Quantum Mechanics Calculations. Quantum mechanics calculations were performed with the MOPAC package[25a] employing the MNDO[25b] approximation, using configuration interaction of four. The distance between the odd-electron center of interest and the migrating methyl was varied; geometries were otherwise fully optimized. The energies for successive points in Figure 2 are for S_0 76.7, 44.0, 58.8, 80.8, 69.8, 61.9, 60.3, 60.2, 68.0, 82.9, 68.3, 53.8, 17.0, and for S_1 101.7, 104.7, 117.4, 153.6, 138.3, 130.2, 124.9, 125.2, 134.1, 149.5, 124.0, 110.9, and 106.3 kcal/mol.

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Conformationally Restricted Leukotriene Antagonists. Synthesis of Chiral 4-Hydroxy-4-alkylcyclohexanecarboxylic Acids as Leukotriene D_4 Analogues

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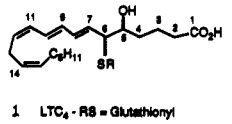
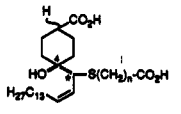
Eight conformationally restricted LTD_4 analogues, **2a–d** (n = 1, 2), were prepared in nine steps from methyl 4-hydroxybenzoate (**3**). The key step in this approach is the Sharpless asymmetric epoxidation of allylic alcohol **8** in which all four possible epoxy alcohol diastereomers **9a–d** were prepared. A single-crystal X-ray analysis of **9b** and application of the Sharpless model for predicting epoxidation stereoselectivity led to the assignment of relative stereochemistry and absolute configuration of **9a–d**. These high optical purity epoxy alcohols were then converted to chiral LTD_4 analogues **2a–d** (n = 1, 2) in three steps.

Introduction

The peptidoleukotrienes, leukotrienes C_4, D_4, and E_4 (**1**), comprise a family of closely related arachidonic acid metabolites which possess most of the biological activity attributed to slow-reacting substance of anaphylaxis (SRS-A). Released upon antigenic stimulation of sensitized human and animal lung tissue, they cause potent bronchoconstriction, increased microvascular permeability and altered mucous production and transport.[1] It is widely



1 LTC_4 - RS = Glutathionyl
LTD_4 - RS = Cysteinylglycinyl
LTE_4 - RS = Cysteinyl

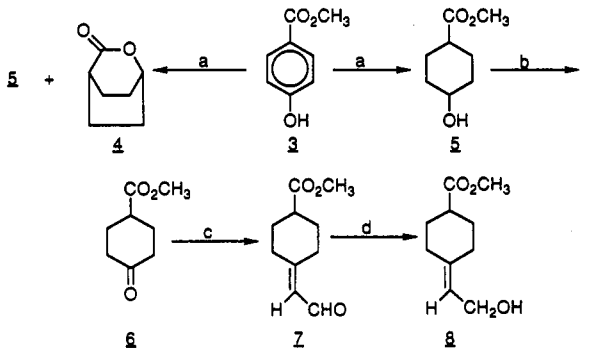


2a-d (n=1,2)

believed that a leukotriene antagonist would provide a new and effective therapy for allergic asthma and other immediate hypersensitivity diseases.

In vitro biological evaluation of synthetic leukotriene analogues has provided some insight into the portions of the molecule critical to receptor affinity. Several conclusions may be made concerning the molecular features characterizing a good leukotriene agonist and hence what factors constitute the critical recognition elements for the leukotriene receptor. The most important functional moieties of the leukotrienes are the peptidyl carboxyl group,[2a] the C-5 hydroxyl group,[2b] and the C-7 olefin.[2c]

Scheme I[a]



[a] Conditions: (a) H_2, 5% Rh/alumina, MeOH, 55 psi, 18 h; (b) PCC, CH_2Cl_2, room temperature; (c) $CH_3CH{=}NC(CH_3)_3$, LDA, -78 °C, $(EtO)_2POCl$, then H_3O^+; (d) $NaBH_4$, MeOH, 0 °C.

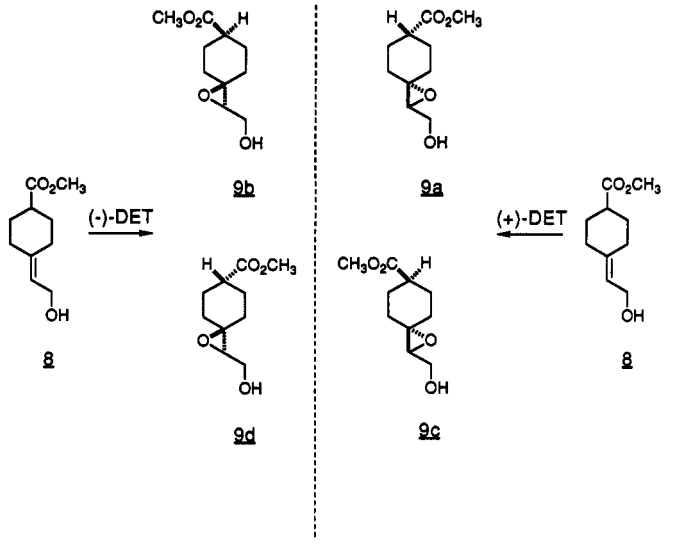
The 5(S),6(R) absolute configuration is extremely important,[2d] suggesting that a particular orientation of this region is necessary for binding. Also, the maintenance of lipophilicity in the hydrophobic region (C-13 to C-20) is needed.[2e]

(1) Chakrin, L. W.; Bailey, D. M. *The Leukotrienes: Chemistry and Biology*; Academic Press: New York, 1984.

(2) (a) Lewis, R. A.; Drazen, J. M.; Austen, K. F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4579. (b) Corey, E. J.; Hoover, D. J. *Tetrahedron Lett.* **1982**, *23*, 3463. (c) Baker S. R.; Boot, J. R.; Dawson, W.; Jamieson, W. B.; Osborne, D. J.; Sweatman, W. J. F. *Adv. Prostaglandin, Thromboxane Leukotriene Res.* **1982**, *9*, 223. (d) Lewis, R. A.; Austen, K. F.; Drazen, J. M.; Soter, N. A.; Figueiredo, J. C.; Corey, E. J. *Adv. Prostaglandin, Thromboxane Leukotriene Res.* **1982**, *9*, 137. (e) Drazen, J. M.; Lewis, R. A.; Austen, K. F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 3195.

0022-3263/91/1956-1758$02.50/0

Scheme II[a]



[a] Conditions: $Ti(OC_3H_7\text{-}i)_4$, t-C_4H_9OOH, L-(+)-diethyl tartrate or D-(−)-diethyl tartrate, CH_2Cl_2, −20 °C, 24 h.

The major premise underlying our rationale for the syntheses of conformationally restricted LTD_4 receptor antagonists[3] assumes that the recognition site for agonist activity will have similar demands on a competitive antagonist. Our main objective was to design antagonists based upon conformationally restricted LTD_4 analogues, incorporating key structural features of the native agonist, with known absolute stereochemistry, to "freeze-out" the conformation necessary for maximal binding at the active site. The synthetic targets, **2a–d**, incorporate a six-membered ring between the C-2 and C-5 portions of the agonist in order to impart conformational stability in the polar region of the molecule. The labile triene system is replaced by a single olefinic bond for chemical stability and a mercaptoalkanoic acid residue replaces the peptide residue.

In this paper, we report a stereocontrolled nine-step approach to series **2a–d**. The key step in this sequence is a Sharpless asymmetric epoxidation[4] of the racemic allylic alcohol **8** to produce pairs of chromatographically separable diastereomers (see Scheme II). In this way, all four possible epoxy alcohol diastereomers **9a–d** were prepared, with known absolute stereochemistry, and converted to chiral final products **2a–d**.

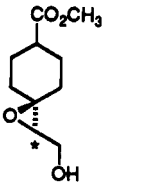
Results and Discussion

The synthesis commences with hydrogenation of commercially available methyl 4-hydroxybenzoate (**3**) using 5% rhodium on alumina[5] as catalyst (Scheme I). Failure to remove all the alumina prior to distillation affords a mixture of lactone **4** and hydroxy ester **5**. However, complete removal of alumina resulted in a 98% yield of the desired 4-carbomethoxycyclohexanol (**5**). Oxidation of **5** with pyridinium chlorochromate (PCC)[6] produces 4-carbomethoxycyclohexanone (**6**) in 98% yield. Two-carbon homologation of **6**, using Meyers'[7] "in situ" generated lithioenaminophosphonate, conveniently affords an intermediate α,β-unsaturated aldehyde **7**, which is subsequently reduced with sodium borohydride to allylic alcohol **8** in 35% yield for the two steps.

The key step in the overall synthetic sequence involves the Sharpless asymmetric epoxidation[4] of allylic alcohol **8** (Scheme II). Use of L-(+)-diethyl tartrate yields a chromatographically separable mixture of diastereomers **9a** and **9c** in 78% and 70% enantiomeric excess (ee), respectively.[8] The oxygen is delivered to the α-face as predicted by the Sharpless model. Recrystallization of each diastereomer increases the optical purity of **9a** and **9c** to >95% ee and 80% ee, respectively. Similar treatment of allylic alcohol **8** with D-(−)-diethyl tartrate produces the mirror-image diastereomeric pair **9b** and **9d** (>95% ee and 90% ee, respectively) after chromatography and recrystallization. Table I shows the optical rotation for each epoxy alcohol **9a–d**. As expected, each pair of enantiomers (**9a** and **9b**, **9c** and **9d**) have opposite optical rotations nearly equal in magnitude. An X-ray analysis[9] of the lower R_f component of the chromatographically separable **9b**, **9d** mixture established the relative stereochemistry of the epoxide oxygen and carbomethoxy group of **9b** (Figure 1) as syn. The application of the Sharpless mnemonic[4] then allows for the assignment of relative stereochemistry and absolute configuration for **9b** and **9d**. By analogy, **9a** and **9c** have the relative stereochemistry and absolute configuration as shown.

With all asymmetric centers now in place and well-defined, the completion of the synthesis was straightforward and followed our previously published sequence[3] (Scheme III, Tables II and III). Epoxy alcohols **9a–d** were oxidized under Swern conditions[10] using a nonaqueous workup to produce epoxy aldehydes **10a–d** in good yields. Stereo-

Table I. Optical Purities of Epoxy Alcohols 9a–d



compd	CO_2CH_3	config	$[\alpha]^{20}_D$, deg	% ee
9a	β	S	−13.3	>95
9b	β	R	+14.6	>95
9c	α	S	−10.6	80
9d	α	R	+13.2	90

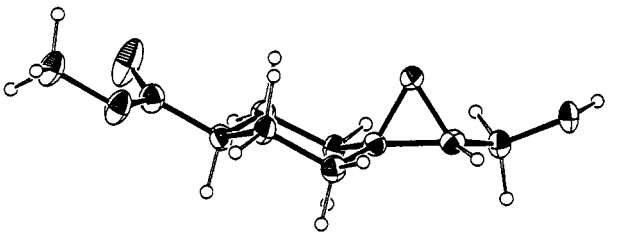


Figure 1. ORTEP drawing of epoxy alcohol **9b**.

(3) Sabol, J. S.; Cregge, R. J. *Tetrahedron Lett.* **1989**, *30*, 3377. Sabol, J. S.; Cregge, R. J. *Ibid.* **1989**, *30*, 6271. Sabol, J. S.; Cregge, R. J. *Ibid.* **1990**, *31*, 27. Sabol, J. S.; Weintraub, P. M.; Cregge, R. J.; Gieske, T. H. *Tetrahedron*, in press.

(4) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 247–308.

(5) (a) Carlson, R. G.; Zey, E. G. *J. Org. Chem.* **1972**, *37*, 2468. (b) House, H. O.; Babao, H.; Toothill, R. B.; Noltes, A. W. *J. Org. Chem.* **1962**, *27*, 4141.

(6) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.

(7) Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788.

(8) Enantiomeric excess (ee) was determined by ^1H NMR ($CDCl_3$, 300 MHz) analysis of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] ester, see: Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

(9) The single-crystal X-ray analysis was carried out by Dr. John Huffman, Indiana University, Bloomington, IN.

(10) Swern, D.; Omura, K. *Tetrahedron* **1978**, *34*, 1651.

Table II. Structures and Optical Rotations of Intermediates 10–13

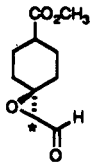
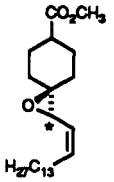
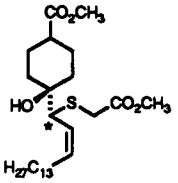
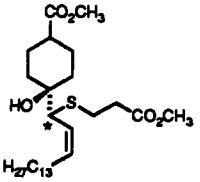
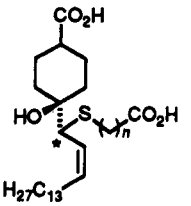
	compd	CO_2CH_3	config	$[\alpha]^{20}_D$ in $CHCl_3$, deg	% yield
	**10a**	β	*S*	+132.0	95
	10b	β	*R*	−81.8	86
	10c	α	*S*	+68.6	84
	10d	α	*R*	−99.0	97
	**11a**	β	*S*	+25.7	82
	11b	β	*R*	−26.6	69
	11c	α	*S*	+31.9	78
	11d	α	*R*	−36.7	42
	**12a**	β	*R*	+12.5	79
	12b	β	*S*	−10.9	95
	12c	α	*R*	+25.0	92
	12d	α	*S*	−31.0	89
	**13a**	β	*R*	+33.5	93
	13b	β	*S*	−30.3	93
	13c	α	*R*	+36.7	77
	13d	α	*S*	−43.4	81

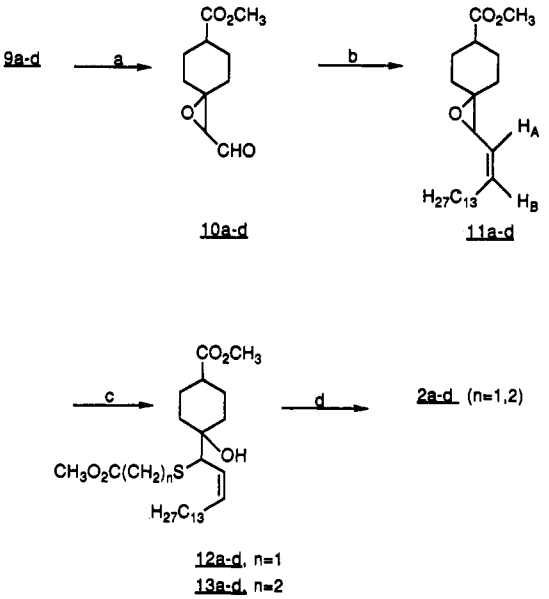
Table III. Structures and Optical Rotations of Diacids 2a–d



compd	*n*	CO_2H	config	$[\alpha]^{20}_D$ in $CHCl_3$, deg
2a	1	β	*R*	+23.9
	2	β	*R*	+32.0
2b	1	β	*S*	−11.5
	2	β	*S*	−38.1
2c	1	α	*R*	+3.3
	2	α	*R*	+34.8
2d	1	α	*S*	−11.8
	2	α	*S*	−41.5

selective Wittig olefination[11] then afforded the *Z* olefins **11a–d**. The olefin geometry was determined through measurement of the olefinic coupling constants[12] in which J_{A-B} was typically ~11 Hz, while J_{A-B} = 15 Hz was found for the *E* olefin, which was isolated in a small amount from one reaction. Regiospecific opening of vinyl oxiranes **11a–d** with either methyl mercaptoacetate or methyl 3-mercaptopropionate produced the diesters **12a–d** and **13a–d**, respectively, with inversion of configuration. In every case, only S_N2 products were detected; the sulfur methine resonance (typically a doublet) clearly excludes any S_N2' derived product. Saponification of the diesters afforded diacids **2a–d**. Tables II and III list the intermediates and final products that were prepared. The optical rotations for each set of enantiomers (**a** vs **b**, **c** vs **d**) are opposite in sign and similar in magnitude.

Scheme III[a]



[a] Conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (b) $(CH_3)_3CO^-K^+$, $CH_3(CH_2)_{13}PPh_3^+Br^-$, THF; (c) MeOH, $HS(CH_2)_nCO_2CH_3$, Et_3N, room temperature; (d) KOH, H_2O, EtOH.

Conclusion

Eight conformationally restricted LTD_4 analogues **2a–d** (n = 1, 2) with known absolute stereochemistry, were prepared. The Sharpless asymmetric epoxidation was successfully employed to produce intermediate epoxy alcohols **9a–d** of high optical purity. A single-crystal X-ray analysis of **9b**, taken together with the Sharpless model, which has proven infallible to date, was used to assign the relative stereochemistry and absolute configuration of **9a–d**. These high optical purity epoxy alcohols were then carried on to final products in a straightforward manner.

(11) Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327.
(12) Silverstein, R. M.; Bassler, G. C.; Merrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1981; p 235.

When tested in a guinea pig ileum model, certain members of this series were very potent antagonists with variable agonist activity.[13]

Experimental Section

All melting points are uncorrected.

4-Carbomethoxycyclohexanol (5). A mixture of 25 g (160 mmol) of methyl *p*-hydroxybenzoate (3) and 2.5 g of 5% rhodium on alumina in methanol (MeOH, 150 mL) was shaken under hydrogen (55 psi) for 18 h. The catalyst was removed by filtration through Celite and then rinsed with MeOH (3 × 50 mL). The combined filtrates were evaporated to dryness under reduced pressure and then taken up in diethyl ether (Et_2O, 200 mL), and anhydrous potassium carbonate (K_2CO_3, 3 g) was added. The precipitated alumina and K_2CO_3 were removed by filtration through Celite. The Celite was rinsed (Et_2O), the filtrates were combined, and the solvent was removed under reduced pressure to give crude ester 5 as an oil. Bulb-to-bulb Kugelrohr distillation (80–100 °C/ca. 1 Torr, lit.[5] 96–98 °C/0.35 Torr) gave 25.0 g (158 mmol, 98%) of 5 as a colorless oil: ^1H NMR (60 MHz) δ 1.30–2.30 (10 H, br m), 3.61 (3 H, s), 3.90 (1 H, m). If the alumina is not removed prior to distillation, lactone 4[5b] will form and appear in the distillate as a solid: lit.[5] mp 126–127 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40–2.20 (8 H, m), 2.65 (1 H, br s), 4.70 (1 H, br s); IR (CCl_4) 1760 cm^{-1} (lit.[5b] 1755 cm^{-1}).

4-Carbomethoxycyclohexanone (6). To a mixture of dry methylene chloride (CH_2Cl_2, 400 mL), 24 g of oven-dried Celite, and 11..42 g (84 mmol) of sodium acetate, under N_2, was added 90.5 g (420 mmol) of pyridinium chlorochromate. After the addition of more CH_2Cl_2 (350 mL), a solution of 44.5 g (280 mmol) of alcohol 5 in CH_2Cl_2 (40 mL) was added with a syringe. After 3.5 h, Et_2O (800 mL) was added with stirring and the reaction mixture was suction filtered through silica gel (250 g), and the silica gel was eluted with Et_2O (4 × 150 mL). The combined filtrates were concentrated to a green oil which was taken up in Et_2O (150 mL) and again suction filtered through silica gel (50 g). The silica gel was rinsed with Et_2O (4 × 50 mL). The combined filtrates were concentrated to a clear oil, which was Kugelrohr distilled (65–85 °C/ca. 1 Torr, lit.[5] 94–95 °C/0.65 Torr) to yield 42.6 g (273 mmol, 97.5%) of keto ester 6 as a colorless oil: ^1H NMR (60 MHz) δ 3.70 (s, 3 H), 2.9–1.8 (9 H); IR (CCl_4) 2950, 2900, 2880, 1720 cm^{-1}.

Methyl 4-(2-Oxoethylidene)cyclohexanecarboxylate (7). A solution of 76.4 mL (545 mmol) of dry diisopropylamine in THF (730 mL) at 3 °C under N_2 was treated with 340 mL (545 mmol) of *n*-butyllithium (1.6 M in hexane) dropwise (45 min). After 15 min, the solution was cooled to −75 °C and 26.9 g (272 mmol) of acetaldehyde *tert*-butylimine was added dropwise with a syringe (20 min). After the mixture was stirred an additional 30 min at −75 °C, 47.0 g (272 mmol) of diethyl chlorophosphate was added by a dropping funnel over 1 h. The reaction mixture was allowed to stir an additional hour at −75 °C, then warmed to −11 °C over 2 h, and again cooled to −75 °C. Then 28.39 g (182 mmol) of keto ester 6 in THF (50 mL) was added with a dropping funnel over 1 h. The reaction mixture was allowed to warm to room temperature overnight and then poured into a mixture of 49.0 g (545 mmol) of oxalic acid in 1.8 L of water and 1.8 L of toluene. This was vigorously stirred for 24 h. The aqueous layer was separated and extracted with Et_2O (2.5 L). The combined toluene and Et_2O extracts were washed with 5% oxalic acid (2 × 500 mL), saturated $NaHCO_3$ (500 mL), and saturated NaCl (500 mL). The organic layer was dried (K_2CO_3), filtered, and concentrated under vacuum. The resulting oil was purified (Prep LC, 25% EtOAc/hexane, 300 mL/min, 2 columns, t_R 7.5 min) to yield 18.5 g (101 mmol, 55%) of α,β-unsaturated aldehyde 7 as an oil: ^1H NMR (60 MHz) δ 10.05 (d, 1 H), 5.85 (d, 1 H), 3.70 (s, 3 H), 2.8–1.5 (9 H); IR (CCl_4) 2950, 2840, 2750, 1740, 1680, 1640 cm^{-1}.

Methyl 4-(2-Hydroxyethylidene)cyclohexanecarboxylate (8). A solution of 13.0 g (71 mmol) of α,β-unsaturated aldehyde 7 in MeOH (77 mL) was cooled to 3 °C. With vigorous stirring, 3.1 g (81 mmol) of $NaBH_4$ added in portions over 0.5 h. The reaction was allowed to stir for an additional hour at 3 °C. Glacial acetic acid (1 mL) was added, and the MeOH was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (200 mL) and extracted with water (400 mL). The organic layer was washed with saturated NaCl (200 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The resulting oil was purified (Prep LC, 30% EtOAc/hexane, 250 mL/min, 2 columns, t_R 13 min) to yield 11.52 g of mostly 8. Bulb-to-bulb Kugelrohr distillation (150–150 °C/0.8 Torr) yielded 9.03 g (49 mmol, 69%) of allylic alcohol 8 as a clear oil: ^1H NMR (60 MHz) δ 5.40 (t, 1 H), 4.10 (d, 2 H), 3.70 (s, 3 H), 2.9–1.3 (10 H); IR (CCl_4) 3600–3400, 2950, 1730, 1670 cm^{-1}.

Methyl 2-(Hydroxymethyl)-[3(*S*)-*cis*]-1-oxaspiro[2.5]octane-6-carboxylate (9a) and Diastereomer (9c). With stirring, 12.9 mL (43.5 mmol) of titanium(IV) isopropoxide and 8.9 mL (43.5 mmol) of (+)-diethyl tartrate (in 10 mL of CH_2Cl_2) were added successively by syringe to CH_2Cl_2 at −25 °C to −30 °C under N_2. After 10 min, 8.0 g (43.5 mmol) of allylic alcohol 8 (in 20 mL of CH_2Cl_2) was added, followed by a CH_2Cl_2 (20 mL) rinse of the flask and syringe. Then 18.4 mL (87.0 mmol) of *tert*-butyl hydroperoxide (4.7 M in toluene) was added immediately. The reaction flask was then transferred to a freezer and allowed to sit at −20 °C for 24 h. The reaction was suction filtered through silica gel and rinsed through with 25% EtOAc/CH_2Cl_2 (500 mL). The combined filtrates were concentrated under vacuum to yield a yellow oil. TLC (20% EtOAc/hexane) of the crude mixture indicated that the syn and anti diastereomers were separable by chromatography with R_f(syn) 0.14 and R_f(anti) 0.17. These were separated (Prep LC, 10% *i*-PrOH/hexane, 250 mL/min, 2 columns, t_R(anti) 16 min, t_R(syn) 23 min) to yield 2.7 g of anti epoxide (9c) and 2.5 g of syn epoxide (9a) as oils.

Syn epoxide 9a was recrystallized twice from 3% Et_2O/pentane to yield 0.411 g (9.5%) of 9a as long, flat, white crystals: mp 67–68 °C; $[\alpha]^{20}_D$ −13.3 (*c* 1.15, $CHCl_3$); ee >95%.[8] For 9a: ^1H NMR (300 MHz) δ 3.80 (m, 2 H), 3.70 (s, 3 H), 3.01 (dd, 1 H, J = 4.6, 6.7 Hz), 2.00–1.40 (9 H); IR (KBr) 3560–3200, 1740 cm^{-1}; MS *m/z* 201 (M^+ + 1, 10), 183 (20), 165 (100), 151 (30), 123 (15), 105 (20).

The anti epoxide was recrystallized twice from 30% Et_2O/pentane to yield 0.57 g (13%) of 9c as long, flat white crystals: mp 31–33 °C; $[\alpha]^{20}_D$ −10.6 (*c* 1.22, $CHCl_3$); ee 80%.[8] For 9c: ^1H NMR (300 MHz) δ 3.91–3.83 (m, 1 H), 3.74–3.66 (m, 4 H), 2.99 (dd, 1 H, J = 4.4, 6.6 Hz), 2.48–2.45 (m, 1 H), 2.10–2.03 (m, 2 H), 1.91–1.50 (m, 7 H); IR (KBr) 3700–3100, 1720 cm^{-1}; MS *m/z* 201 (M^+ + 1, 10), 183 (20), 165 (100), 151 (40), 141 (15), 123 (15), 105 (20).

Methyl 2-(Hydroxymethyl)-[3(*R*)-*cis*]-1-oxaspiro[2.5]octane-6-carboxylate (9b) and Diastereomer (9d). Treatment of 8 g (43.5 mmol) of allylic alcohol 8 under identical conditions as above except using the (−)-isomer of diethyl tartrate gave, after chromatography, 4.56 g of 9b (t_R(anti) 15 min) followed by 2.49 g of 9d (t_R(syn) 19 min).

The syn epoxide was recrystallized twice from 3% Et_2O/pentane to yield 0.18 g of 9b as hexagonal plates: mp 67.5–68.5 °C; $[\alpha]^{20}_D$ +14.6° (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz) δ 3.89–3.80 (m, 1 H), 3.77–3.68 (m, 4 H), 3.04–2.99 (dd, 1 H, J = 4.4, 6.6 Hz), 2.50–2.40 (m, 1 H), 2.05–1.55 (br m, 9 H); IR (KBr) 3600–3100, 1720 cm^{-1}; MS *m/z* 201 (M^+ + 1, 10) 183 (100).

The anti epoxide was recrystallized from 30% Et_2O/pentane to yield 1.89 g (18.5%) of 9d as long, flat, white needles: mp 40–41 °C; $[\alpha]^{20}_D$ +13.2° (*c* 1.14, $CHCl_3$); ^1H NMR (300 MHz) δ 3.91–3.83 (m, 1 H), 3.74–3.66 (m, 4 H), 2.99 (dd, 1 H, J = 4.4, 6.7 Hz), 2.49–2.43 (m, 1 H), 2.11–2.03 (m, 2 H), 1.81–1.62 (m, 7 H); IR (KBr) 3700–3100, 1720 cm^{-1}; MS *m/z* 201 (M^+ + 1, 15), 183 (25), 165 (100), 151 (25), 141 (10), 123 (15), 105 (20).

General Procedure for Preparing Aldehydes 10a–d. A solution of 0.20 mL (2.3 mmol) of oxalyl chloride in dry CH_2Cl_2 (27 mL) under N_2 was cooled to −75 °C, and 0.35 mL (4.9 mmol) of DMSO was added dropwise over 5 min with stirring. After an additional 10 min, 381 mg (1.9 mmol) of epoxy alcohol 9a (in 3 mL of CH_2Cl_2) was added dropwise. After 20 min of stirring, 1.45 mL (10.2 mmol) of triethylamine (Et_3N) was added dropwise (5 min). The reaction was allowed to warm to room temperature over 45 min. The solvent was removed under reduced pressure. The resulting white solid was taken up in Et_2O (50 mL) and filtered. The filtrate was concentrated under vacuum to yield a yellow oil which was purified (Prep LC, 20% EtOAc/hexane, 250 mL/min, 1 column, t_R 4.75 min) to yield 355 mg (95%) of

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epoxy aldehyde **10a** as an oil. Compounds **10b–d** were similarly obtained from **9b–d** in yields of 86, 84, and 97%, respectively.

Methyl 2-formyl-[3(*S*)-*cis*]-1-oxaspiro[2.5]octane-6-carboxylate (10a): ^{1}H NMR (300 MHz) δ 9.50 (d, 1 H), 3.70 (s, 3 H), 3.20 (d, 1 H), 2.60–1.30 (9 H); IR (neat) 2945, 2860, 2720, 1730 cm^{-1}; MS *m/z* 199 (M^+ + 1, 100), 181 (80), 167 (15), 149 (12); $[\alpha]^{20}_D$ +132° (*c* 0.71, $CHCl_3$).

Methyl 2-formyl-[3(*R*)-*cis*]-1-oxaspiro[2.5]octane-6-carboxylate (10b): ^{1}H NMR (300 MHz) δ 9.50 (d, 1 H, *J* = 4.88 Hz), 3.70 (s, 3 H), 3.21 (d, 1 H, *J* = 4.88 Hz), 2.47–2.44 (m, 1 H), 2.05–1.77 (m, 8 H); IR (neat) 2960, 1725; MS *m/z* 199 (M^+ + 1, 100), 181 (55), 167 (20), 153 (10); $[\alpha]^{20}_D$ −81.8° (*c* 1.08, $CHCl_3$).

Methyl 2-formyl-[3(*S*)-*trans*]-1-oxaspiro[2.5]octane-6-carboxylate (10c): ^{1}H NMR (300 MHz) δ 9.50 (d, 1 H, *J* = 4.76 Hz), 3.69 (s, 3 H), 3.21 (d, 1 H, *J* = 4.76 Hz), 2.51–2.46 (m, 1 H), 2.16–2.06 (m, 2 H), 1.87–1.58 (m, 6 H); IR (neat) 2940, 1715 cm^{-1}; MS *m/z* 199 (M^+ + 1, 100), 181 (15); $[\alpha]^{20}_D$ +68.6° (*c* 0.77, $CHCl_3$).

Methyl 2-formyl-[3(*R*)-*trans*]-1-oxaspiro[2.5]octane-6-carboxylate (10d): ^{1}H NMR (300 MHz) δ 9.50 (d, 1 H, *J* = 4.88 Hz), 3.69 (s, 3 H), 3.21 (d, 1 H, *J* = 4.88 Hz), 2.50–2.46 (m, 1 H), 2.14–2.06 (m, 2 H), 1.87–1.59 (m, 6 H); IR (neat) 2960, 1730 cm^{-1}; MS *m/z* 199 (M^+ + 1, 100), 181 (25), 167 (15); $[\alpha]^{20}_D$ −99° (*c* 1.69, $CHCl_3$).

General Procedure for Preparing Olefins 11a–d. A solution of 1.80 g (3.4 mmol) of *n*-tetradecyltriphenylphosphonium bromide in dry THF (20 mL) at room temperature under N_2 was treated with 6.4 mL (3.23 mmol) of potassium *tert*-butoxide (*t*-BuOK, 0.5 M in THF) dropwise, causing the solution to turn orange. After 5 min, 342 mg (1.7 mmol) of epoxy aldehyde **10a** (in 3 mL of THF) was added dropwise to the reaction, turning the solution to pale yellow. Six additional 0.5-mL aliquots of the *t*-BuOK solution were added at 10-min intervals to drive the reaction to completion. Water (5 mL) was added, and the reaction was poured into Et_2O (200 mL). The organic phase was washed with saturated NaCl (2 × 100 mL) and concentrated under vacuum to ~100 mL. Then hexane (900 mL) was added, and the cloudy solution was suction filtered through silica gel. The silica gel was rinsed with 10% Et_2O/hexane (500 mL). The combined filtrates were concentrated under vacuum to yield a yellow oil. This was purified (Prep LC, 5% EtOAc/hexane, 250 mL/min, 1 column, silica gel, t_R 5 min) to yield 527 mg (82%) of epoxy olefin **11a** as an oil. Compounds **11b–d** were similarly obtained from **10b–d** in yields of 69, 78, and 42%, respectively.

Methyl 2-(1-pentadecenyl)-[3(*S*)-[3β(*Z*),6β]]-1-oxaspiro[2.5]octane-6-carboxylate (11a): ^{1}H NMR (300 MHz) δ 5.75 (m, 1 H), 5.25 (dd, 1 H, *J* = 8.05, 11.2 Hz), 3.70 (s, 3 H), 3.45 (d, 1 H, *J* = 8.05 Hz), 2.43 (m, 1 H), 2.20–1.22 (32 H), 0.89 (t, 3 H, *J* = 6.6 Hz); IR (neat) 2940, 2860, 1730, 1640 cm^{-1}; MS *m/z* 379 (M^+ + 1, 100), 361 (25); $[\alpha]^{20}_D$ +25.7° (*c* 0.92, $CHCl_3$).

Methyl 2-(1-pentadecenyl)-[3(*R*)-[3β(*Z*),6β]]-1-oxaspiro[2.5]octane-6-carboxylate (11b): ^{1}H NMR (300 MHz) δ 5.75 (m, 1 H), 5.25 (dd, 1 H, *J* = 8.2, 11.1 Hz), 3.70 (s, 3 H), 3.45 (d, 1 H, *J* = 8.2 Hz), 2.41 (m, 1 H), 2.25–1.23 (32 H), 0.88 (t, 3 H, *J* = 7 Hz); IR (neat) 2940, 2860, 1740 cm^{-1}; MS *m/z* 379 (M^+ + 1, 100), 361 (25); $[\alpha]^{20}_D$ −26.6° (*c* 1.95, $CHCl_3$).

Methyl 2-(1-pentadecenyl)-[3(*S*)-[3β(*Z*),6α]]-1-oxaspiro[2.5]octane-6-carboxylate (11c): ^{1}H NMR (300 MHz) δ 5.76 (m, 1 H), 5.23 (dd, 1 H, *J* = 8.3, 10.8 Hz), 3.68 (s, 3 H), 3.43 (d, 1 H, *J* = 8.3 Hz), 2.45–1.20 (33 H), 0.88 (s, 3 H); IR (neat) 2920, 2850, 1730 cm^{-1}; MS *m/z* 379 (M^+ + 1, 100), 361 (20), 235 (100); $[\alpha]^{20}_D$ +31.9° (*c* 0.95, $CHCl_3$).

Methyl 2-(1-pentadecenyl)-[3(*R*)-[3β(*Z*),6α]]-1-oxaspiro[2.5]octane-6-carboxylate (11d): ^{1}H NMR (300 MHz) δ 5.75 (m, 1 H), 5.26 (m, 1 H, *J* = 7.95, 11 Hz), 3.68 (s, 3 H), 3.43 (d, 1 H, *J* = 7.95 Hz), 2.45 (m, 1 H), 2.30–1.20 (32 H), 0.88 (t, 3 H); IR (neat) 2930, 2860, 1740 cm^{-1}; MS *m/z* 379 (M^+ + 1, 100), 361 (30), 157 (60); $[\alpha]^{20}_D$ −36.7° (*c* 1.10, $CHCl_3$).

General Procedure for Preparing Diesters 12a–d (*n* = 1) and 13a–d (*n* = 2). A stirred solution of 250 mg (0.66 mmol) of epoxy olefin **11a** in MeOH (2.6 mL) was treated with 0.30 mL (2.18 mmol) of Et_3N followed by 0.17 mL (1.98 mmol) of methyl mercaptoacetate. After 24 h the MeOH was removed under reduced pressure, and the oil was taken up in Et_2O (100 mL). This was then washed with HCl (50 mL, 0.5 N) and saturated NaCl (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to give a yellow oil. This was purified (Prep LC, 10% EtOAc/hexane, 250 mL/min, 1 column, silica gel, t_R 19 min) to yield 253 mg (79%) of diester **12a** as an oil. Compounds **12b–d** (*n* = 1) were similarly obtained from **11b–d** in yields of 95, 92, and 89%, respectively, and **13a–d** (*n* = 2) were obtained from **11a–d** in yields of 93, 93, 77, and 81%, respectively, by analogous reaction with methyl 3-mercaptopropionate.

Methyl [4(*R*)-[1β,4β,4(*Z*)]]-4-hydroxy-4-[1-[(2-methoxy-2-oxoethyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (12a): ^{1}H NMR (300 MHz) δ 5.68 (m, 1 H), 5.36 (t, 1 H), 3.78 (d, 1 H, *J* = 11 Hz); 3.72 (s, 3 H), 3.67 (s, 3 H), 3.22 (q, 2 H), 2.30–1.20 (34 H), 0.88 (t, 3 H); IR (neat) 3600–3200, 2920, 2860, 1735 cm^{-1}; MS *m/z* 485 (M^+ + 1, 5), 467 (10), 379 (15), 361 (100), 157 (20), 107 (60); $[\alpha]^{20}_D$ +12.5° (*c* 0.92, $CHCl_3$).

Methyl [4(*S*)-[1β,4β,4(*Z*)]]-1-hydroxy-4-[1-[(2-methoxy-2-oxoethyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (12b): ^{1}H NMR (300 MHz) δ 5.68 (m, 1 H), 5.36 (t, 1 H), 3.78 (d, 1 H, *J* = 10.7 Hz), 3.72 (s, 3 H), 3.66 (s, 3 H), 3.22 (q, 2 H), 2.21–1.25 (34 H), 0.88 (t, 3 H); IR (neat) 3600–3200, 2930, 2860, 1730 cm^{-1}; MS *m/z* 485 (M^+ + 1, 15), 467 (30), 361 (55), 157 (20), 107 (100), 1 (100); $[\alpha]^{20}_D$ −10.9° (*c* 1.07, $CHCl_3$).

Methyl [4(*R*)-[1α,4β,4(*Z*)]]-4-hydroxy-4-[1-[(2-methoxy-2-oxoethyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (12c): ^{1}H NMR (300 MHz) δ 5.70 (m, 1 H), 5.38 (t, 1 H), 3.94 (d, 1 H, *J* = 10.8 Hz), 3.73 (s, 3 H), 3.68 (s, 3 H), 3.22 (q, 2 H), 2.54 (m, 1 H), 2.27 (s, 1 H), 2.06–1.22 (32 H), 0.88 (t, 3 H); IR (neat) 3600–3300, 2930, 2860, 1735 cm^{-1}; MS *m/z* 467 (50), 379 (25), 361 (90), 157 (60), 125 (20), 107 (50), 75 (100); $[\alpha]^{20}_D$ +25.0° (*c* 1.36, $CHCl_3$).

Methyl [4(*S*)-[1α,4β,4(*Z*)]]-4-hydroxy-4-[1-[(2-methoxy-2-oxoethyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (12d): ^{1}H NMR (300 MHz) δ 5.70 (m, 1 H), 5.40 (t, 1 H), 3.94 (d, 1 H, *J* = 10.7 Hz), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.22 (q, 2 H), 2.53 (m, 1 H), 2.28 (s, 1 H), 2.09–1.22 (32 H), 0.88 (t, 3 H); IR (neat) 3650–3200, 2930, 2860, 1735 cm^{-1}; MS *m/z* 467 (M^+ + 1 − H_2O, 10), 379 (20), 361 (70), 157 (60), 107 (80), 75 (100); $[\alpha]^{20}_D$ −31.0° (*c* 0.93, $CHCl_3$).

Methyl [4(*R*)-[1β,4β,4(*Z*)]]-4-hydroxy-4-[1-[(3-methoxy-3-oxopropyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (13a): ^{1}H NMR (300 MHz) δ 5.61 (m, 1 H), 5.39 (t, 1 H), 3.69 (s, 3 H), 3.66 (s, 3 H), 3.60 (d, 1 H, *J* = 11.2 Hz), 2.77–2.56 (m, 4 H), 2.21–1.26 (34 H), 0.88 (t, 3 H); IR (neat) 3600–3300, 2920, 2860, 1735 cm^{-1}; MS *m/z* 481 (M^+ + 1 − H_2O, 15), 379 (25), 363 (50), 207 (20), 195 (15), 185 (10), 157 (70), 121 (20), 105 (20); $[\alpha]^{20}_D$ +33.5° (*c* 0.88, $CHCl_3$).

Methyl [4(*S*)-[1β,4β,4(*Z*)]]-4-hydroxy-4-[1-[(3-methoxy-3-oxopropyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (13b): ^{1}H NMR (300 MHz) δ 5.68 (m, 1 H), 5.42 (t, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.65 (d, 1 H, *J* = 11 Hz), 2.82–2.60 (m, 4 H), 2.30–2.05 (m, 4 H), 1.95–1.21 (30 H), 0.91 (t, 3 H); IR (neat) 3600–3300, 2930, 2860, 1735 cm^{-1}; MS *m/z* 499 (M^+ + 1, 5), 481 (20), 379 (10), 361 (40), 207 (20), 89 (100); $[\alpha]^{20}_D$ −30.3° (*c* 1.09, $CHCl_3$).

Methyl [4(*R*)-[1α,4β,4(*Z*)]]-4-hydroxy-4-[1-[(3-methoxy-3-oxopropyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (13c): ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.40 (t, 1 H), 3.71 (d, 1 H, *J* = 10.99 Hz), 3.69 (s, 3 H), 3.68 (s, 3 H), 2.74–2.55 (m, 5 H), 2.18 (s, 1 H), 2.07–1.21 (32 H), 1 (t, 3 H); IR (neat) 3700–3100, 2960, 2880, 1730 cm^{-1}; MS *m/z* 481 (M + 1 − H_2O, 10), 467 (15), 379 (50), 361 (60), 342 (100), 157 (70), 125 (40); $[\alpha]^{20}_D$ +36.7 ° (*c* 0.84, $CHCl_3$).

Methyl [4(*S*)-[1α,4β,4(*Z*)]]-4-hydroxy-4-[1-[(3-methoxy-3-oxopropyl)thio]-2-hexadecenyl]cyclohexanecarboxylate (13d): ^{1}H NMR (300 MHz) δ 5.61 (m, 1 H), 5.40 (t, 1 H), 3.72 (d, 1 H, *J* = 11.1 Hz), 3.69 (s, 3 H), 3.68 (s, 3 H), 2.77–2.54 (m, 5 H), 2.18 (s, 1 H), 1 (32 H), 0.88 (t, 3 H); IR (neat) 3700–3300, 2940, 2860, 1735 cm^{-1}; MS *m/z* 481 (M^+ + 1 − H_2O, 20), 379 (20), 361 (60), 157 (40), 121 (60), 89 (100); $[\alpha]^{20}_D$ −43.4° (1.36, $CHCl_3$).

General Procedure for Preparing Diacids 2a–d (*n* = 1, 2). A solution of 240 mg (0.5 mmol) of diester **12a** was in absolute EtOH (4 mL) was treated with a solution of KOH (327 mg, 5.1 mmol) in water (3 mL) with stirring. After 4.5 h the resultant clear solution was diluted with water (75 mL), washed with Et_2O (75 mL), and then acidified with HCl (15 mL, 0.5 N). The aqueous layer was then extracted with EtOAc (3 × 150 mL), and the combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated to yield 200 mg (0.44 mmol, 88%) of diacid **2a** (*n*

= 1) as an oil. Compounds **2b-d** (n = 1) and **2a-d** (n = 2) were similarly prepared form **12b-d** and **13a-d**, respectively.

[4(*R*)-[1β,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2a, n = 1): ^{1}H NMR (300 MHz) δ 5.69 (m, 1 H), 5.39 (t, 1 H), 3.81 (d, 1 H, J = 10.9 Hz), 3.22 (q, 2 H), 2.3-2.2 (m, 1 H), 2.08-1.21 (13 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 439 ($M^+ + 1 - H_2O$, 10), 347 (50), 143 (20), 123 (15), 93 (70), 75 (100); $[\alpha]^{20}_D$ +23.9° (c 0.66, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.83; H, 9.55.

[4(*R*)-[1β,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2a, n = 2): white powder, 64% from **13a**; mp 121-123 °C; ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.38 (t, 1 H), 3.62 (d, 1 H, J = 10.9 Hz), 2.76-2.60 (m, 4 H), 2.29-2.19 (m, 1 H), 2.07-1.21 (33 H), 0.88 (t, 3 H); IR (KBr) 3600-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 25), 365 (60), 347 (40), 193 (20), 143 (25), 123 (50), 107 (70), 89 (100), 73 (50); $[\alpha]^{20}_D$ +32.0° (c 0.95, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_5S$: C, 66.34; H, 9.85. Found: C, 66.15; H, 9.75.

[4(*S*)-[1β,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2b, n = 1): clear oil, 63% from **12b**; ^{1}H NMR (300 MHz) δ 5.68 (m, 1 H), 5.36 (t, 1 H), 3.82 (d, 1 H, J = 11 Hz), 3.22 (q, 2 H), 2.25 (m, 1 H), 2.09-1.12 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 457 ($M^+ + 1$, 10), 439 (70), 375 (25), 365 (40), 347 (100), 239 (10), 143 (15), 93 (30), 75 (45); $[\alpha]^{20}_D$ -11.5° (c 1.42, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.83; H, 9.55.

[4(*S*)-[1β,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2b, n = 2): white powder, 89% from **13b**; mp 122-123 °C; ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.39 (t, 1 H), 3.62 (d, 1 H, J = 10.9 Hz), 2.75-2.60 (m, 4 H), 2.29-2.20 (m, 1 H), 2.07-1.22 (33 H), 0.88 (t, 3 H); IR (KBr) 3400-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 30), 347 (60), 239 (25), 193 (30), 143 (50), 125 (40), 107 (60), 89 (100); $[\alpha]^{20}_D$ -38.1° (c 0.89, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_5S$: C, 66.34; H, 9.85. Found: C, 66.19; H, 9.76.

[4(*R*)-[1α,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2c, n = 1): clear oil, 60% form **12c**; ^{1}H NMR (300 MHz) δ 5.73 (m, 1 H), 5.42 (t, 1 H), 4.26 (d, 1 H, J = 11 Hz), 3.17 (q, 2 H), 2.44 (m, 1 H), 2.11-1.18 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 439 ($M^+ + 1 - H_2O$, 75), 365 (25), 347 (100), 314 (15), 143 (25), 125 (10), 93 (10), 83 (20), 75 (15); $[\alpha]^{20}_D$ +3.3° (c 0.73, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.51; H, 9.74.

[4(*R*)-[1α,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2c, n = 2): clear oil, 77% from **13c**; ^{1}H NMR (300 MHz) δ 5.66 (m, 1 H), 5.41 (t, 1 H), 3.75 (d, 1 H, J = 10.7 Hz), 2.75-2.59 (m, 5 H), 2.08-1.26 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 25), 365 (20), 347 (20), 143 (30), 125 (15), 107 (25), 89 (100), 75 (40); $[\alpha]^{20}_D$ +34.8° (c 0.81, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_5S$: C, 66.34; H, 9.85. Found: C, 66.44; H, 9.96.

[4(*S*)-[1α,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2d, n = 1): clear oil, 25% from **12d**; ^{1}H NMR (300 MHz) δ 5.72 (m, 1 H), 5.49 (t, 1 H), 4.26 (d, 1 H, J = 11 Hz), 3.16 (m, 2 H), 2.50-2.40 (m, 1 H), 2.30-1.17 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 439 ($M^+ + 1 - H_2O$, 30), 365 (20), 347 (100), 314 (20), 143 (40), 125 (20), 107 (10), 93 (40), 75 (50); $[\alpha]^{20}_D$ -11.8° (c 0.97, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.99; H, 9.72.

[4(*S*)-[1α,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2d, n = 2): clear oil, 38% from **13d**; ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.42 (t, 1 H), 3.76 (d, 1 H, J = 10.9 Hz), 2.75-2.58 (m, 5 H), 2.09-1.22 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 30) 365 (20), 347 (40), 239 (15), 193 (15), 143 (20), 125 (15), 107 (20), 89 (100), 75 (20); $[\alpha]^{20}_D$ -41.5° (c 1.26, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}OS$: C, 66.34; H, 9.85. Found: C, 66.47; H, 9.85.

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Supplementary Material Available: X-ray data for compound **9b** and ^{1}H NMR spectra of all new compounds (53 pages); structure factor tables (4 pages). Ordering information is given on any current masthead page.

Intramolecular Ullmann Condensation Reaction: An Effective Approach to Macrocyclic Diaryl Ethers

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The demonstration and definition of the scope of the intramolecular Ullmann condensation reaction suitable for use in macrocyclization reactions leading to 14-membered para- and metacyclophanes possessing a diaryl ether are detailed.

Bouvardin (1, NCS 259968) and deoxybouvardin (2), bicyclic hexapeptides isolated initially from *Bouvardia ternifolia* (Rubiacea) and unambiguously identified by single-crystal X-ray structure analysis (bouvardin) and chemical correlation (deoxybouvardin),[1] constitute the initial members of a class of potent antitumor antibiotics now including 1-8.[1-7] The unusual 14-membered para- and metacyclophane of the naturally occurring agents has been suggested to arise from the oxidative coupling of two adjacent L-tyrosine residues in cyclic hexapeptide precursors, although the direct incorporation of naturally derived isodityrosine (9)[8] has not been excluded. Related isodityrosine-derived 17-membered and 14-membered diaryl ether structural subunits have been found in a number of additional naturally occurring agents now in-

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