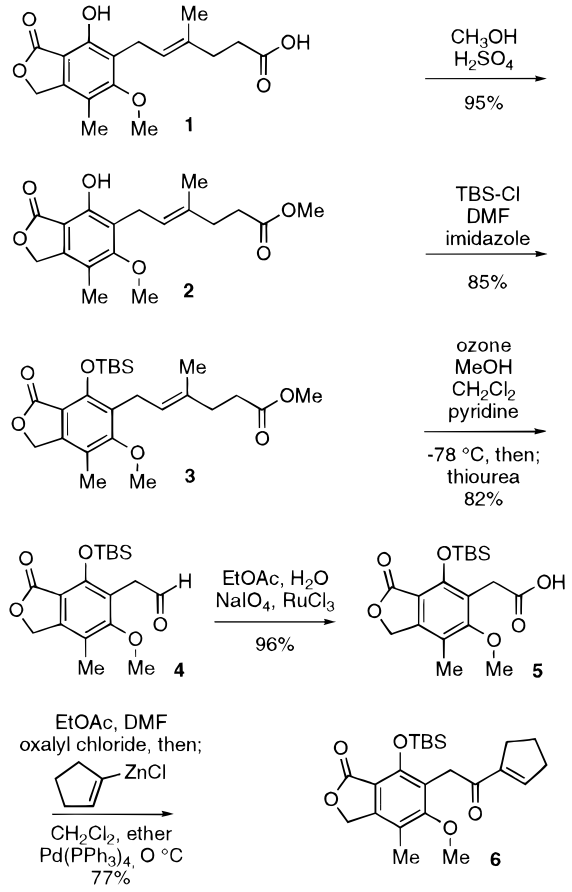


Figure 1. Mycophenolic acid (**1**) and RS-97613.

Scheme 1



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‡ Institute of Analytical Research.

(1) Previous work from these laboratories: Nelson, P. H.; Eugui, E.; Wang, C. C.; Allison, A. C. *J. Med. Chem.* **1990**, *33*, 833. Original isolation of mycophenolic acid: Gosio, B. *Riv. Igiene Sanita Pub. Ann.* **1896**, *7*, 825. Biological activities of mycophenolic acid: Antitumor; Jones, D. F.; Mills, S. D. *J. Med. Chem.* **1971** *14*, 305. Antiviral; Hupe, D. J.; Azzolina, B. A.; Behrens, N. D. *J. Biol. Chem.* **1986**, *261*, 8363. Antipsoriatic; Epinette, W. W.; Parker, C. M.; Jones, E. L. Greist, M. C. *J. Am. Acad. Dermatol.* **1987**, *17*, 962. Immunosuppressive; Ohsugi, Y.; Suzuki, S; Takagaki, Y. *Cancer Res.* **1976**, *36*, 2923. Antiinflammatory; Nelson, P. H.; Allison, A. C.; Eugui, E. M. U.S. Patent 4686234, 1987.

(2) For the sake of clarity, the absolute and relative stereochemistry as determined herein is depicted throughout this work.

(3) For leading references relating to the formation and removal of the *tert*-butyldimethylsilyl ether, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991; pp 77−83.

(4) Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* **1982**, *38*, 3013.

(5) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. We have also examined this and similar procedures for utility in the oxidative cleavage of **3** and related esters to **5**. To date, we have not been able to achieve greater than about 50% yield for the direct transformation.

(6) The following two procedures proved useful for the preparation of 1-bromocyclopentene: (a) Ndebeka, G.; Raynal, S.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 5394. (b) Maitte, P. *Bull. Soc. Chim. Fr.* **1959**, 499. Several of us were unable to reproduce the procedures given in (c) Bandodakar, B. S.; Nagendrappa, G. *Synthesis*, **1990**, 843.

(7) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1951**, 1755.

(8) (a) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181. (b) Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288.

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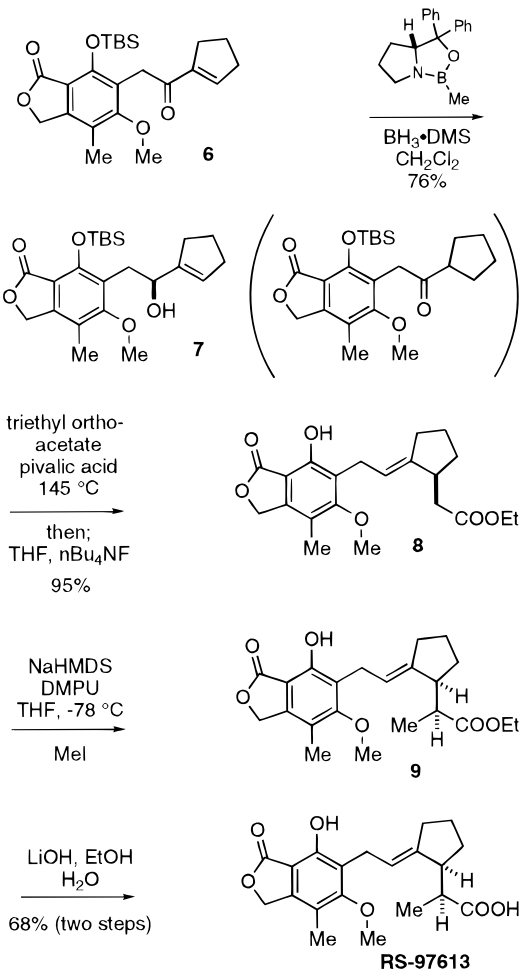
Scheme 2



(BH_3·DMS) in a noncoordinating solvent as the stoichiometric reductant provided allylic alcohol **7** in 92−97% enantiomeric excess (ee). The application of the previously reported conditions for the CBS[9a] reduction of enones using either borane·THF[9b] or catecholborane[9c] as the reductant provided **7** in lower yield and lower enantiomeric purity. Additionally, we found it critical for the success of this step to remove from **6** all traces of palladium-related materials. When such impurities were present, we observed lower yields with concomitant formation of the 1,4-reduction product. Following the CBS reduction, the enantiomeric excess (ee) of the carbinol formed (92−97% ee) could be upgraded beyond detection limits (>99% ee, nonracemic HPLC, see Experimental Section) by recrystallization. It is of interest to note that enantioenrichment occurred in the mother liquor; the crystals of **7** that were recovered in this manner were near racemic. When pure **7** was then subjected to the conditions of the Johnson Claisen rearrangement[10] (using freshly distilled triethyl orthoacetate), followed by treatment of the rearrangement product with tetra-*n*-butylammonium fluoride, compound **8** could be isolated in excellent yield (ee > 99%, nonracemic HPLC, see Experimental Section). Use of triethyl orthoacetate directly from the supplier, or after distillation and storage for more than a few hours, had a detrimental effect on the yield of the reaction.

From **8**, all that remained to complete the synthesis was stereoselective introduction of the methyl group and saponification of the ethyl ester. We were gratified to discover that the dianion of **8**, formed at −78 °C in THF with sodium hexamethyldisilazide in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), reacted with methyl iodide to form compound **9** with >20/1 selectivity.[11] We believe that the diastereoselectivity of this step can be explained by invoking a enolate dianion in which the enolate double bond eclipses the adjacent C−H allylic bond (minimizing allylic 1,3-strain).[12] In this conformation nucleophilic attack onto methyl iodide from the less hindered pro-*S* face of the enolate leads to the observed product. We speculate that the role of DMPU in this process may be as a modifier of enolate aggregation state.

Treatment of **9** with lithium hydroxide in aqueous ethanol then afforded RS-97613 after acidic workup and chromatography.[13] Analysis (nonracemic HPLC, see Experimental Section) of compound prepared in this manner indicated >98% chemical, diastereomeric, and enantiomeric purity. To date, over 100 g of RS-97613 has been prepared *via* this procedure, enabling a more detailed investigation of the pharmacological profile of the compound.[14]

Having established a route to multigram quantities of RS-97613, we turned our attention to the question of the relative stereochemistry of the compound.[2] The absolute stereochemistry at the cyclopentyl center had been assigned based on the diphenylprolinol enantiomer used in the CBS reduction of **6**, as well as from previous work involving a Sharpless kinetic resolution of racemic **7**.[15,16] We were frustrated in our spectroscopic attempts to determine the relative stereochemistry, so we turned to a degradative approach (Scheme 3).

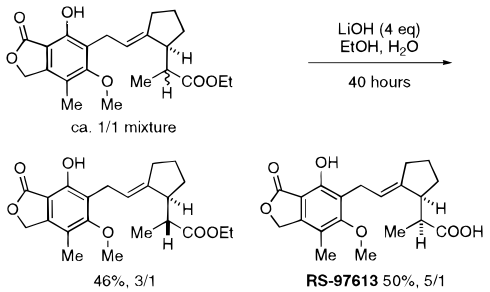
(9) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Corey, E. J.; Da Silva Jardine, P. *Tetrahedron Lett.* **1989**, *30*, 7297. (c) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(11) In the absence of DMPU, the stereoselectivity drops to ca. 8/1. For a highly related dianion alkylation, see: Rohloff, J. C.; Gardner, J. O.; Towne, R. W. *Tetrahedron Lett.* **1995**, *36*, 7803.

(12) For a review of allylic 1,3-strain containing several related examples, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

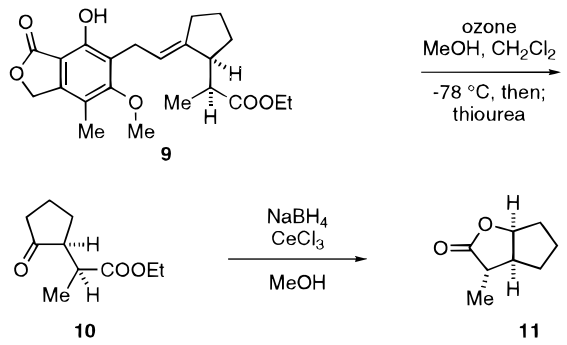
(13) As part of our studies in this area, we prepared a 1:1 mixture of esters **9** via reaction of **7** with triethyl orthopropionate. Under the conditions of hydrolysis used here, we observed a selective reaction of the diastereomer leading to RS-97613. Along with the selective alkylation of ester **8**, this kinetic resolution in the hydrolysis of **9** accounts for the very high diastereomeric excess observed in the final product.



(14) Manuscripts detailing the synthesis and biological profile of our most potent analogues are in progress and will appear in due course.

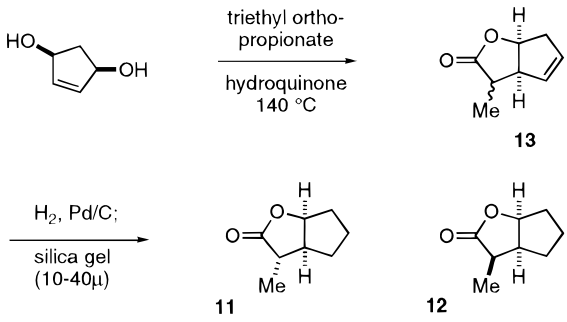
(15) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. Racemic **7** was readily obtained via the addition of cyclopentenylmagnesium bromide to aldehyde **4**.

Scheme 3



9 **10** **11**

Scheme 4



13 **11** **12**

Treatment of intermediate **9** with excess ozone in the usual manner afforded keto ester **10**. Reduction of **10** under Luche[17] conditions then provided lactone **11**. Compound **11** and the α-methyl epimeric lactone **12** could be prepared in racemic form following a variation of a literature procedure (Scheme 4).[18] Reaction of *cis*-cyclopent-4-ene-1,3-diol with triethyl orthopropionate at 145 °C in the presence of hydroquinone gave the unsaturated lactones **13**, which upon reduction afforded a fully separable 1:1 mixture of **11** and **12**. Based on ^{1}H NOE and ^{13}C resonances[19] obtained for these compounds (Figure 2), it was possible to assign relative stereochemistry and thus derive the relative stereochemistry of RS-97613.

Conclusion

In summary, a practical asymmetric synthesis of RS-97613 has been achieved. The synthesis begins with mycophenolic acid as the starting material and utilizes as key steps the coupling of cyclopentenylzinc chloride to an acid chloride, a CBS reduction of an achiral enone, a Johnson Claisen rearrangement, and a diastereoselective alkylation of an ester. The overall yield for the nine-step sequence to RS-97613 is 25%. Both the absolute and relative stereochemistry of the compound have been unambiguously established. *In vitro* studies have shown RS-97613 to be a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH). *In vivo* (mouse hemolytic plaque-forming assay, rat adjuvant-induced arthritis), the compound has proven to be more than 5 times as potent as mycophenolic acid (**1**) as an immunosuppressive and antiinflammatory agent.[14]

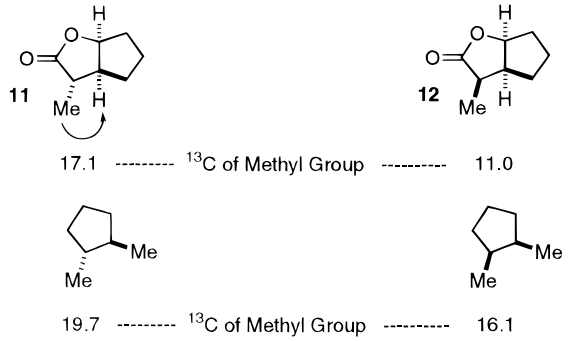


Figure 2. ^{13}C spectral data for lactone **11** shows a downfield shift of the methyl group relative to the methyl group of **12**, similar to that observed in the 1,2-dimethylcyclopentanes.[19] In addition, only in lactone isomer **11** is an NOE observed from the methyl group to the proximal ring fusion proton (indicated by an arrow above).

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled under nitrogen atmosphere from sodium/benzophenone directly before use. Concentration of organic extracts was performed under reduced pressure (house vacuum) with the aid of a rotary evaporator. Reactions and chromatography fractions were monitored by thin layer chromatography (TLC) using Analtech 250−μm silica gel plates. Chromatography was carried out using Merck 60 230−400 mesh silica gel, except as otherwise noted. With the exception of HPLC analyses, analytical data (microanalyses, NMR spectra, mass spectra, IR spectra, optical rotations and melting points) were collected by the Syntex Institute of Analytical Research. ^{1}H NMR measurements were recorded at 300.13 MHz, and ^{13}C NMR measurements were recorded at 75.40 MHz using a Bruker AMX 300 instrument. Spectra are reported in ppm downfield from tetramethylsilane as the internal standard. Melting points are uncorrected. IR spectra were recorded as thin films.

Methyl (*E*) 6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (2). To a mechanically stirred suspension of mycophenolic acid (**1**) (500 g, 1.56 mol) in methanol (4 L) under a nitrogen atmosphere was added sulfuric acid (10 mL) dropwise, and the suspension was stirred at room temperature. After 2 h the reaction became homogeneous, and soon thereafter a precipitate began to come out of solution. The reaction was allowed to stir at room temperature for 20 h at which time TLC indicated complete reaction (80/20/0.5 hex/EtOAc/HOAc). The reaction was cooled in an ice bath to 10 °C and then filtered using a 2 L Buchner funnel. The filter cake was washed with ice cold methanol (750 mL) followed by hexanes (750 mL) and then dried in a vacuum oven at 45 °C to give 497 g (95%) of the desired product **2** as a light beige solid (mp 96−97 °C). ^{1}H ($CDCl_3$): 7.17 (s, 1H), 5.23 (m, 1H), 5.20 (s, 2H), 3.76 (s, 3H), 3.62 (s, 3H), 3.38 (d, J = 6.8 Hz, 2H), 2.3−2.5 (m, 4H), 2.15 (s, 3H), 1.8 (s, 3H). ^{13}C ($CDCl_3$): 173.8, 173.0, 163.7, 153.7, 144.0, 134.2, 122.8, 122.2, 116.74, 106.4, 77.5, 77.1, 76.7, 70.1, 61.0, 51.5, 34.6, 32.9, 22.6, 16.1, 11.6. IR (3426 cm^{-1}, 1732 cm^{-1}). MS (M^+, 334). Anal. Calcd for $C_{18}H_{22}O_6$: C 64.66, H 6.63. Found: C 64.50, H 6.50.

Methyl (*E*)-6-[4-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate (3). Mycophenolic acid methyl ester (**2**) (208 g, 0.622 mol) was dissolved in DMF (1.5 L) under a nitrogen atmosphere. To this was added imidazole (84.7 g, 1.24 mol) in one portion followed by *tert*-butyldimethylsilyl chloride (122 g, 0.81 mol) in one portion. The solution was stirred at room

(16) The empirical models that predict the sense of asymmetric induction to be expected in the Sharpless asymmetric epoxidation of racemic allylic alcohol **7** and in the CBS reduction of enone **6** are in agreement with the results described here. We have also assumed a stereospecific reaction *via* a chair transition state for the Claisen rearrangement of intermediate **7**. See reference 12 for a related example.

(17) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(18) Kondo, K.; Matsumoto, M.; Mori, F. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 103.

(19) Christl, M.; Reich, H. J.; Roberts, J. D. *J. Amer. Chem. Soc.* **1971**, *93*, 3463.

temperature for 20 h at which time TLC indicated complete reaction (60/40 hex/EtOAc). The reaction was partitioned in a 5 L separatory funnel between ethyl acetate (2 L) and water (2 L). After the emulsion settled, the ethyl acetate layer was removed and the aqueous layer was extracted twice with ethyl acetate (1 L each). The ethyl acetate layers were combined and washed with 5% HCl (1 L), saturated $NaHCO_3$ (1 L), and brine (1 L) and then dried over magnesium sulfate and filtered. The solvent was removed on a rotary evaporator to afford an orange oil which crystallized after being placed under high vacuum. The solid was dissolved in hot hexanes (1 L) and transferred to a 2 L Erlenmeyer flask with stirring. The flask was placed in an ice bath causing the product to precipitate. The solution was filtered using a Buchner funnel, and after drying there was obtained **3** as a colorless solid (235 g, 85%)(mp 48−49 °C). ^{1}H ($CDCl_3$): 5.21 (m, 1H), 5.07 (s, 2H), 3.74 (s, 3H), 3.62 (s, 3H), 3.38 (d, J = 6.4 Hz, 2H), 2.21−2.41 (m, 4H), 2.15 (s, 3H), 1.75 (s, 3H), 1.03 (s, 9H), 0.25 (s, 6H). ^{13}C ($CDCl_3$): 173.7, 169.2, 163.2, 151.7, 146.1, 133.7, 127.6, 123.7, 117.9, 111.6, 67.6, 60.7, 51.4, 34.5, 32.9, 25.9, 23.7, 18.8, 18.7, 16.3, 11.4, −3.6. IR (1761 cm^{-1}, 1734 cm^{-1}). MS (M^+, 448). Anal. Calcd for $C_{24}H_{36}SiO_6$: C 64.25, H 8.08. Found: C 64.36, H 7.93.

2-[4-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dihydro-6-methoxy-7-methyl-5-isobenzofuranyl]acetaldehyde (4). The TBDMS-protected methyl ester **3** (100 g, 0.223 mol) was dissolved in methylene chloride (930 mL) and methanol (930 mL). To this was added pyridine (7 mL), and the solution was cooled to −70 °C with a dry ice/acetone bath under a nitrogen atmosphere. A stream of ozone (Fischer Ozonizer, O_2 pressure of 15 psi, flow = 150, power = 200, 2.8 A) was bubbled through the reaction via a gas dispersion tube until the reaction became blue in color (1.5 h). The ozone line was replaced with a stream of nitrogen and bubbling continued until the blue color was discharged (30 min). To this clear solution at −70 °C was added thiourea (11.9 g, 0.16 mol, 0.7 equiv) in one portion, and the cooling bath was removed. The reaction was allowed to stir at room temperature for 20 h (no ozonides/peroxides present after 3 h by starch/aqueous KI). The cloudy solution was filtered to remove solid thiourea *S*-dioxide and then partitioned in a separatory funnel between methylene chloride (1 L) and water (2 L). The organic layer was removed, and the aqueous layer was extracted with methylene chloride (1 L). The combined organic layers were washed with 5% HCl (1 L), saturated $NaHCO_3$ (1 L), and brine (1 L) and then dried over magnesium sulfate and filtered. The filtrate was stripped on a rotary evaporator to afford a yellow solid. Hexanes (200 mL) were added and after trituration the solution was filtered and dried in a Buchner funnel to afford **4** (64 g, 82%) as a light yellow solid (mp 86−87 °C). ^{1}H ($CDCl_3$): 9.63 (m, 1H), 5.12 (s, 2H), 3.73 (s, 5H), 2.19 (s, 3H), 1.03 (s, 9H), 0.22 (s, 6H). ^{13}C ($CDCl_3$): 199.0, 189.1, 168.8, 163.2, 152.1, 148.0, 119.7, 118.0, 112.0, 67.75, 60.4, 39.7, 25.7, 18.6, 11.5, −3.6, −4.0. IR (1757 cm^{-1}, 1716 cm^{-1}). MS (M^+, 350). Anal. Calcd for $C_{18}H_{26}SiO_5$: C 61.68, H 7.48. Found: C 61.64, H 7.39.

2-[4-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dihydro-6-methoxy-7-methyl-5-isobenzofuranyl]acetic Acid (5). The aldehyde **4** (67 g, 0.191 mol) was dissolved in ethyl acetate (950 mL), to this was added water (950 mL), and the mixture was stirred under a nitrogen atmosphere. To this was added sodium periodate (81.8 g, 0.38 mol) in one portion followed by ruthenium(III) trichloride hydrate (48 mg, 0.23 mmol). The mixture was stirred at room temperature for 5 h at which time TLC indicated complete reaction (75/25/0.5 hex/EtOAc/HOAc). The ethyl acetate layer was removed in a separatory funnel, and the aqueous layer was extracted with ethyl acetate (2 × 500 mL). The combined ethyl acetate layers were washed with 5% sodium metabisulfite (2 × 300 mL) and brine (1 L), dried over magnesium sulfate, and filtered. The filtrate was stripped on a rotary evaporator to afford a beige solid. The solid was triturated using hexanes (500 mL) for 30 min and then filtered and dried in a Buchner funnel to afford **5** (67 g, 96%) as a colorless solid (mp 181−184 °C). ^{1}H ($CDCl_3$): 4.83 (s, 2H), 3.56 (s, 3H), 3.44 (s, 2H), 1.93 (s, 3H), 0.79 (s, 9H), 0.22 (s, 6H). ^{13}C ($CDCl_3$): 173.8, 169.0, 163.2, 151.9, 147.5, 121.7, 117.6, 111.5, 67.7, 60.7, 30.3, 26.0, 18.6, 11.5, −3.7. IR (1765 cm^{-1}, 1714 cm^{-1}). MS (M^+, 366). Anal. Calcd for $C_{18}H_{26}SiO_6$: C 58.99, H 7.15. Found: C 58.97, H 6.97.

[4-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl]acetyl Chloride. To an ice/water bath cooled suspension of 36.66 g (0.100 mol) of arylacetic acid **5** in 400 mL of ethyl acetate was added 11.3 mL (0.13 mol) of oxalyl chloride and 4 drops of DMF. After 1 h, the ice bath was removed and the mixture was allowed to warm to room temperature. After 2 h, the now homogeneous solution was concentrated on the rotary evaporator. The residue was then dissolved in ethyl acetate and again concentrated to give a yellow solid, which was kept on the vacuum pump overnight before use.

1-Lithio-1-cyclopentene. Lithium with high (0.5%) sodium content (13.2 g of a 30% dispersion in mineral oil) was suspended in 175 mL of ether and stirred under argon. 1-Chloro-1-cyclopentene (23.0 g, 224 mmol; freshly distilled (b.p. ∼60 °C/∼100 torr)) was dissolved in 50 mL of ether and added to the lithium suspension via addition funnel. After about half the chlorocyclopentene solution had been added, the addition was stopped until a gentle reflux was observed. The remainder of the chlorocyclopentene solution was then added dropwise at a rate sufficient to maintain gentle reflux. The mixture was allowed to stir overnight, at which time it was filtered through a Schlenk filter. Titration, using diphenylacetic acid in THF (−30 °C), indicated the clear, yellow filtrate was 0.84 M in cyclopentenyllithium.

6-[7-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopent-1-enyl-2-oxoethyl]-5-methoxy-4-methyl-3*H*-isobenzofuran-1-one (6). Under a dry nitrogen atmosphere, zinc chloride in ether (130 mL of a 1.0 M solution) was chilled to <0 °C using an ice/brine bath. Then 130 mL (109 mmol) of a 0.84 M solution of 1-lithio-1-cyclopentene in ether was added at a rate such that the temperature did not exceed 0 °C. Tetrakis(triphenylphosphine)-palladium(0) (2.87 g, 2.5 mmol) was then added, followed by a solution of 100 mmol of [4-[(*tert*-butyldimethylsilyl)oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)acetyl chloride in 100 mL of dichloromethane, which was added via addition funnel while keeping the temperature of the reaction below 0 °C. The reaction mixture was stirred at −5 to 0 °C. After 3 h, TLC (30/70 EtOAc/hexane) indicated the acid chloride was consumed, and the mixture was poured into a separatory funnel containing 500 mL of ice cold 1 M HCl and 1 L of EtOAc. The EtOAc phase was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated onto 300 g of flash (230−400 mesh) silica gel. This material was placed at the top of a 1.5 kg flash column which was eluted with 15/85 and then 20/80 EtOAc/hexane. This gave 37.6 g of product, contaminated with a less polar impurity. The material was then suspended in 200 mL of 10/90 ether/hexane, triturated at room temperature for 1 h, and then filtered to give 31.88 g (77%) of **6** as an off-white powder (mp 122.4−125.7 °C). ^{1}H NMR ($CDCl_3$): 6.81 (m, 1H), 5.08 (s, 2H), 4.06, (s, 2H), 3.69 (s, 3H), 2.59 (m, 4H), 2.16 (s, 3H), 1.94 (m, 2H), 1.00 (s, 9H), 0.21 (s, 6H). ^{13}C NMR ($CDCl_3$): 195.4, 169.3, 163.6, 152.0, 147.6, 145.5, 143.4, 122.3, 117.8, 111.6, 67.9, 60.9, 35.9, 34.2, 31.1, 26.2, 23.0, 18.8, 11.8, −3.4. IR (1759 cm^{-1}, 1676 cm^{-1}). MS (M^+ − 15, 401). Anal. Calcd for $C_{23}H_{32}O_5Si$: C 66.31, H 7.74. Found: C 66.51, H 7.68.

1-[2-[4-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-1(*S*)-hydroxyeth-1-yl]cyclopent-1-ene (7). To the ketone **6** (32.26 g, 77 mmol) under a nitrogen atmosphere was added (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*][1,3,2] oxazaborole (7.7 mL of a 1 M solution in toluene, 7.7 mmol, 10 mol %) via syringe. The mixture was placed under high vacuum for 2 h to remove most of the toluene. The mixture was then purged with nitrogen, dry methylene chloride (65 mL) was added, and the reaction was cooled to −30 °C with a Kryocooler. To this solution at −30 °C was added borane dimethyl sulfide complex (8.1 mL of a 10 M solution, 81.3 mmol) dropwise via a syringe pump over a period of 7 h. After complete addition, the reaction was allowed to stir at −30 °C for 16 h at which time TLC indicated complete reaction (75/25 hex/EtOAc). To this mixture at −30 °C was added 1 M HCl in methanol (11.9 mL) dropwise over 10 min (hydrogen evolution). The reaction was then allowed to come to room temperature and stirred for 30 min, which resulted in a grey precipitate. To this solution was then added toluene (75 mL), and the methylene chloride was removed on a rotary evaporator. The resulting solution was filtered and the filter cake washed with ethyl acetate (25 mL) to afford diphenylpro-

linol hydrochloride. The filtrate was diluted with ethyl acetate (750 mL), washed with 5% HCl (500 mL), saturated $NaHCO_3$ (500 mL), and brine (500 mL), and then dried over magnesium sulfate and filtered. To the filtrate was added silica gel (250 g, Whatman 230−400 mesh). The solvent was removed, and the silica gel was placed at the top of a flash column (10 cm × 40 cm) and eluted with a gradient of ethyl acetate (15% to 25%) and hexanes. The product-containing fractions were combined and evaporated to afford 28.94 g (89%) of a white solid. Analysis of this material by HPLC (Chiralcel OD-H, 94% hexanes/6% isopropyl alcohol, flow = 0.8 mL/min, 210 nm) indicated 92.0% ee. This material was suspended in hexanes (932 mL) and to this was added warm ethyl acetate (279 mL). The solution was warmed on a hot plate until complete dissolution and then allowed to stand at room temperature. After 30 h, HPLC (same conditions as above) of the supernatant indicated >99.0% ee. The supernatant was decanted from the crystals and evaporated to afford the product **7** as a white solid, 24.5 g (76%) (mp 104−105 °C). ^{1}H ($CDCl_3$): 5.62 (m, 1H), 5.07 (s, 2H), 4.45 (m, 1H), 3.82 (s, 3H), 2.97 (m, 2H), 2.33 (m, 4H), 2.18 (s, 3H), 1.91 (m, 2H), 1.04 (s, 9H), 0.22 (s, 6H). ^{13}C ($CDCl_3$): 169.0, 163.4, 152.2, 147.0, 125.3, 125.1, 118.2, 112.0, 71.0, 67.7, 60.9, 32.2, 31.5, 31.34, 26.0, 23.4, 18.7, 11.5, −3.3, −3.5, −3.6. IR (3541 cm^{-1}, 1768 cm^{-1}). MS (M^+, 418). Anal. Calcd for $C_{23}H_{34}SiO_5$: C 65.99, H 8.18. Found: C 65.97, H 7.99. $[\alpha]^{25}_D = 33.1$, $c = 0.46$, methanol.

{2-[2-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)ethylidene]cyclopentyl}acetic Acid Ethyl Ester (8). To a 1 L round bottom flask equipped with a magnetic stirbar, short path distillation head, and nitrogen line and containing alkenol **7** (24.5 g, 58.5 mmol) was added freshly distilled triethyl orthoacetate (550 mL, still warm from the distillation). After stirring for about 5 min, the alkenol had completely dissolved. Pivalic acid (0.926 g, 9.08 mmol) was then added and the mixture stirred another few minutes to allow complete dissolution. The reaction was then placed in an oil bath heated to 145 °C and stirred at that temperature for 4.5 h. The reaction, initially colorless, became a bit yellow during the course of the reaction. During the first hour or so of reaction, a colorless liquid (presumably ethanol) distilled over from the reaction. The heating bath was turned off and when the temperature had reached about 80 °C the flask was placed on the rotary evaporator and all solvents were removed under reduced pressure. The crude light yellow oil thus obtained was carried on without further purification.

To the above oil in the original 1 L flask was added THF (400 mL) and a stirbar, and the whole was cooled to 0 °C under nitrogen. Tetrabutylammonium fluoride (60 mL, 1 M in THF, 60 mmol) was added dropwise over about 10 min. After a total of 0.5 h, 5% HCl was added (about 100 mL) and the product extracted with ethyl acetate (two extractions). After drying over $MgSO_4$, the solution was filtered and solvent removed to leave a solid residue. Chromatography using 125 g 230−400 mesh silica (elution with 85/15 hexanes/ethyl acetate, then 80/20 hexanes/ethyl acetate) gave after solvent removal 20.73 g (95%) of **8** as a colorless solid (mp 88.6−89.2 °C). Analysis of this material by HPLC (Chiralpak AD, 97% hexanes/3% isopropyl alcohol, flow = 1.0 mL/min, 210 nm) indicated >99% ee. ^{1}H ($CDCl_3$): 7.67 (br s, 1H), 5.22 (m, 1H), 5.20 (s, 1H), 4.08 (q, J = 7.1, 2H), 3.76 (s, 3H), 3.36 (d, J = 6.9, 2H), 2.76 (m, 1H), 2.50 (dd, J = 15.0, 5.3, 1H), 2.48 (br m, 2H), 2.17 (dd, J = 15.0, 9.3, 1H), 2.15 (s, 3H), 2.0−1.89 (br m, 1H), 1.87−1.74 (br m, 1H), 1.70−1.56 (br m, 1H), 1.49−1.25 (br m, 1H), 1.21 (t, J = 7.1, 3H). ^{13}C ($CDCl_3$): 173.1, 173.0, 163.7, 153.7, 146.0, 144.0, 122.2, 118.0, 116.7, 106.4, 70.1, 61.0, 60.1, 40.9, 39.4, 33.0, 29.1, 24.0, 23.9, 14.2, 11.6. IR (3700−3200 cm^{-1} broad, 1765 cm^{-1}, 1736 cm^{-1}, 1719 cm^{-1}). MS (M^+, 374). Anal. Calcd for $C_{21}H_{26}O_6$: C 67.36 H 7.00. Found: C 67.54 H 6.95. $[\alpha]^{25}_D = -30.0$, $c = 1$, chloroform.

2-{2-[2-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)ethylidene]cyclopentyl}-propionic Acid (RS-97613). To a solution of sodium bis(trimethylsilyl)amide (165.9 mL, 1 M in THF, 165.9 mmol) cooled to −78 °C under nitrogen was added DMPU (16.7 mL, 138.2 mmol). The yellow solution was allowed to stir for 15 min at which time the ethyl ester **8** (20.7 g, 55.28 mmol) was added via cannula over 45 min as a 0.5 M solution in THF. Upon addition, the mixture turned a deep orange. After stirring for 0.5 h, methyl iodide (11.2 mL, 179.9 mmol) was added via syringe over 5 min. Over approximately 15 min the reaction mixture went from deep orange to yellow-orange. The mixture was allowed to stir for 2 h and was then quenched by addition of saturated aqueous ammonium chloride (400 mL). After warming to about 0 °C (the point at which the solid mass that results from addition of the ammonium chloride solution has become liquid) the solution was extracted with ethyl acetate (700 mL). The ethyl acetate layer was washed with ammonium chloride (400 mL). The combined aqueous layers were extracted with ethyl acetate (700 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford 36 g of an orange brown oil (theoretical yield 21.5 g). The orange brown oil **9** was carried on.

The ethyl ester **9** from above was dissolved in EtOH (700 mL), and then water (350 mL) and $LiOH\cdot H_2O$ (14 g, 334.8 mmol) were added. The mixture was allowed to stir at room temperature under nitrogen for 65.5 h. The reaction mixture was then acidified with 5% aqueous HCl (1 L) and extracted with ethyl acetate (1 L). The ethyl acetate layer was washed with 5% aqueous HCl (400 mL), and the combined aqueous layers were extracted with ethyl acetate (400 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resultant orange oil was chromatographed using 800 g of 230−400 mesh silica eluting with 80/20 hexanes/ethyl acetate containing 1% acetic acid, to afford 13.5 g of a colorless solid RS-97613 (68% yield) (mp 113−115 °C). Analysis of this material by HPLC (Chiralpak AD, 90% (0.1% trifluoroacetic acid in hexanes)/10% isopropyl alcohol, flow = 1.0 mL/min, 210 nm) indicated >99% ee. ^{1}H ($CDCl_3$): 7.7 (br s, 1H), 5.25 (m, 1H), 5.2 (s, 2H), 3.76 (s, 3H), 3.4 (br d, J = 7.1, 2H), 2.65 (dq, J = 6.93, 6.85, 1H), 2.2−2.35 (m, 1H), 2.5 (m, 1H), 2.14 (s, 3H), 1.7−1.85 (m, 2H), 1.4−1.6 (m, 2H), 1.0 (d, J = 7.0, 3H). ^{13}C ($CDCl_3$): 192.4, 180.9, 163.7, 153.8, 144.5, 144.0, 122.1, 118.6, 116.6, 106.4, 70.0, 61.0, 46.0, 41.7, 29.6, 28.2, 24.2, 24.1, 12.1, 11.5. IR (3650−3400 cm^{-1} broad, 1732 cm^{-1}). MS (M^+, 360). Anal. Calcd for $C_{19}H_{22}O_6$: C 66.65, H 6.71. Found: C 66.73, H 6.72. $[\alpha]^{25}_D = -14.3$, $c = 0.55$, chloroform.

Ethyl 2-(2-Oxocyclopentyl)propionate (10). A solution of ester **9** (0.26 g, 0.69 mmol) in 30 mL of 1/1 methylene chloride/methanol containing 2 mL pyridine was cooled to −78 °C, and ozone was bubbled through the solution until the blue color persisted. After warming the reaction to ambient temperature, thiourea (54 mg, 0.71 mmol) was added and the reaction was stirred overnight. Filtration to remove the insoluble precipitate was followed by solvent removal and flash chromatography (7/1 hexanes/ethyl acetate) to afford ketone **10** (77 mg, 62%) as an oil. ^{1}H ($CDCl_3$): 4.17 (m, 2H), 2.81 (dq, J = 6.1, 7.1, 1H), 2.61−2.52 (m, 1H), 2.39−2.31 (m, 1H), 2.19−2.00 (m, 3H), 1.89−1.59 (m, 2H), 1.27 (t, J = 7.1, 3H), 1.11 (d, J = 7.1, 3H). ^{13}C ($CDCl_3$): 218.7, 175.4, 60.4, 51.3, 38.6, 37.9, 25.6, 20.3, 14.0, 13.5. IR (1732 cm^{-1}). MS (M^+, 184).

3-Methylhexahydrocyclopenta[*b*]furan-2-one (11). A solution of ketone **10** (63 mg, 0.342 mmol) in 5 mL of methanol was treated with cerium chloride heptahydrate (0.129 g, 0.346 mmol) followed by sodium borohydride (13 mg, 0.34 mmol). After 5 min, water was added and the product was extracted into ether. The ethereal layer was washed with brine and dried over magnesium sulfate. Filtration was followed by solvent removal, and the residue was chromatographed on silica gel using 4/1 hexanes/ether. A single diasteromeric lactone **11** (27.7 mg, 58%) was thus obtained. ^{1}H ($CDCl_3$): 5.00−4.95 (m, 1H), 2.55−2.48 (m, 1H), 2.37 (dq, J = 7.4, 3.9, 1H), 2.05−2.00 (m, 1H), 1.89−1.59 (m, 5H), 1.32 (d, J = 7.4, 3H). ^{13}C ($CDCl_3$): 180.7, 84.2, 46.7, 42.3, 33.3, 32.7, 23.4, 17.4. IR (1769 cm^{-1}). MS (M^+, 140). HRMS Calcd for $C_8H_{12}O_2$: 140.08373. Found: 140.08325.

3-Methylhexahydrocyclopenta[*b*]furan-2-ones 11 and 12. *cis*-Cyclopent-4-ene-1,3-diol (0.47 g, 4.69 mmol) was dissolved in 6 mL of triethyl orthopropionate, and hydroquinone (75 mg, 0.68 mmol) was added. The mixture was heated in an oil bath at 145 °C under nitrogen atmosphere for 16 h. After cooling, the dark reaction was diluted with 1/1 hexanes/ethyl acetate and washed successively with 5% HCl, water, and brine. Drying was effected using magnesium sulfate, and then the solution was filtered and solvent removed to leave a dark oil. Chromatography using 8/1 hexanes/ether gave 0.35 g oil that was used for the next reaction.

The oil from the above reaction was dissolved in ethyl acetate (10 mL), and palladium (0.11 g, 10% on carbon) was added. The solution was stirred under hydrogen atmosphere (balloon) for 18 h. Filtration through Celite removed the palladium, and solvent was then removed to leave the products as an oil. Flash chromatography using 10−40 μm silica gel (9/1 hexanes/ethyl acetate) was carried out twice to achieve complete separation of the diastereomeric products **11** and **12** (124 mg total, 18.8%). Lactone **11** (68 mg, 10.3%): identical to above derived from RS-97613. Lactone **12** (56 mg, 8.5%): ^{1}H ($CDCl_3$): 4.86 (dt, J = 1.7, 5.4, 1H), 2.85 (dq, J = 8.8, 7.0, 1H), 2.85−2.74 (m, 1H), 2.05−1.83 (m, 2H), 1.74−1.54 (m, 4H), 1.21 (d, J = 7.0, 3H). ^{13}C ($CDCl_3$): 179.4, 84.1, 43.9, 37.9, 32.4, 25.7, 24.1, 11.0. IR (1767 cm^{-1}). MS (M^+, 140). HRMS Calcd for $C_8H_{12}O_2$: 140.08373. Found: 140.08372.

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