In summary, the combination of Heathcock's aldol methodology and the kinetic resolution of 2-furylcarbinols using the Sharpless reagent offers a practical route for the synthesis of all the four possible stereoisomers of **1**.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were measured either on a HITACHI R-40 (90 MHz) or on a JEOL FX-90Q (90 MHz) spectrometer, whereas ^{13}C NMR spectra were recorded on a JEOL FX-90Q instrument. Both ^{1}H and ^{13}C NMR spectra were obtained with CCl_4 or $CDCl_3$ as a solvent, and values are reported in ppm (δ) downfield from tetramethylsilane or residual $CHCl_3$ as an internal standard unless otherwise noted. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; br s, broad singlet. Infrared (IR) spectra were measured on a JASCO A-100 spectrometer. Optical rotations were measured on a YANACO OR-50 polarimeter using a 20-cm^3 capacity (0.5-dm path length) cell. Elemental analyses were performed by the Research Laboratory of Resources Utilization, Tokyo Institute of Technology.

Materials. Methylene chloride was freshly distilled from calcium hydride. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Titanium isopropoxide and L-(+)-DIPT were distilled under high vacuum and stored under an argon atmosphere before use. A stock solution of TBHP in CH_2Cl_2 was prepared and stored as described by Sharpless.[8] The optical purity of the kinetic resolution product was determined by ^{1}H NMR analysis of the corresponding acetate in the presence of (+)-Pr(dppm)$_3$ (Daiichi Pure Chemicals Co., Ltd.).

Preparation of Methyl (2*R,3*R**)-3-(2-Furyl)-3-hydroxy-2-methylpropionate (1 (R = Me)).** To a solution of diisopropylamine (1.42 mL, 10.1 mmol) in THF (15 mL) was added *n*-butyllithium (5.02 mL, 9.20 mmol, 1.83 M in hexane) at 0 °C under argon. After 10 min at 0 °C, the solution was cooled to −78 °C, and 2-methyl-2-[(trimethylsilyl)oxy]-3-pentanone (**2**)[5] (1.50 g, 7.97 mmol) dissolved in THF (1 mL) was added. After 30 min at −78 °C, furfural (0.51 mL, 6.13 mmol) was added. The solution was stirred for 1 min and poured into saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil, which was purified by column chromatography on silica gel to afford **3** (1.53 g, 88%): IR (neat) 3420, 1700, 1180, 1020, 830 cm^{-1}; ^{1}H NMR (CCl_4, D_2O, CH_2Cl_2 as an internal standard) δ 0.04 (s, 9 H), 0.92 (d, J = 7.2 Hz, 3 H), 1.02 and 1.12 (2 s, 6 H), 3.44 (dq, J = 6.0, 7.2 Hz, 1 H), 4.63 (d, J = 6.0 Hz, 1 H), 5.90–6.10 (m, 2 H), 7.03 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 218.4, 154.8, 141.5, 110.1, 106.7, 80.6, 68.9, 44.1, 27.5, 27.1, 12.4, 2.3. Anal. Calcd for $C_{14}H_{24}O_4Si$: C, 59.12; H, 8.50. Found: C, 58.91; H, 8.65.

To a solution of **3** (1.57 g, 5.53 mmol) in MeOH (15 mL) was added H_5IO_6 (6.30 g, 27.6 mmol) dissolved in H_2O (30 mL) at 0 °C. After 3 h at 0 °C, the solution was neutralized by adding saturated aqueous $NaHCO_3$ at room temperature. The solvents were removed in vacuo to leave the crude acid, which was dissolved in ether (10 mL) and treated with diazomethane for 10 min at 0 °C. Concentration of the solution and purification by column chromatography on silica gel afforded (2*R**,3*R**)-**1** (R = Me) (812 mg, 80%): Spectral data (IR, ^{1}H NMR, and ^{13}C NMR) were in good agreement with values reported in the literature.[1a] Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.62; H, 6.62.

Kinetic Resolution of (2*R,3*R**)-1 (R = Me).** To a mixture of crushed 4A molecular sieves (300 mg) and 0.2 equiv of Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.73 mmol) in CH_2Cl_2 (3 mL) was added 0.24 equiv of L-(+)-DIPT (0.18 mL, 0.87 mmol) at −21 °C under argon. The mixture was stirred for 10 min at −21 °C and cooled to −30 °C. To this mixture was added (2*R**,3*R**)-**1** (R = Me) (670 mg, 3.64 mmol) dissolved in CH_2Cl_2 (2 mL), and the mixture was stirred between −30 °C and −20 °C for 30 min. The mixture was again cooled to −30 °C, and 0.6 equiv of TBHP (0.51 mL, 2.19 mmol, 4.32 M in CH_2Cl_2) was slowly added. After the solution was stirred for 20 h at −21 °C, Me_2S (0.16 mL, 2.19 mmol) was added, and the mixture was stirred for 30 min at −21 °C. To this mixture were added 10% aqueous tartaric acid (1 mL), ether (10 mL), and NaF (2 g), and the resulting mixture was vigorously stirred for 2 h at room temperature. The white precipitate was filtered off through a pad of Celite with ether (20 mL). The filtrate was concentrated to give an oil, which was purified by column chromatography on silica gel to afford (2*R*,3*R*)-**1** (R = Me) (302 mg, 45% based on racemic **1**, >99% ee, R_f 0.52 (hexane–AcOEt, 1:1)) and the corresponding oxidation product (350 mg, 48%, R_f 0.35). (2*R*,3*R*)-**1**: $[\alpha]^{25}_D$ +14.7° (*c* 1.64, $CHCl_3$) [lit.[1a] $[\alpha]^{25}_D$ +14.75° (*c* 1.8, $CHCl_3$)]. Spectral data (IR and ^{1}H NMR) of the oxidation product are identical with those reported for its enantiomer.[1a]

Preparation of 2,6-Di-*tert*-butyl-4-methylphenyl (2*S,3*R**)-3-(2-Furyl)-3-hydroxy-2-methylpropionate (1 (R = BHT)).** To a solution of diisopropylamine (1.35 mL, 9.66 mmol) in THF (15 mL) was added *n*-butyllithium (5.39 mL, 9.05 mmol, 1.68 M in hexane) at 0 °C under argon. After 10 min at 0 °C, the solution was cooled to −78 °C and BHT propionate (**4**)[6] (2.17 g, 7.85 mmol) dissolved in THF (5 mL) was added. After 45 min at −78 °C, furfural (0.5 mL, 6.04 mmol) was added. The solution was stirred for 1 min at −78 °C and poured into saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil, which was purified by column chromatography on silica gel to afford (2*S**,3*R**)-**1** (R = BHT) (2.03 g, 90%) as a white solid: mp 101–102 °C (recrystallized from hexane); IR (Nujol) 3460, 1730, 725 cm^{-1}; ^{1}H NMR (CCl_4, D_2O) δ 1.16–1.35 (m, 21 H), 2.18 (s, 3 H), 3.07 (qui, J = 7.8 Hz, 1 H), 4.68 (d, J = 7.8 Hz, 1 H), 6.10 (br s, 2 H), 6.88 (s, 2 H), 7.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.5, 153.7, 142.0, 141.9, 134.7, 127.2, 126.8, 110.1, 108.0, 69.5, 45.5, 35.2, 31.4, 21.3, 13.3. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.27; H, 8.48.

Kinetic Resolution of (2*S,3*R**)-1 (R = BHT).** The reaction was run as described above for the kinetic resolution of (2*R**,3*R**)-**1** (R = Me) using (2*S**,3*R**)-**1** (R = BHT) (1.66 g, 4.46 mmol), Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.89 mmol), L-(+)-DIPT (0.23 mL, 1.1 mmol), 4A molecular sieves (500 mg), TBHP (0.62 mL, 2.7 mmol, 4.32 M in CH_2Cl_2), and CH_2Cl_2 (3 mL) for 48 h. Workup as described above and purification by column chromatography on silica gel afforded (2*S*,3*R*)-**1** (R = BHT) (812 mg, 49% yield based on racemic **1**, >99% ee, R_f 0.49 (hexane–ether, 2:1)) as a white solid and the corresponding oxidation product (R_f 0.23) as an inseparable mixture with L-(+)-DIPT (1.12 g). The yield of the oxidation product was estimated to be 50% based on ^{1}H NMR analysis of the crude reaction mixture. (2*S*,3*R*)-**1** (R = BHT): mp 80–81 °C (recrystallized from hexane); $[\alpha]^{25}_D$ +9.52° (*c* 1.39, $CHCl_3$).

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Stereospecific Synthesis of Leukotriene Antagonists

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Leukotrienes C_4, D_4, and E_4 comprise a family of arachidonic acid metabolites that have been implicated in a variety of immediate hypersensitivity diseases, including allergic asthma.[1] It was recently noted that 2-nor-leu-

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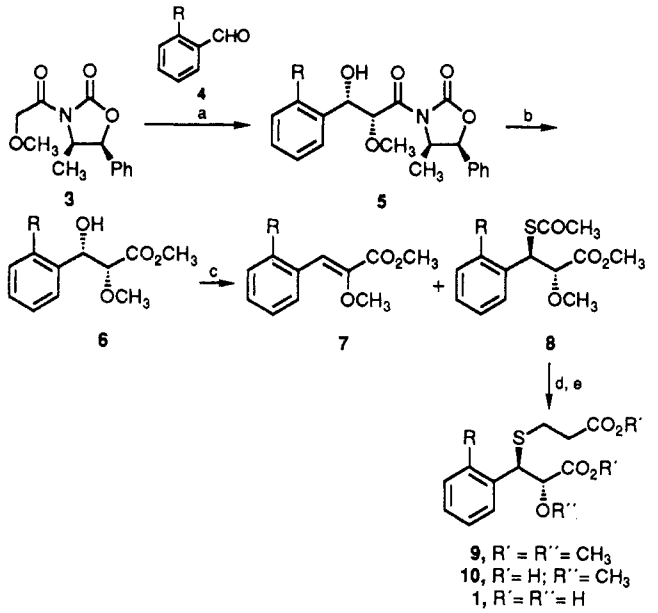
Scheme I[a,b]

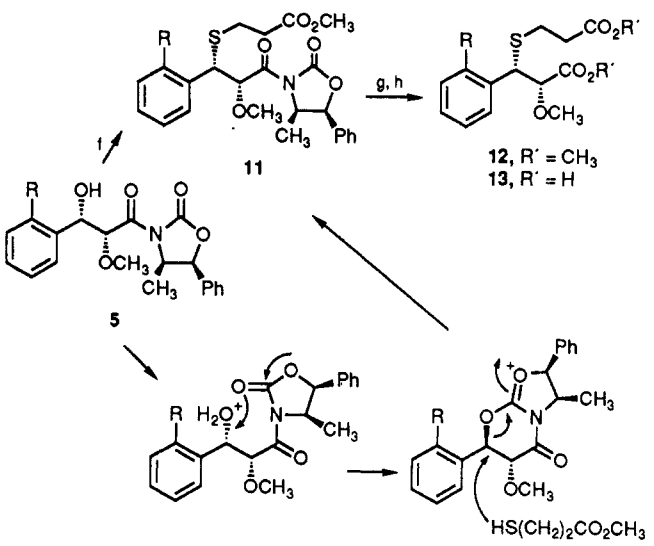


[a] (a) n-Bu_2BOT_f, i-Pr_2EtN; (b) K_2CO_3, CH_3OH; (c) $HSCOCH_3$, n-Bu_3P, (i-$PrO_2CN{=}$)$_2$; (d) $CH_2{=}CHCO_2CH_3$, $NaOCH_3$; (e) 10% NaOH. [b] R = $(CH_2)_8Ph$.

kotriene analogues[2] exhibit weak but significant antagonist properties. The 4*R*,5*S* stereoisomer appears to possess less agonist activity than the corresponding 4*S*,5*R* enantiomer, and the triene tail may be replaced with a metabolically more stable (phenyloctyl)phenyl group.[3] Further structure–activity relationship studies have led to the discovery of a series of 3-[2-(8-phenyloctyl)phenyl]propanoic acids represented by [*R*-(*R**,*S**)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid (1) which show greatly enhanced peptidoleukotriene receptor antagonist activity.[4] We have explored the potential utility of the Evans' chiral boron enolate methodology[5] as an efficient entry into this class of leukotriene analogues and wish to describe in this report a stereospecific synthesis of the methoxy analogue of 1 (Scheme I).

The synthetic approach utilized optically active (methoxyacetyl)oxazolidinone **3**, which was prepared by acylation of the chiral auxiliary **2** with methoxyacetyl chloride (*n*-BuLi, THF, −78 °C, 98% yield). The norephedrine-derived auxiliary **2** was prepared in 67% yield from (1*S*,2*R*)-norephedrine (35.0 g, 0.22 mmol), phosgene (450 mL), and 10% sodium hydroxide solution (480 mL) in diethyl ether (750 mL). Methoxyacetyl imide **3**, containing the chiral oxazolidinone auxiliary well documented as an inducer with high enantio and erythro selectivity, was converted to the boron enolate (n-Bu_2BOT_f, i-Pr_2EtN, CH_2Cl_2, 0 °C),[6] which was then treated with **4**[3b] to afford, after oxidative workup, optically active erythro adduct **5**[7] in better than 92% diastereoisomeric purity by HPLC (Zorbax SiO_2 column, 30% EtOAc/hexane). Direct methanolysis of **5** (K_2CO_3, CH_3OH) provided hydroxy methyl ester **6** (47% yield based on 4) after flash chromatography (SiO_2, 25% EtOAc/hexane); the chiral auxiliary **2** was recovered in good yield.

Scheme II[a,b]



[a] (f) TFA,$HS(CH_2)_2CO_2CH_3$; (g) $NaOCH_3$, CH_3OH; (h) 10% NaOH. [b] R = $(CH_2)_8Ph$.

The Mitsunobu thioacetoxylation (AcSH, n-Bu_3P, (i-$PrO_2CN{=}$)$_2$, toluene)[8] of **6** gave **8** in 14.5% isolated yield with inversion of configuration at the benzylic carbon. However, the major product in 65% yield was the enol ether **7**, resulting from competitive β-H elimination pathway. Further attempts to optimize the displacement reaction by using more hindered triphenylphosphines resulted exclusively in β-H elimination. The same ratio of thioacetoxy product and enol ether was obtained from achiral threo alcohol **6a**. The configuration at the benzylic carbon was determined from the ^1H NMR spectra of the erythro and threo thioacetoxy esters **8a** and **8b**, prepared under identical conditions from the respective achiral erythro and threo isomers, **6a** and **6b**, synthesized from methyl methoxyacetate and **4**. Subsequent methanolysis of **8** and Michael addition of the resulting mercaptide to methyl acrylate ($NaOCH_3/CH_3OH$) afforded **9** in 98% yield. Saponification provided chiral dicarboxylic acid **10** ($[\alpha]^{22}_D = -28.5°$ (c = 1.0, $CHCl_3$)) in 83% yield after flash chromatography (SiO_2, 30% EtOAc/hexane/0.5% formic acid). The optical purity of **10** was determined to be greater than 97% on the basis of a comparison of its 360-MHz ^1H NMR ($CDCl_3$) spectrum and with that of its racemate **10a**[9] in the presence of 6 equiv of (*S*)-(+)-2,2,2-

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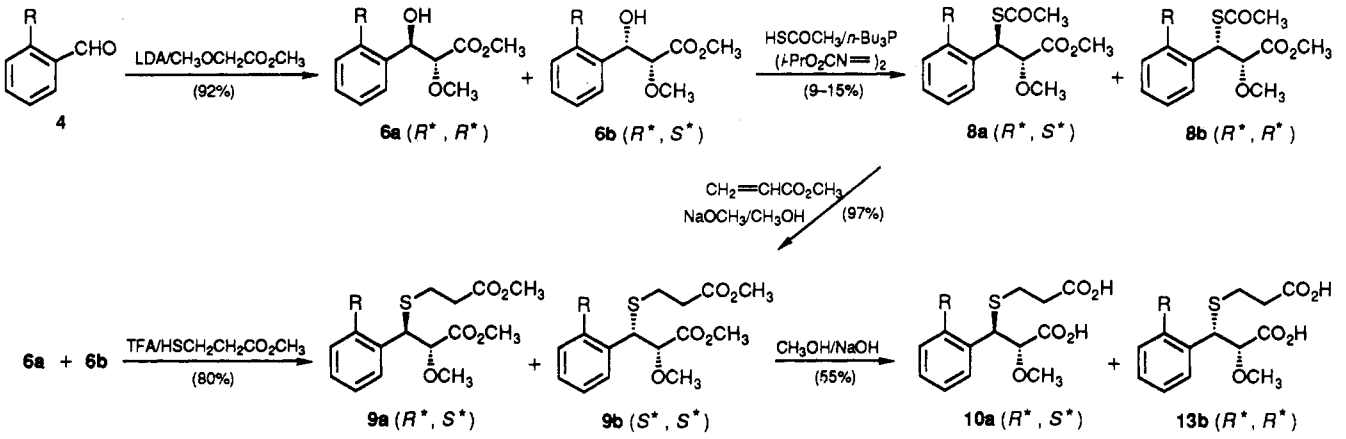
(9) The threo racemate **10a** was synthesized from **4** by a nonchiral aldol condensation with methyl methoxyacetate and LDA (Scheme III; compounds depicted herein are racemates with relative stereochemistry). The diastereomers **6a** and **6b** were solvolyzed with methyl mercaptopropionate in TFA followed by saponification and HPLC to remove the erythro isomeric diacid **10b**.

Scheme III[a] **(Relative Stereochemistry Shown)**



[a] R = $(CH_2)_8Ph$.

trifluoro-1-(9-anthryl)ethanol.[10]

Solvolysis of **5** in methyl 3-mercaptopropionate and TFA gave **11** (70% after flash chromatography (SiO_2/10% EtOAc/hexane) with retention of configuration at the benzylic carbon. The apparent double inversion of configuration is envisioned (Scheme II, absolute stereochemistry as depicted) as proceeding through an initial acid-catalyzed dehydration step involving participation of the carbonyl oxygen of oxazolidinone. The resulting [4.3.0]-bicyclic iminium carbonate intermediate may undergo a nucleophilic displacement by thiol with overall net retention of configuration. Methanolysis of **11** afforded **12** ($NaOCH_3/CH_3OH$, 47%, $[\alpha]^{22}_D = +72.6°$ (c = 0.7, $CHCl_3$)). ^1H NMR spectra analysis confirmed that **12** is the erythro diastereomer of **9**. Hydrolysis ($NaOH/CH_3OH$) gave optically active erythro dicarboxylic acid **13** in 69% yield ($[\alpha]^{22}_D = +73.9°$ (c = 1, $CHCl_3$)).

In conclusion, we have demonstrated that the dibutylboron enolate of oxazolidinone **3** readily undergoes an aldol addition reaction with 2-(8-phenyloctyl)benzaldehyde (**4**) with high diastereofacial selectivity. Thioacetoxylation of chiral benzyl carbinol **6** proceeds with inversion of configuration to give the anti thioacetoxy ester **8**, which was hydrolyzed and alkylated under mildly basic conditions to provide the optically active anti diester **9**. On the other hand, TFA-catalyzed solvolysis of aryl carbinol **5** was shown to proceed with a net retention of configuration, giving rise to **11** in good yield, which upon methanolysis affords the syn diastereomeric diester **12**. This sequence thus provides ready access to analogues of a novel class of potent leukotriene antagonists in optically pure form. The pharmacology of these new leukotriene antagonists will be discussed elsewhere.

Experimental Section

The purity of all title compounds was determined to be greater than 95% by HPLC, TLC, proton NMR spectral analysis, and/or elemental analysis. NMR spectra were recorded at 90 MHz. Melting points are uncorrected. Di-*n*-butylboron triflate was freshly prepared and distilled according to literature reference cited. Tetrahydrofuran (THF) was distilled from benzophenone ketyl prior use.

[4*R*-(4α,5α)]-4-Methyl-5-phenyl-2-oxazolidinone (2). To a magnetically stirred, cooled (0 °C) solution of (1*S*,2*R*)-norephedrine (35.0 g, 0.22 mol) and 10% NaOH solution (480 mL) in diethyl ether (750 mL) was added dropwise a solution of phosgene (12% in toluene, 480 mL). The reaction mixture was stirred at room temperature for 2.5 h and layers were separated. The aqueous phase was extracted with diethyl ether (22 × 100 mL), washed with saturated sodium chloride solution, dried ($MgSO_4$), filtered, and evaporated to give a white solid (26.0 g, mp 117–9 °C, $[\alpha]^{22}_D = +155.9°$ (c = 0.3, CH_3Cl), 68% yield): ^1H NMR ($CDCl_3$) δ 0.78 (d, J = 6.0 Hz, 3 H), 4.2 (dq, J = 7.5, 6.0 Hz, 1 H), 5.68 (d, J = 7.5 Hz, 1 H), 6.8 (bs, 1 H), 7.2–7.4 (m, 5 H).

[4*R*-(4α,5α)]-3-(Methoxyacetyl)-4-methyl-5-phenyl-2-oxazolidinone (3). To a magnetically stirred, cooled (−40 °C) solution of (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone (**2**) (10.0 g, 56 mmol) in tetrahydrofuran (100 mL) was added dropwise a solution of *n*-butyllithium (22 mL, 57 mmol). The mixture was stirred for 30 min and cooled (−74 °C). To the resulting reddish brown solution was added dropwise over 10 min a solution of methoxyacetyl chloride (5.2 mL, 56 mmol) in tetrahydrofuran (20 mL). After 30 min at −74 °C, the reaction was quenched with a saturated solution of ammonium chloride (10 mL) and diluted with ice–water (150 mL). The aqueous phase was extracted with diethyl ether (3 × 100 mL), washed with saturated sodium chloride solution, dried ($MgSO_4$), filtered, evaporated, and triturated in hexane to give a white solid (13.7 g, 98% yield, mp 57–9 °C, $[\alpha]^{22}_D = +42.8°$ (c = 1, CH_3Cl): ^1H NMR ($CDCl_3$) δ 0.82 (d, J = 6.0 Hz, 3 H), 3.5 (s, 1 H), 4.65 (s, 2 H), 4.8 (dq, J = 6.0, 7.5 Hz, 1 H), 4.75 (d, J = 6.5 Hz, 1 H), 5.75 (d, J = 7.5 Hz, 1 H), 7.2–7.6 (m, 5 H).

[4*R*-[3(2*R,3*S**),4α,5α]]-3-[3-Hydroxy-2-methoxy-1-oxo-3-[2-(8-phenyloctyl)phenyl]propyl]-4-methyl-5-phenyl-2-oxazolidinone (5).** To a magnetically stirred, cooled (0 °C) solution of (methoxyacetyl)oxazolidinone **3** (9.0 g, 36 mmol) in dichloromethane (100 mL) was added dropwise over 3 min di-*n*-butylboryl triflate[7] (10 mL, 40 mmol). After 5 min, diisopropylethylamine (7.5 mL, 43 mmol) was added. The mixture was stirred at 0 °C for 30 min and re-cooled (−74 °C). To this solution was added aldehyde **4** (10.6 g, 36 mmol)[3b] neat. After 0.5 h at −78 °C and 20 min at 0 °C, the reaction was quenched by sequential addition of aqueous pH 7 phosphate buffer (38 mL), methanol (150 mL), and 30% hydrogen peroxide (38 mL) in methanol (75 mL). After 20 min, the mixture was concentrated in vacuo and the product was extracted into dichloromethane. The combined extracts were washed with saturated sodium bisulfate and sodium chloride solutions, dried ($MgSO_4$), and concentrated under reduced pressure to give 19.0 g (oil, 99% yield) of product: ^1H NMR ($CDCl_3$) δ 0.82 (d, J = 6.0 Hz, 3 H), 1.2–1.7 (m, 12 H), 2.5–2.7 (m, 4 H), 3.05 (d, J = 2.0 Hz, 1 H), 4.16 (quintet, J = 6.0 Hz, 1 H), 4.75 (d, J = 6.5 Hz, 1 H), 5.15 (dd, J = 2.0, 6.5 Hz, 1 H), 5.52 (d, J = 6.0 Hz, 1 H), 7.2–7.7 (m, 14 H); MS, m/e (DCI, NH_3) 543; >92% de by HPLC; t_R 3.63 min (Zorbax SiO_2/30% EtOAc/hexane; $[\alpha]^{22}_D$ +2.9° (c = 1.1, $CHCl_3$)).

[*R*-(*R,*S**)]-Methyl β-Hydroxy-α-methoxy-2-(8-phenyloctyl)benzenepropanoate (6).** To a magnetically stirred, cooled (0 °C) solution of **5** in methanol (450 mL) was added in portions powdered anhydrous potassium carbonate (5.5 g, 40 mmol). After 45 min, the mixture was filtered and the filtrate was concentrated

(10) The methoxymethyl signal for the racemate was resolved into two singlets (ca.2 Hz) of equal intensity whereas it remained as a singlet under the same conditions for the optically active **9**.

to give an oil, which was taken up in diethyl ether (400 mL), washed with cold ammonium chloride solution, and cooled at 0 °C. The white precipitates were removed by filtration and the filtrate was purified by flash chromatography (SiO_2/25% EtOAc/hexane) to give 6.8 g (47% overall yield from **4**) of an oil as product: ^1H NMR ($CDCl_3$) δ 1.3–1.7 (m, 12 H), 2.5–2.7 (m, 4 H), 3.05 (d, J = 4.5 Hz, 1 H), 3.4 (s, 3 H), 3.6 (s, 3 H), 3.9 (d, J = 6.0 Hz, 1 H), 5.2 (dd, J = 4.5, 6.0 Hz, 1 H), 7.2–7.5 (m, 9 H); $[\alpha]^{22}_D$ = +36.1° (c = 1.1, $CHCl_3$)).

(*R,*R**)-Methyl β-Hydroxy-α-methoxy-2-(8-phenyloctyl)benzenepropanoate (6a) and (*R**,*S**)-Methyl β-Hydroxy-α-methoxy-2-(8-phenyloctyl)benzenepropanoate (6b).** To a magnetically stirred, cooled (−78 °C) solution of diisopropylamine (5.7 mL, 48 mmol) in THF (50 mL) was added dropwise *n*-butyllithium (16 mL, 41.6 mmol). After 30 min, methyl methoxyacetate (4.25 g, 40 mmol) was added. The mixture was stirred at 0 °C for 30 min and re-cooled (−74 °C). The reaction mixture was stirred for 30 min, to which was added a solution of aldehyde **4** (10.0 g, 34 mmol)[3b] in THF (10 mL). After 1 h at 22 °C, the reaction was quenched by adding saturated ammonium chloride solution (100 mL), diluted with ice water, and extracted with diethyl ether. The combined extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated under reduced pressure to give 12 g (92% yield) of oil as a mixture of anti and syn products. Flash chromatography (SiO_2/20% EtOAc/hexane) yielded **6a** (5.6 g, HPLC t_R = 4.73 min (Zorbax SiO_2 20% EtOAc/hexane/2 mL/min)) [^1H NMR ($CDCl_3$) δ 1.3–1.7 (m, 12 H), 2.5–2.7 (m, 4 H), 3.0 (d, J = 4.0 Hz, 1 H), 3.3 (s, 3 H), 3.62 (s, 3 H), 3.95 (d, J = 6.5 Hz, 1 H), 5.25 (dd, J = 4.0, 6.5 Hz, 1 H), 7.2–7.5 (m, 9 H)] and **6b** (5.0 g, HPLC t_R = 5.95 min (Zorbax SiO_2 20% EtOAc/hexane/2 mL/min)) [^1H NMR ($CDCl_3$) δ 1.3–1.7 (m, 12 H), 2.5–2.7 (m, 4 H), 3.05 (d, J = 4.5 Hz, 1 H), 3.4 (s, 3 H), 3.6 (s, 3 H), 3.9 (d, J = 6.0 Hz, 1 H), 5.2 (dd, J = 4.5, 6.0 Hz, 1 H), 7.2–7.5 (m, 9 H)].

(*Z*)-Methyl 2-Methoxy-3-[2-(8-phenyloctyl)phenyl]-2-propenoate (7) and [*R*-(*R,*S**)]-Methyl β-(Acetylthio)-α-methoxy-2-(8-phenyloctyl)benzenepropanoate (8).** To a magnetically stirred, cooled (0 °C) solution of tri-*n*-butylphosphine (1.25 mL, 5 mmol) in toluene (5 mL) was added diisopropyl azodicarboxylate (1.0 mL, 5 mmol) over 30 min. After 45 min, a solution of **6** (1.0 g, 2.5 mmol) and thiolacetic acid (0.9 mL, 5 mmol) in toluene (5 mL) was added. The resulting mixture was stirred at room temperature for 18 h. The reaction was concentrated and the oil residue was flash chromatographed (SiO_2/8% EtOAc/hexane) to give enol ether byproduct **7** (0.8 g, oil, 65% yield) [^1H NMR ($CDCl_3$) δ 1.3–1.7 (m, 12 H), 2.5–2.7 (m, 4 H), 3.7 (s, 3 H), 3.9 (s, 3 H), 7.1–7.3 (m, 10 H), 7.8–8.0 (m, 1 H)] and the desired product **8** (160 mg, oil, 14.5% yield) [^1H NMR ($CDCl_3$) δ 1.3–1.7 (m, 12 H), 2.3 (s, 3 H), 2.5–2.7 (m, 4 H), 3.4 (s, 3 H), 3.6 (s, 3 H), 4.17 (d, J = 6.0 Hz, 1 H), 5.41 (d, J = 6.0 Hz, 1 H), 7.15–7.55 (m, 9 H)].

(*R,*R**)-Methyl β-(Acetylthio)-α-methoxy-2-(8-phenyloctyl)benzenepropanoate (8b).** To a magnetically stirred, cooled (0 °C) solution of tri-*n*-butylphosphine (1.25 mL, 5 mmol) in toluene (5 mL) was added diisopropyl azodicarboxylate (1.0 mL, 5 mmol) over 30 min. After 45 min, a solution of **6a** and **6b** (1.0 g, 2.5 mmol) and thiolacetic acid (0.9 mL, 5 mmol) in toluene (5 mL) was added. The resulting mixture was stirred at room temperature for 18 h. The reaction was concentrated to give a mixture of products **7**, **8a**, and **8b** (TLC), which was flash chromatographed (SiO_2/8% EtOAc/hexane) to give **8b** (80 mg, oil, 7.5% yield): ^1H NMR ($CDCl_3$) δ 1.3–1.7 (m, 12 H), 2.3 (s, 3 H), 2.5–2.7 (m, 4 H), 3.4 (s, 3 H), 3.7 (s, 3 H), 4.1 (d, J = 3.0 Hz, 1 H), 5.9 (d, J = 3.0 Hz, 1 H), 7.1–7.4 (m, 9 H).

[*R*-(*R,*S**)]-Methyl α-Methoxy-β-[(3-methoxy-3-oxopropyl)thio]-2-(8-phenyloctyl)benzenepropanoate (9).** To a magnetically stirred, cooled (0 °C) solution of **8** (160 mg, 0.35 mmol) and methyl acrylate (0.3 mL, 3.4 mmol) in methanol (25 mL) was added sodium methylate (0.1 g, 1.65 mmol). After 30 min at room temperature, the reaction was concentrated to give the desired product (170 mg, oil, 97% yield): ^1H NMR ($CDCl_3$) δ 1.25–1.75 (m, 12 H), 2.3–2.8 (m, 8 H), 3.3 (s, 3 H), 3.62 (s, 3 H), 3.74 (s, 3 H), 4.15 (d, J = 7.5 Hz, 1 H), 4.50 (d, J = 7.5 Hz, 1 H), 7.1–7.3 (m, 8 H), 7.4–7.6 (m, 1 H); MS, m/e (DCI, NH_3) 500; $[\alpha]^{22}_D$ = −0.7° (c = 1, $CHCl_3$), HPLC t_R = 6.68 min (Zorbax/SiO_2/12% EtOAc/hexane/2 mL/min).

[*R*-(*R,*S**)]-β-[(2-Carboxyethyl)thio]-α-methoxy-2-(8-phenyloctyl)benzenepropanoic Acid (10).** To a magnetically stirred solution of **9** (150 mg, 0.3 mmol) in methanol (15 mL) at room temperature was added a 10% sodium hydroxide solution (0.4 mL, 1 mmol). After 18 h, the reaction was concentrated and residue was acidified with cold 3 N hydrochloric acid solution to pH 3, and extracted with diethyl ether. The combined extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to give the desired product (118 mg, oil, 83% yield) after flash chromatography (SiO_2/30% EtOAc/hexane/0.5% formic acid): ^1H NMR ($CDCl_3$) δ 1.2–1.75 (m, 12 H), 2.5–2.8 (m, 8 H), 3.30 (s, 3 H), 4.06 (d, J = 8.2 Hz, 1 H), 4.45 (d, J = 8.2 Hz, 1 H), 7.1–7.3 (m, 8 H), 7.35–7.57 (m, 1 H); $[\alpha]^{22}_D$ = −28.5° (c = 1, $CHCl_3$), HPLC t_R = 6.44 min (Dynamax/SiO_2/30% EtOAc/hexane/0.5% formic acid/2 mL/min). Anal. Calcd for $C_{27}H_{36}O_5S \cdot {}^1/_2H_2O$: C, 67.33; H, 7.74. Found: C, 67.51; H, 7.62.

[4*R*-[3(2*S,3*S**),4α,5α]]-Methyl 2-[[2-Methoxy-3-(4-methyl-2-oxo-5-phenyl-3-oxazolidinyl)-3-oxo-1-[2-(8-phenyloctyl)phenyl]propyl]thio]propanoate (11).** To a magnetically stirred, cooled (0 °C) solution of **5** (1.5 g, 2.76 mmol) and methyl 3-mercaptopropionate (3 mL, 25 mmol) was added trifluoroacetic acid (100 mL). After 18 h, the reaction was concentrated and residue taken up in diethyl ether (350 mL). The organic phase was washed with cold 5% sodium hydroxide solution (75 mL), water (75 mL), and saturated sodium chloride solution (75 mL), dried ($MgSO_4$), and concentrated to give **11** (1.25 g, oil, 70% yield) after flash chromatography (SiO_2/10% EtOAc/hexane): ^1H NMR ($CDCl_3$) δ 0.8 (d, J = 6.0 Hz, 3 H), 1.2–1.7 (m, 12 H), 2.5–3.2 (m, 8 H), 3.62 (s, 3 H), 3.95 (quintet, J = 6.0 Hz, 1 H), 4.45 (d, J = 9.0 Hz, 1 H), 4.67 (d, J = 6.0 Hz, 1 H), 5.7 (d, J = 9.0 Hz, 1 H), 7.1–7.6 (m, 14 H).

[*S*-(*R,*R**)]-Methyl α-Methoxy-β-[(3-methoxy-3-oxopropyl)thio]-2-(8-phenyloctyl)benzenepropanoate (12).** To a magnetically stirred, cooled (0 °C) solution of **11** (1.2 g, 1.86 mmol) in methanol (50 mL) was added sodium methylate (0.11 g, 2 mmol). After 20 min, the reaction was evaporated under reduced pressure. The residue was taken up in diethyl ether, washed with cold saturated ammonium chloride solution, dried ($MgSO_4$), and concentrated to give a residue, which was triturated with hexane to remove oxazolidinone **2** and the filtrate was concentrated. The desired product **12** (0.45 g, oil, 47% yield) was obtained after flash chromatography (SiO_2/15% EtOAc/hexane): ^1H NMR ($CDCl_3$) δ 1.25–1.80 (m, 12 H), 2.4–2.95 (m, 8 H), 3.4 (s, 3 H), 3.54 (s, 3 H), 3.61 (s, 3 H), 4.1 (d, J = 6.0 Hz, 1 H), 4.51 (d, J = 6.0 Hz, 1 H), 7.1–7.3 (m, 8 H), 7.35–7.55 (m, 1 H); $[\alpha]^{22}_D$ = +72.6° (c = 0.7, $CHCl_3$), HPLC t_R = 6.35 min (Zorbax/SiO_2/12% EtOAc/hexane/2 mL/min).

[*S*-(*R,*R**)]-β-[(2-Carboxyethyl)thio]-α-methoxy-2-(8-phenyloctyl)benzenepropanoic Acid (13).** To a magnetically stirred solution of **12** (0.3 g, 0.6 mmol) in methanol (30 mL) was added 10% sodium hydroxide solution (0.8 mL, 2 mmol). After 18 h, the reaction was concentrated and residue was acidified with cold 3 N hydrochloric acid to pH 3 and then taken up in diethyl ether. The organic phase was washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to give the desired product (195 mg, 69% yield): ^1H NMR ($CDCl_3$) δ 1.2–1.8 nm, 12 H), 2.45–2.85 (m, 8 H), 3.38 (s, 3 H), 4.0 (d, J = 3.0 Hz, 1 H), 4.75 (d, J = 3.0 Hz, 1 H), 7.1–7.35 (m, 8 H), 7.7–7.9 (m, 1 H); MS, m/e (DCI, NH_3) 472; $[\alpha]^{22}_D$ = +73.9° (c = 1, $CHCl_3$), HPLC t_R = 5.93 min (Dynamax/SiO_2/30% EtOAc/hexane/0.5% formic acid/2 mL/min). Anal. Calcd for $C_{27}H_{36}O_5S \cdot {}^1/_8H_2O$: C, 68.29; H, 7.69. Found: C, 68.17; H, 7.72.

(*R,*S**)-β-[(2-Carboxyethyl)thio]-α-methoxy-2-(8-phenyloctyl)benzenepropanoic Acid (10a) and (*R**,*R**)-β-[(2-Carboxyethyl)thio]-α-methoxy-2-(8-phenyloctyl)-benzenepropanoic Acid (13b).** To a magnetically stirred solution of methyl mercaptopropanoate (0.5 mL, 4.5 mmol) in TFA (100 mL) at 0 °C was added a mixture of **6a** and **6b** (2.0 g, 5.0 mmol). After 18 h at room temperature, the reaction mixture was concentrated and residue was concentrated to give a mixture of diesters **9a** and **9b** (2.0 g, oil, 80% yield) after flash chromatography. To a magnetically stirred solution of **9a** and **9b** (0.58 g, 1.1 mmol) in methanol (15 mL) at room temperature was added a 10% sodium hydroxide solution (1.5 mL, 3.4 mmol). After 18 h, the reaction was concentrated and the residue was acidified

with a cold 3 N hydrochloric acid solution to pH 3 and extracted with diethyl ether. The combined extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to give a mixture of diastereomers **10a** and **13b** (0.3 g, oil, 55% yield), which were separated by HPLC (Perkin-Elmer SiO_2/23% EtOAc/hexane/5% formic acid/20 mL/min/at 260 nm). **10a** (0.137 g): ^1H NMR ($CDCl_3$) δ 1.2–1.75 (m, 12 H), 2.5–2.8 (m, 8 H), 3.30 ns, 3 H), 4.06 (d, J = 8.2 Hz, 1 H), 4.45 (d, J = 8.2 Hz, 1 H), 7.1–7.3 (m, 8 H), 7.35–7.57 (m, 1 H); MS, m/e (DCI, NH_3) 472; HPLC t_R = 6.44 min (Dynamax/SiO_2/30% EtOAc/hexane/0.5% formic acid/2 mL/min). Anal. Calcd for $C_{27}H_{36}O_5S \cdot {}^1/_8H_2O$: C, 68.29; H, 7.69. Found: C, 68.17; H, 7.63. **13b** (0.154 g): ^1H NMR ($CDCl_3$) δ 1.2–1.8 (m, 12 H), 2.45–2.85 (m, 8 H), 3.38 (s, 3 H) 4.0 (d, J = 3.0 Hz, 1 H), 4.75 (d, J = 3.0 Hz, 1 H), 7.1–7.35 (m, 8 H), 7.7–7.9 (m, 1 H); HPLC t_R = 5.93 min (Dynamax/SiO_2/30% EtOAc/hexane/0.5% formic acid/2 mL/min). Anal. Calcd for $C_{27}H_{36}O_5S \cdot {}^1/_2H_2O$: C, 67.33; H, 7.53. Found: C, 68.17; H, 7.54.

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Supplementary Material Available: ^1H NMR spectra of compounds **2**, **3**, and **5–13** (15 pages). Ordering information is given on any current masthead page.

Limalongine, a Modified Hasubanan Type Alkaloid, and Clolimalongine, Its Chlorinated Derivative

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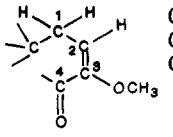
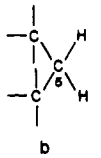
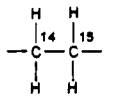
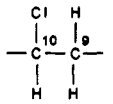
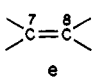
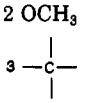
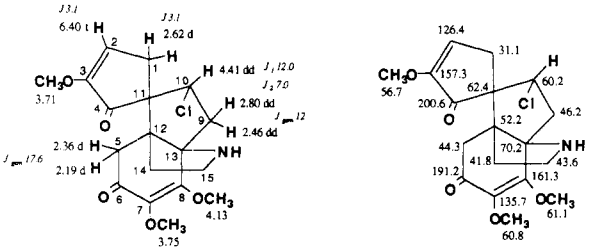
The hasubanan alkaloids are a small group of about 30 compounds, found mainly in *Stephania* species.[1,2] In this investigation, two new alkaloids related to this structural type have been obtained from *Limacia oblonga* (Miers) Hook. f. & Thoms. (Menispermaceae). (+)-Clolimalongine (1) and (+)-limalongine (2) differ from each other only by the presence of a chlorine atom in the first compound.

The UV spectra of both species are simple and show a maximum at 265 nm. The IR spectra indicate the presence of two carbonyls (1715, 1660 cm^{-1}). The formula $C_{18}H_{22}NO_5Cl$ of (+)-clolimalongine (1) is deduced from the mass spectrum, which has a molecular ion at m/z 367 and a base peak at m/z 195. The m/z 369 ion, corresponding to $[M + 2]^+$, has one third of the intensity of the molecular ion. This isotopic pattern is characteristic of the presence of a chlorine atom. The high-resolution mass spectrum confirms this conclusion (Experimental Section).

Table I. Structural Components of (+)-Clolimalongine (1)

structural fragments	^1H NMR: δ, ppm	^{13}C NMR: δ, ppm
 a	CH_2-1: 2.62 (d, 2 H, J = 3.1 Hz) CH-2: 6.40 (t, 1 H, J = 3.1 Hz) OCH_3: 3.71 (s)	C-1: 31.1 C-2: 126.4 C-3: 157.3 C-4: 191.2 OCH_3: 56.7
 b	2.19 (d, 1 H, J = 17.6 Hz), 2.36 (d, 1 H, J = 17.6 Hz)	C-5: 44.3
 c	CH_2-14: 2.85 (ddd, 1 H, J = 11, 12, 4 Hz), 3.05 (dd, 1 H, J = 11, 7 Hz) CH_2-15: 1.97 (ddd, 1 H, J = 12, 12, 7 Hz), 1.61 (dd, 1 H, J = 12, 4 Hz)	C-14: 43.6 C-15: 41.8
 d	CH-10; 4.41 (dd, 1 H, J = 11.9, 7 Hz) CH_2-9: 2.80 (dd, 1 H, J_{gem} = 12, J = 11.9 Hz), 2.46 (dd, 1 H, J_{gem} = 12, J = 7 Hz)	C-10: 60.2 C-9: 46.2
 e		C-7: 135.7 C-8: 161.3
2 OCH_3	4.13, 3.75	61.1, 60.8
		52.2, 62.4, 70.2
		200.6

The ^1H NMR spectrum of (+)-clolimalongine incorporates three methoxyl singlets and is summarized in the accompanying drawing of 1. Particularly important is the fact that no signal due to an aromatic proton is present, while the most downfield signal is a triplet at δ 6.40 (J = 3.1 Hz). The signals of other protons appear between δ 1.60 and 4.41 ppm. A complete homodecoupling study of the ^1H NMR spectrum, and ^{13}C NMR spectrum complemented by a ^1H–^{13}C direct correlation, led to the determination of the various structural components of the molecule presented in Table I. The triplet at δ 6.40 is due to the C-2 vinylic proton, and the two C-1 methylene protons have the same δ value.



(+)-clolimalongine (1)

The results are in agreement with a structural network closely related to a hasubanan or morphinan skeleton.

(1) Inubushi, Y.; Ibuka, T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1977; Vol. 16, pp 394–430.
(2) Matsui, M.; Yamamura, Y.; Takebayashi, T.; Iwaki, K.; Takami, Y.; Kunitake, K.; Koga, F.; Urasaki, S.; Watanabe, Y. *J. Nat. Prod.* **1984**, *47*, 858.

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