methane was added 0.1 mL of trifluoroacetic acid. The mixture was stirred for 1 h at room temperature, diluted with 30 mL of dichloromethane, and washed with 20 mL of saturated aqueous sodium bicarbonate. The aqueous wash was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the residue was chromatography over 4 g of silica gel (ethyl acetate–methanol, 10:1) to give 18 mg (78%) of **3** as a white solid: mp 62–68 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (ddd, J = 15.0, 4.8, 2.3 Hz, 1 H, $C_{10}H$), 1.81 (dd, J = 14.4, 3.0 Hz, 1 H, C_4H), 1.84 (dt, J = 15.0, 3.3 Hz, 1 H, $C_{10}H$), 2.05 (br s, 2 H, $C_{4a}H$ and C_9H), 2.10 (dqu, J = 14.4, 2.3 Hz, 1 H, C_4H), 2.26 (br s, 1 H, $C_{8a}H$), 2.78 (s, 3 H, NCH_3), 3.42 (s, 3 H, OCH_3), 3.61 (br s, 1 H, C_8H), 3.68 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.78 (d, J = 11.7 Hz, 1 H, OC_1H), 3.89 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.95 (d, J = 11.7 Hz, 1 H, OC_1H), 4.0 (br s, 1 H, C_3H); ^{13}C NMR ($CDCl_3$) δ 24.5 (t), 27.4 (q, NCH_3), 31.0 (t), 32.5 (d), 43.2 (d), 44.1 (d), 57.2 (s, C_5), 59.7 (q, OCH_3), 60.8 (t, CH_2OMe), 66.4 (d, C_8), 67.5 (t, C_1), 68.6 (d, C_3), 177.8 (s, C_6); exact mass calcd for $C_{13}H_{19}NO_3$ m/e 237.1365, found 237.1347.

(1α,3aβ,4α,7aβ,8R*)-(±)-Ethyl 2,3,3a,4,5,7a-Hexahydro-6-methoxy-3a-(methoxymethyl)-2-methyl-3-oxo-1,4-methano-1H-isoindole-8-acetate (44). A mixture of 24 mg (0.080 mmol) of the ketone **39** and 300 mg (1.58 mmol) of *p*-toluenesulfonic acid in 4 mL of trimethyl orthoformate and 1 mL of methanol was warmed at reflux for 60 h. The resulting solution was concentrated in vacuo. The residue was diluted with 20 mL of dichloromethane and washed with three 10-mL portions of saturated sodium bicarbonate followed by 10 mL of brine. The organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed over 2 g of silica gel (ethyl acetate) to yield 19 mg (72%) of **44** as a clear oil: IR (CH_2Cl_2) 1730, 1690, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H, OCH_3), 1.72 (qu, J = 2.6 Hz, 1 H, $C_{7a}H$), 2.20 (dd, J = 17, 2.7 Hz, 1 H, C_7H), 2.31 (m, 2 H, CH_2CO_2Et), 2.41 (dd, J = 17.5, 2.3 Hz, 1 H, C_7H), 2.50 (m, 1 H, C_8H), 2.70 (dt, J = 6.8, 1.8 Hz, 1 H, C_4H), 2.89 (s, 3 H, NCH_3), 3.39 (s, 3 H, OCH_3), 3.47 (d, J = 9.5 Hz, 1 H, CH_2OMe), 3.53 (s, 3 H, $=COCH_3$), 3.68 (t, J = 2.3 Hz, 1 H, C_1H), 3.69 (d, J = 9.5 Hz, 1 H, CH_2OMe), 4.13 (q, J = 7 Hz, 2 H, OCH_2), 4.53 (d, J = 6.8 Hz, 1 H, C_5H); exact mass calcd for $C_{17}H_{25}NO_5$ m/e 323.1734, found 323.1724.

Acknowledgment. We thank the National Institutes of Health for their generous support of this research (Grant GM-27647). One of us (D.J.H.) thanks Professor Leo A. Paquette for a stimulating discussion.

Supplementary Material Available: Experimental procedures for the preparation of compounds i–iv and crystallographic details for compound **39** (9 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Butenolide and Tetronic Acid Analogues of Thiolactomycin[1,2]

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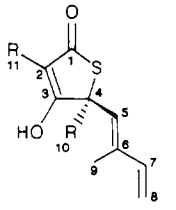
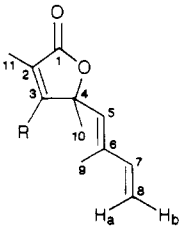
A synthetic route to the three lactone analogues **2a–c** of the interesting antibiotic thiolactomycin (**1a**) is described. The synthetic strategy used is flexible in that it allows in principle for variation in the nature of the substituents introduced at C-2, C-3, or C-4 of the 2-butenolide nucleus. Of the three synthetic analogues of thiolactomycin that we describe, **2a** lacks the acidic C-3 hydroxyl group while **2b** and **2c** are tetronic acid analogues of the antibiotic.

Introduction

In 1982, the structure and antibiotic properties of thiolactomycin (**1a**), isolated from a soil sample containing an organism of the genus *Nocardia*, were first reported by Oishi et al.[3] This is the first example of a naturally occurring thiolactone to exhibit antibiotic activity. The compound displayed only moderate in vitro activity against a broad spectrum of pathogens, including Gram-positive cocci and enteric bacteria, but revealed a unique synergistic effect, in combination with β-lactam antibiotics, in inhibiting inducible β-lactamase-producing microorganisms.[4] Thiolactomycin was also found to display effective in vivo activity against *S. marcescens* and *K. pneumoniae* in mice and showed only moderate toxicity.[5] More recently, interest in the biological activity of thiolactomycin has focused on its inhibition of fatty acid synthetases.[6] The isolation and structure determination of the closely related antibiotic thiotetromycin (**1b**) have been reported by Omura et al.[7] In contrast to thiolactomycin, the absolute configuration of **1b** does not appear to have been determined.



1a, R = CH_3
b, R = CH_2CH_3



2a, R = H
b, R = OMe
c, R = OH

Despite the obvious interest in these compounds, only one synthesis of racemic thiolactomycin has been reported

(1) The formal name is (4*S*)-(2*E*,5*E*)-2,4,6-trimethyl-3-hydroxy-2,5,7-octatriene-4-thiolide.

(2) (a) Abstracted in part from the Ph.D. Thesis of M. J. Drewery, University of Toronto, 1988. (b) These results have been presented in part at the 3rd Chemical Congress of North America (Abstract Number ORG-471), Toronto, Ontario, Canada, June 5–10, 1988.

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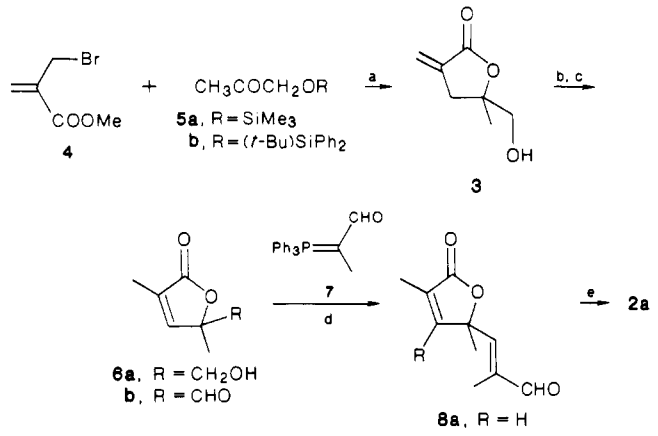
0022-3263/89/1954-0290$01.50/0

Scheme I[a]



[a] (a) Zn^0, THF, 45–60 °C, 36 h (63%); (b) $RhCl_3 \cdot 3H_2O$, 95% EtOH, reflux (72%); (c) $(COCl)_2$, DMSO, CH_2Cl_2, −65 °C, 1.5 h; Et_3N, −65 °C → 25 °C (22%); (d) THF, reflux, 36 h (75%); (e) $CH_3PPh_3^+I^-$, THF, n-C_4H_9Li (hexane), 25 °C, 18 h (80%).

to date,[8] while Omura and co-workers[9] have described the synthesis of some thiotetromycin analogues. A recent report by Thomas and co-workers[10] provides an elegant general procedure for the asymmetric synthesis of thiotetronic acids. We felt that it would be of interest to attempt to synthesize close structural analogues of thiolactomycin with a similar substitution pattern but with a lactone unit replacing the thiolactone moiety of the natural product. The compounds chosen for our study were the 2-butenolide analogue **2a**, the tetronic acid **2c**, and its methyl ester **2b**. The general field of γ-butyrolactone synthesis has been reviewed recently,[11] and there are also reviews available of the synthesis of tetronic acids (3-hydroxy-2-butenolides),[12] as well as numerous recent reports.[13] Several methods for the interconversion of lactones and thiolactones have been reported previously.[14]

Results and Discussion

Our approach to the synthesis of **2a** (Scheme I) lay in first synthesizing the appropriately substituted α-methylenebutyrolactone **3** by adapting the general method of Schmidt et al.[15] We were able to take advantage of the improved procedure of Charlton and co-workers[16] for the synthesis of methyl α-(bromomethyl)acrylate **4**, the reaction of which with zinc and the silylated acetol **5a**[17] afforded **3** in 63% yield.[18] It will be noted that the (trimethylsilyl)oxy group is removed during the workup. Compound **3** is quite stable as the γ-lactone, and the potential alternative δ-lactone is never observed, on the basis of the IR evidence. When the same reaction was carried out with [(*tert*-butyldimethylsilyl)oxy]acetone or [(*tert*-butyldiphenylsilyl)oxy]acetone, these silyl groups remained intact.

The ^1H NMR spectrum (acetone-d_6) of **3** displayed a singlet (3 H) at δ 0.99 due to the methyl group. The vinylic and allylic protons make up a AA′XX′ system, which gives rise to an interesting set of peaks.[19a] The allylic methylene protons are diastereotopic and display both geminal coupling (17 Hz) and identical allylic coupling (J = 2.6 Hz) with each of the vinylic protons. Consequently, a characteristic doublet of triplets (J = 2.6, 17 Hz) is observed for each allylic proton, at δ 2.2 and 2.7, respectively. The vinylic protons apparently do not couple with each other ($J_{XX'}$ = 0). The vinylic proton triplet at δ 5.6 can be assigned to the proton cis to the carbonyl group because the anisotropic effect of the latter would be expected to shift it farther downfield.[19b,c] Another interesting aspect of the ^1H NMR spectrum of **3** is that the hydroxymethyl group exhibits a coupling between the methylene protons and the hydroxyl proton that is concentration dependent. When the ^1H NMR spectrum was run at higher concentrations, no coupling could be observed, but at lower concentrations a triplet (J = 5 Hz) due to the hydroxyl proton appeared at δ 3.9 and a doublet (J = 5 Hz) due to the methylene protons was observed at δ 3.15.

Rearrangement of the α-methylene lactone **3** to the endocyclic butenolide **6a** was readily achieved, in 72% yield, with use of rhodium(III) chloride as the catalyst.[20] While rhodium chloride has frequently found application for the rearrangement of double bonds, we believe this to be the first successful application to the rearrangement of an α-methylene lactone. The reaction could be followed quite easily by ^1H NMR spectroscopy. The disappearance of the vinylic protons of **3** at δ 5.15 and 5.6, and the allylic protons at 2.2 and 2.7, along with the appearance of a new allylic methyl doublet at 1.86 and a vinylic quartet at 6.93, revealed the progress of the reaction. When this isomerization was carried out with the *tert*-butyldimethylsilyl derivative of **3**, the silyl ether was cleaved during the reaction, yielding **6a** and the corresponding disiloxane, $(t\text{-}BuMe_2Si)_2O$. Partial desilylation occurred even when the *tert*-butyldiphenylsilyl derivative was isomerized under these conditions.

Oxidation of **6a** to the corresponding aldehyde turned out to be surprisingly difficult, due perhaps to the presence of a fully substituted α-carbon atom, or to the potential for ready β-elimination of the carboxylate leaving group,

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(18) Better yields were obtained when zinc activated by the procedure of Cava and co-workers was employed in this reaction: Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992.
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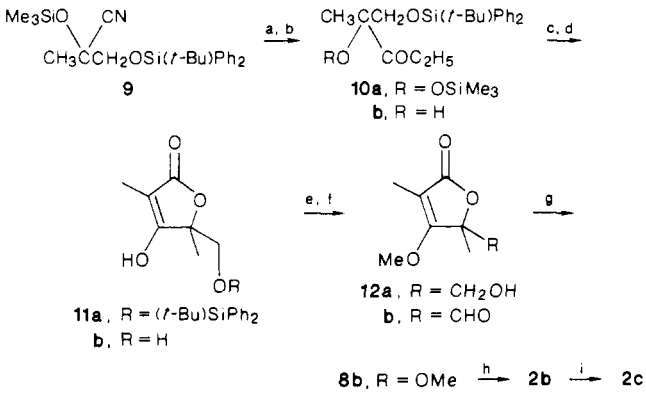
Scheme II[a]



[a] (a) EtMgBr (ether), ether–benzene, 0 °C → 25 °C, 48 h (95%); (b) acetic acid–THF–water (3:1:1), 25 °C, 48 h (95%); (c) LDA, THF, Im_2CO, −78 °C (5 h) → 25 °C (16 h) (41%); (d) 2 M aqueous NaOH, 60 °C, 24 h (82%); (e) 40% aqueous $(n\text{-}C_4H_9)_4N^+OH^-$, 25 °C, 1 h (96%); $(CH_3)_2SO_4$, CH_2Cl_2, 35–40 °C, 60 h (80%); (f) $(COCl)_2$, DMSO, CH_2Cl_2, −65 °C, 1 h; Et_3N, −65 °C → 25 °C (60%); (g) 7, THF, reflux, 48 h (65%); (h) $CH_3PPh_3^+I^-$, THF, $n\text{-}C_4H_9Li$ (hexane), 25 °C, 18 h (75%); (i) 0.5 M $n\text{-}C_3H_7SLi$ (hexamethylphosphoramide), HMPA, 25 °C, 10 min (80%).

or both. After numerous attempts, employing a wide variety of oxidants, the conversion of **6a** to **6b** was achieved in 22% yield by using a Swern-type procedure.[21]

Construction of the C-4 side chain was achieved in two steps, with use of the useful α-formylethylidenephosphorane reagent **7** developed by Schlessinger[22] to first produce the chain-extended aldehyde **8a**, followed by standard Wittig methylenation to form **2a**, in an overall yield of 60% (Scheme I).

The ^1H NMR spectrum ($CDCl_3$) of **2a** displays five vinyl protons. The β-vinyl proton of the 2-butenolide unit gives a quartet (J = 2 Hz) at δ 7.05. The rest of the vinyl protons were assigned to the butadiene system. The proton attached to C-7 gives rise to a doublet of doublets at δ 6.19 (J_{cis} = 10 Hz, J_{trans} = 17 Hz), and the proton at C-5 gives a broad singlet at 5.54. The protons at C-8 give a pair of doublets. The H_b proton leads to a doublet at δ 5.05 (J_{cis} = 10 Hz) while the H_a proton gives a doublet at 5.2 (J_{trans} = 17 Hz). The chemical shifts and splitting pattern fit the values expected for a butadiene system with this type of substitution and the *E* geometry.[23] The pattern observed in **2a** is almost the same as that seen for thiolactomycin itself.[3b] This in turn has confirmed that the precursor **8a** also possesses the desired *E* geometry in the α,β-unsaturated aldehyde unit. The remaining ^1H NMR and IR data, along with the mass spectrum and elemental analysis, provided conclusive proof that we had successfully synthesized 2,4-dimethyl-4-(2′-methyl-1′(*E*),3′-butadienyl)-2-butenolide, the 3-deoxy lactone analogue of (±)-thiolactomycin.

A quite different strategy was employed for the synthesis of **2b** and **2c** (Scheme II), based upon incorporation of the C-3 oxygenated carbon atom at an early stage although, as in the synthesis above, the substituted C-4 carbon in the tetronic acid nucleus is again derived from a simple acetone synthon. Acetol (hydroxyacetone), protected as its *tert*-butyldiphenylsilyl ether,[17] was readily converted into the *O*-silyl cyanohydrin **9** in 95% yield.[24] An attempt to convert **9** into the tetronic acid **11a** directly, by reaction with the Reformatsky reagent derived from ethyl 2-bromopropanoate by the method of Rasmussen and coworkers,[13k] was completely without success. Grignard addition of ethylmagnesium bromide,[25] followed by standard workup, however, gave a mixture of **10a** and **10b** in almost quantitative yield. Mild acidic hydrolysis completed the conversion of **10a** into **10b**. The ^1H NMR and IR spectra (see the Experimental Section) clearly showed **10b** to be the desired α-hydroxy ketone.

Generation of the dianion of **10b** with at least 2 equiv of LDA, followed by reaction of the dianion with 1,1′-carbonyldiimidazole according to the procedure of Smith and co-workers,[26] afforded the tetronic acid **11a** in 41% yield. Alkaline hydrolysis was required for desilylation[27] to form the corresponding primary alcohol **11b** in excellent yield.

Attempts to oxidize the primary alcohol group in **11b** itself to the corresponding aldehyde having proved fruitless, we decided to protect the tetronic acid as its methyl ester before carrying out this oxidation. Since direct methylation of tetronic acids is known[29] to give rise to mixtures of the isomeric (C-1 and C-3) methoxy compounds, we proceeded via the tetrabutylammonium salt,[29] followed by treatment of the crude salt with dimethyl sulfate, and obtained a single product **12a** in 80% yield. The IR spectrum of this methyl tetronate revealed a carbonyl stretching band at 1716 cm^{-1}. This value is considerably lower than the range (1745–1780 cm^{-1}) usually observed for such 4-alkoxy-5*H*-furan-2-ones.[29] Intermolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen is a possible explanation for this surprisingly low value (vide infra).

To our surprise, the Swern oxidation[21] of **12a** proceeded readily to give **12b** in 60% yield, in marked contrast to our experience with the analogous conversion of **6a** to **6b**. The explanation for the apparently beneficial effect of the C-3 methoxyl group is not obvious, but is probably linked to its electron-releasing property. The ^1H NMR and IR evidence strongly supports the formation of **12b**, but it is noteworthy that in the conversion of **12a** to **12b** the observed lactone carbonyl stretching frequency changed from 1716 to 1764 cm^{-1}. This lends support to the argument above that the low carbonyl stretching value observed for **12a** may be caused by intermolecular hydrogen bonding.

With the key aldehyde intermediate **12a** in hand, the side chain was constructed in two steps via **8b**, as discussed in the synthesis of **2a** above, to furnish the methyl tetronate **2b** in about 50% overall yield (Scheme II). The IR and ^1H NMR spectra of **2b** were fully in accord with expectation. As discussed in detail above for the simpler analogue **2a**, the ^1H NMR characteristics (chemical shifts and coupling constants) for the side-chain protons in **2b** confirmed the presence of a single isomer and were virtually identical with those reported for thiolactomycin itself,[3b] thus establishing that the geometrical isomer shown for **2b** (and hence **8b**) is the correct one. The combined spectral data, along with the elemental analysis of **2b**, provide conclusive evidence for the successful synthesis of the methyl tetronate analogue of (±)-thiolactomycin.

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The conversion of **2b** into the corresponding tetronic acid **2c** was not expected to be trivial, based upon literature precedents.[13f,30] After several unsuccessful attempts using dilute acid hydrolysis and trimethylsilyl iodide promoted demethylation,[13i,31] this conversion was finally achieved in 80% yield, with use of lithium 1-propanethiolate under anhydrous conditions,[32] with brief reaction times. The IR and ^{1}H NMR spectra of the tetronic acid so obtained, along with the high-resolution mass spectrum, confirmed that **2c** is 2,4-dimethyl-4-(2′-methyl-1′(*E*),3′-butadienyl)tetronic acid, the tetronic acid analogue of (±)-thiolactomycin.

The syntheses described in this account, especially the synthesis of the tetronic acid analogues **2b,c**, appear to offer a convenient route to a wide variety of potentially interesting lactone analogues of thiolactomycin. For example, the use of the readily available 1-hydroxy-2-butanone in place of acetol, and replacement of ethyl- by *n*-propylmagnesium bromide, would appear to offer a route to the corresponding thiotetromycin analogues. Further, the mode of construction used for the side chain in **2b,c**, as well as in **2a**, via a reactive aldehyde intermediate, clearly allows for the introduction of a wide variety of side chains, not necessarily alkadienyl in nature, at C-4.

Experimental Section

The ^{1}H NMR spectra were obtained at 60 MHz. Column and flash chromatography were carried out on silica gel supplied by E. Merck (Darmstadt), with 70–230 and 230–400 mesh size, respectively. TLC (analytical and preparative) was carried out on silica gel supplied by E. Merck (Darmstadt). Melting points are uncorrected. The purity of titled compounds was shown to be ≥98% by ^{1}H NMR and TLC analyses.

Anhydrous reactions were performed in oven-dried glassware (140 °C, 6 h), which was then cooled under nitrogen. All syringes were oven-dried and cooled in a desiccator before use. Dichloromethane and ethyl formate were distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Dimethyl sulfoxide was fractionally distilled (discarding the first 20% of distillate), followed by sequential drying over 3-Å molecular sieves. Benzene, toluene, diethyl ether, and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl before use. Hexanes, diisopropylamine, triethylamine, pyridine, and hexamethylphosphoramide were stirred over calcium hydride (72 h) and distilled, followed by storage over 3-Å molecular sieves. 1-Propanethiol was distilled from magnesium turnings just before use.

1-[(Trimethylsilyl)oxy]-2-propanone (5a). (For analogue **5b**, see under preparation of compound **9**.) Chlorotrimethylsilane (38 mL, 0.3 mol) was added dropwise to a solution of acetol (18.5 mL, 0.27 mol), triethylamine (46 mL, 0.33 mol), and 4-(dimethylamino)pyridine (0.3 g, 2.45 mmol) in dichloromethane (150 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred overnight under nitrogen. Water (100 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with saturated ammonium chloride (150 mL) and dried ($MgSO_4$). Evaporation and distillation of the crude product (38.0 g) gave **5a** (31.0 g, 78%): bp 97 °C (30 Torr); IR (CCl_4) ν 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 2.08 (s, 3 H), 4.08 (s, 2 H); MS, *m/z* 141 (27), 131 (56), 103 (36), 75 (67), 73 (100).

4-(Hydroxymethyl)-4-methyl-2-methylenebutanolide (3). Methyl α-(bromomethyl)acrylate[16] (**4**) (42.9 g, 0.24 mol) in dry THF (120 mL) was added dropwise to a vigorously stirred mixture of **5a** (36.0 g, 0.25 mol), activated zinc[18] (19.0 g, 0.29 mol), and dry THF (50 mL) under nitrogen. Once the reaction had started, addition was adjusted so that the temperature did not rise above 60 °C. After addition was complete, the mixture was stirred for a further 36 h at 45–50 °C. It was then poured into ice-cold 3 M hydrochloric acid (300 mL). Extraction with dichloromethane (700 mL, 2 × 150 mL) and washing of the combined dichloromethane layers with saturated sodium chloride (500 mL) containing saturated sodium bicarbonate (20 mL), followed by saturated sodium chloride (500 mL), drying ($MgSO_4$), and evaporation, gave the crude lactone (28.0 g). Distillation afforded unreacted bromo ester **4** (7.0 g) and lactone **3** (18.0 g, 63%), bp 162 °C (0.8 Torr), which solidified slowly. The solid was washed with pentane and dried to give a white solid: mp 66–68 °C; IR (KBr) ν 3490–3400, 1760 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 0.99 (s, 3 H), 2.2 (dt, *J* = 2.6 and 17 Hz, 1 H), 2.7 (dt, *J* = 2.6 and 17 Hz, 1 H), 3.15 (d, *J* = 5 Hz, 2 H), 3.90 (t, *J* = 5 Hz, 1 H), 5.15 (t, *J* = 2.6 Hz, 1 H), 5.6 (t, *J* = 2.6 Hz, 1 H) (The signal at δ 3.90 disappeared upon shaking with D_2O and the doublet at δ 3.15 collapsed to a singlet.); MS, *m/z* 124 (6), 112 (7), 111 (86), 68 (8), 43 (100). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.09; H, 7.16.

2,4-Dimethyl-4-(hydroxymethyl)-2-butenolide (6a). Compound **3** (18.0 g, 0.13 mol) and rhodium(III) chloride trihydrate (400 mg, 1.5 mmol) were dissolved in 95% ethanol (200 mL). The solution was refluxed, and the reaction was monitored by ^{1}H NMR spectroscopy. After completion, the solvent was removed by evaporation. The residue was taken up in dichloromethane (150 mL), washed with saturated sodium chloride solution (100 mL), dried ($MgSO_4$), and evaporated to give the crude 2-butenolide (15.6 g). Kugelrohr distillation (oven temperature 155 °C at 0.15 Torr) gave pure **6a** (13.0 g, 72%). Washing the distilled product with pentane and drying gave a white solid: mp 54–56 °C; IR (KBr) ν 3430, 1730 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.2 (s, 3 H), 1.8 (d, *J* = 1.8 Hz, 3 H), 3.4 (s, 2 H), 3.68 (br s, 1 H), 6.85 (q, *J* = 1.8 Hz, 1 H) (The signal at δ 3.68 disappeared upon shaking with D_2O.); MS, *m/z* 112 (43), 111 (36), 99 (7), 69 (8) 43 (100). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.13; H, 7.15.

2,4-Dimethyl-4-formyl-2-butenolide (6b). A solution of oxalyl chloride (3.9 mL, 45.1 mmol) in dichloromethane (60 mL) was stirred and cooled to −78 °C as dimethyl sulfoxide (6.4 mL, 90.2 mmol) in dichloromethane (15 mL) was added, with the temperature maintained below −65 °C. Two minutes after addition was complete, 2,4-dimethyl-4-(hydroxymethyl)-2-butenolide (**6a**) (5.82 g, 41.0 mmol) in dichloromethane (25 mL) was added, with the temperature maintained below −65 °C. After the mixture was stirred for 1.5 h, triethylamine (28 mL, 0.2 mol) was added slowly, with the temperature maintained below −60 °C. The reaction was warmed to room temperature after addition was complete. Water (100 mL) was added, and the dichloromethane layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the organic layers were combined and dried ($MgSO_4$). Evaporation and Kugelrohr distillation (oven temperature 80 °C at 0.2 Torr) yielded the desired aldehyde **6b** (1.28 g, 22%): IR (CH_2Cl_2) ν 1771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.98 (d, *J* = 1.7 Hz, 3 H), 6.88 (q, *J* = 1.7 Hz, 1 H), 9.24 (s, 1 H); MS, *m/z* 111 (50), 69 (28), 57 (36), 43 (100).

2,4-Dimethyl-4-(2′-methyl-3′-oxo-1′(*E*)-propenyl)-2-butenolide (8a). Compound **6b** (0.4 g, 2.9 mmol) and phosphorane **7**[22] (1.36 g, 4.3 mmol) were mixed in anhydrous THF (15 mL). The mixture was degassed with three freeze–pump–thaw cycles and then refluxed under nitrogen for 36 h. The THF was removed under vacuum, and the residue was taken up in diethyl ether. The solid triphenylphosphine oxide was filtered off. The ether was removed under vacuum, and the residue was subjected to flash chromatography (ethyl acetate–hexane, 4:1), giving compound **8a** (0.38 g, 75%), which was further purified by Kugelrohr distillation (oven temperature 100 °C at 0.2 Torr): IR (CH_2Cl_2) ν 1763, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.86 (d, *J* = 1.5 Hz, 3 H), 1.93 (d, *J* = 1.7 Hz, 3 H), 6.39 (q, *J* = 1.5 Hz, 1 H), 7.09 (q, *J* = 1.7 Hz, 1 H), 9.34 (s, 1 H); MS, *m/z* 180 (10), 165 (9), 152 (18), 138 (27), 137 (41), 111 (52), 109 (100), 81 (56).

2,4-Dimethyl-4-(2′-methyl-1′(*E*),3′-butadienyl)-2-butenolide (2a). Methyltriphenylphosphonium iodide (1.0 g, 2.5 mmol) was suspended in anhydrous THF under nitrogen. A 2.5 M solution of *n*-butyllithium in hexanes (1.0 mL, 2.5 mmol) was added, and the solution was stirred for 2 h. Compound **8a** (0.3 g, 1.7 mmol) in anhydrous THF (5 mL) was then added slowly. After the

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mixture was stirred overnight, saturated aqueous ammonium chloride (25 mL) was added. Extraction with ethyl acetate (3 × 30 mL), drying ($MgSO_4$), and evaporation, followed by flash chromatography (ethyl acetate–hexane, 4:1) of the residue, yielded compound **2a** (0.24 g, 80%): bp 100 °C (0.2 Torr); IR (film) ν 1762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.90 (s, 3 H), 1.90 (d, J = 1.8 Hz, 3 H), 5.05 (d, J = 10 Hz, 1 H), 5.2 (d, J = 17 Hz, 1 H), 5.54 (br s, 1 H), 6.29 (dd, J = 10 and 17 Hz, 1 H), 7.05 (q, J = 1.8 Hz, 1 H); MS, m/z 178 (1), 163 (6), 107 (100), 91 (44), 79 (19). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 8.00.

3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methyl-2-[(trimethylsilyl)oxy]propanenitrile (9). A solution of acetol (24.9 mL, 0.36 mol), triethylamine (61 mL, 0.44 mol), and 4-(dimethylamino)pyridine (0.3 g, 2.45 mmol) in dichloromethane (150 mL) was treated with *tert*-butyldiphenylsilyl chloride (94 mL, 0.36 mol). The reaction mixture was stirred for 48 h under nitrogen. After this period, water (200 mL) was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (1 × 100 mL). The combined organic layers were washed with saturated ammonium chloride (200 mL) and dried ($MgSO_4$). Evaporation gave crude silyl ether **5b** (108 g, 96%). Trimethylsilyl cyanide (47 mL, 0.35 mol) was added to a mixture of this crude ketone (108 g, 0.35 mol) and freshly prepared potassium cyanide/18-crown-6 catalyst[24] (1.0 g) at 0 °C. After addition, the reaction mixture was stirred for 48 h at room temperature. Hexane (500 mL) was added, followed by filtration through Celite. The filtrate was washed with water (3 × 200 mL) and brine (400 mL) and dried ($MgSO_4$). Evaporation gave crude **9** (136.5 g, 95%): IR (CH_2Cl_2) ν 2900, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.20 (s, 9 H), 1.1 (s, 9 H), 1.60 (s, 3 H), 3.46 (d, J = 9.6 Hz, 1 H), 3.73 (d, J = 9.6 Hz, 1 H), 7.45 (m, 6 H), 7.6 (m, 4 H); MS, m/z 354 (31), 271 (100), 255 (92), 177 (34), 135 (28), 97 (35), 57 (85), 43 (58).

1-[(*tert*-Butyldiphenylsilyl)oxy]-2-hydroxy-2-methyl-3-pentanone (10b). A 3.0 M ethereal solution of ethylmagnesium bromide (140 mL, 0.42 mol) had the solvent removed under vacuum. Diethyl ether (35 mL, 0.33 mol) and benzene (200 mL) were added.[33] After the Grignard reagent was redissolved, the solution was cooled to 0 °C, followed by addition of the nitrile **9** (136.0 g, 0.33 mol) in benzene (125 mL). After being stirred at room temperature for 48 h, the reaction mixture was poured on to a mixture of ice (400 g) and concentrated sulfuric acid (50 mL). After the ice had melted, ether (400 mL) was added. The organic phase was separated and washed with 10% hydrochloric acid (400 mL) and brine (400 mL) and dried ($MgSO_4$). Evaporation gave the crude α-(trimethylsilyl)oxy ketone **10a** (137.7 g, 95%) with some **10b** present. The crude ketone was dissolved in a 3:1:1 solution of acetic acid, THF, and water (450 mL; 150 mL; 150 mL) and stirred for 48 h at room temperature. The solvents were removed under vacuum at 50–70 °C, and the residue was taken up in dichloromethane (300 mL). This was washed with 5% aqueous sodium bicarbonate (2 × 150 mL) and brine (2 × 150 mL) and dried ($MgSO_4$). Evaporation gave the α-hydroxy ketone **10b** (113 g, 95%). This compound could be used without further purification. A portion was distilled on the Kugelrohr apparatus (oven temperature 210–230 °C/0.2 Torr). Compound **10b** solidified and was recrystallized from hexane to give a white solid: mp 45–48 °C; IR (KBr) ν 3520–3480, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 1.1 (t, J = 7.8 Hz, 3 H), 1.23 (s, 3 H), 2.62 (q, J = 7.8 Hz, 2 H), 3.55 (d, J = 10 Hz, 1 H), 3.89 (d, J = 10 Hz, 1 H), 3.90 (s, 1 H), 7.38 (m, 6 H), 7.64 (m, 4 H) (The signal at δ 3.90 disappeared upon shaking in D_2O.); MS, m/z 313 (2), 271 (47), 235 (100), 199 (44), 135 (21), 57 (27).

2,4-Dimethyl-4-(hydroxymethyl)tetronic Acid (11b). Diisopropylamine (50 mL, 0.36 mol) was dissolved in anhydrous THF (200 mL), cooled to 0 °C, and placed under nitrogen. A 2.5 M solution of n-butyllithium in hexanes (135 mL, 0.34 mol) was added dropwise, followed by stirring for 0.5 h at 0 °C. After the mixture was cooled to −78 °C, the α-hydroxy ketone **10b** (50.0 g, 0.14 mol) in anhydrous THF (100 mL) was added dropwise. After the mixture was stirred at −78 °C for 3 h, 1,1′-carbonyldiimidazole (35.0 g, 0.22 mol) in anhydrous THF (800 mL) was added. The mixture was stirred for 5 h at −78 °C, followed by stirring overnight at room temperature. Sulfuric acid (3 M) (300 mL) was then added slowly, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were evaporated, and the residue was taken up in ether (200 mL) and extracted with 1 M sodium hydroxide (3 × 100 mL). The combined aqueous extracts were acidified to pH 2 and reextracted with ether (3 × 100 mL). The ether solution was washed with brine (1 × 100 mL), dried ($MgSO_4$), and evaporated to give the tetronic acid **11a** (22 g, 41%): mp 135–140 °C; IR ($CHCl_3$) ν 3420–3380, 1755, 1700, 1680 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.02 (s, 9 H), 1.35 (s, 3 H), 1.74 (s, 3 H), 3.85 (s, 2 H), 7.42 (m, 6 H), 7.65 (m, 4 H).

A solution of compound **11a** (30.0 g, 0.075 mol) in 2 M aqueous sodium hydroxide (500 mL) was heated at 60 °C for 24 h, cooled, washed with hexane (400 mL), and acidified to pH 2. Extraction with ethyl acetate (2 × 400 mL), drying ($MgSO_4$), and evaporation gave crude **11a** (2.0 g, 6.7%). The aqueous layer was then continuously extracted for 72 h with ethyl acetate. Removal of the solvent gave the desired tetronic acid **11b** (9.7 g, 82%). The yellow solid was washed with dichloromethane to give a white solid: mp 177–179 °C; IR (KBr) ν 3200–2900, 1738, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.27 (s, 3 H), 1.60 (s, 3 H), 3.47 (s, 2 H), 4.43 (br s, 1 H), 11.46 (br s, 1 H) (The signals at δ 4.43 and 11.46 disappeared upon shaking with D_2O.); MS, m/z 158 (8), 141 (42), 128 (66), 127 (64), 115 (13), 100 (22), 83 (22), 56 (100). Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.10; H, 6.41.

Methyl 2,4-Dimethyl-4-(hydroxymethyl)tetronate (12a). Compound **11b** (6.0 g, 0.038 mol) was added to 25 g of a 40% (w/w) aqueous solution of tetrabutylammonium hydroxide (0.038 mol). Water (25 mL) was added to help dissolve the tetronic acid. The reaction mixture was stirred for 1 h, and water was removed under vacuum. The residue was taken up in ethyl acetate and dried ($MgSO_4$). Evaporation gave the solid tetrabutylammonium tetronate salt (14.6 g, 96%). The solid was taken up in dry dichloromethane (150 mL), and freshly distilled dimethyl sulfate (4 mL, 0.042 mol) was added, followed by stirring for 60 h at 35–40 °C. The dichloromethane was evaporated, and the residue was taken up in water (150 mL). This was continuously extracted with diethyl ether for 48 h after the pH was adjusted to pH 8. The ether was evaporated, giving the desired methyl tetronate **12a** (5.2 g, 80%) as a white solid: mp 117–119 °C; IR (KBr) ν 3350, 1716, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 2.0 (s, 3 H), 2.43 (t, J = 7 Hz, 1 H), 3.65 (d, J = 7 Hz, 2 H), 4.14 (s, 3 H) (The signal at δ 2.43 disappeared, while the doublet (J = 7 Hz) at 3.65 collapsed to a singlet, upon shaking with D_2O.); MS, m/z 172 (9), 141 (100), 129 (9), 99 (16), 83 (13), 59 (13), 43 (64).

Methyl 2,4-Dimethyl-4-formyltetronate (12b). Compound **12b** was obtained in 60% yield as an oil, bp 115 °C (0.2 Torr), by the method described above for **6b**: IR (CH_2Cl_2) ν 1765, 1745, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3 H), 2.0 (s, 3 H), 4.14 (s, 3 H), 9.18 (s, 1 H); MS, m/z 171 (16), 141 (100), 99 (13), 83 (10), 43 (29).

Methyl 2,4-Dimethyl-4-(2′-methyl-3′-oxo-1′(*E*)-propenyl)tetronate (8b). Compound **8b** was obtained in 65% yield by the procedure employed for the preparation of **8a**, but with a longer reflux period (48 h), with final purification by Kugelrohr distillation (oven temperature 110 °C at 0.2 Torr): IR (film) ν 1758, 1693, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 1.90 (d, J = 1.5 Hz, 3 H), 2.01 (s, 3 H), 4.14 (s, 3 H), 6.35 (q, J = 1.5 Hz, 1 H), 9.30 (s, 1 H); MS, m/z 210 (20), 195 (28), 182 (36), 181 (33), 167 (29), 166 (24), 141 (39), 139 (66), 97 (26), 83 (83), 43 (100). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.83; H, 6.73. Found: C, 62.62; H, 6.78.

Methyl 2,4-Dimethyl-4-(2′-methyl-1′(*E*),3′-butadienyl)tetronate (2b). Compound **2b**, bp 110 °C (0.2 Torr), was obtained in 75% yield by the method already described for **2a**: IR (film) ν 1755, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.92 (br s, 3 H), 2.0 (s, 3 H), 4.14 (s, 3 H), 5.15 (d, J = 10 Hz, 1 H), 5.21 (d, J = 17 Hz, 1 H), 5.5 (br s, 1 H), 6.29 (dd, J = 10 and 17 Hz, 1 H); MS, m/z 208 (8), 141 (35), 109 (17), 99 (39), 83 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.20; H, 7.76. Found: C, 69.18; H, 7.84.

2,4-Dimethyl-4-(2′-methyl-1′(*E*),3′-butadienyl)tetronic Acid (2c). A 0.5 M solution of lithium 1-propanethiolate in hexamethylphosphoramide was prepared according to the procedure developed by Ireland and Thompson.[32] Dry 1-propanethiol

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(0.65 mL, 7.2 mmol), freshly distilled from magnesium turnings, was dissolved in hexane (5 mL) under nitrogen, cooled to 0 °C, and treated with a 2.6 M solution of *n*-butyllithium (2.35 mL, 6.1 mmol) in hexanes. The resulting white suspension was stirred for 10 min and then concentrated to dryness under vacuum at 0 °C. Anhydrous hexamethylphosphoramide (12 mL) was then added, giving a 0.5 M solution of lithium 1-propanethiolate.

The methyl tetronate **2b** (0.3 g, 1.4 mmol) was dissolved in hexamethylphosphoramide (1.0 mL) under nitrogen and treated with a 0.5 M solution of lithium 1-propanethiolate (2.9 mL, 1.4 mmol) in hexamethylphosphoramide. After the mixture was stirred for 10 min, 1 M aqueous hydrochloric acid (25 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 15 mL), and the combined extracts were washed with 1 M aqueous hydrochloric acid (10 mL) and brine (25 mL) and dried ($MgSO_4$). Evaporation yielded the crude tetronic acid **2c** (0.22 g, 80%). This was distilled on the Kugelrohr apparatus (oven temperature 240–250 °C/0.2 Torr). Trituration of the distilled oil with hexane gave a white solid: mp 105–108 °C; IR (KBr) ν 3100–2860, 1719, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.7 (s, 3 H), 1.88 (br s, 3 H), 5.02 (d, J = 10 Hz, 1 H), 5.18 (d, J = 17 Hz, 1 H), 5.55 (br s, 1 H), 6.25 (dd, J = 10 and 17 Hz, 1 H), 10.4 (br s, 1 H) (The signal at δ 10.4 disappears upon shaking in D_2O.); MS, m/z 194 (4), 166 (7), 152 (17), 124 (24), 123 (18), 111 (52), 109 (41), 95 (100), 67 (34); MW calcd for $C_{11}H_{14}O_3$ 194.0943, found (HRMS) m/z 194.0935.

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Preparation and Photoreaction of $6^A,6^B$-, $6^A,6^C$-, $6^A,6^D$-, and $6^A,6^E$-Bis(anthracene-9-carbonyl)-γ-cyclodextrins. A New Method for Regulation of Product Stereochemistry

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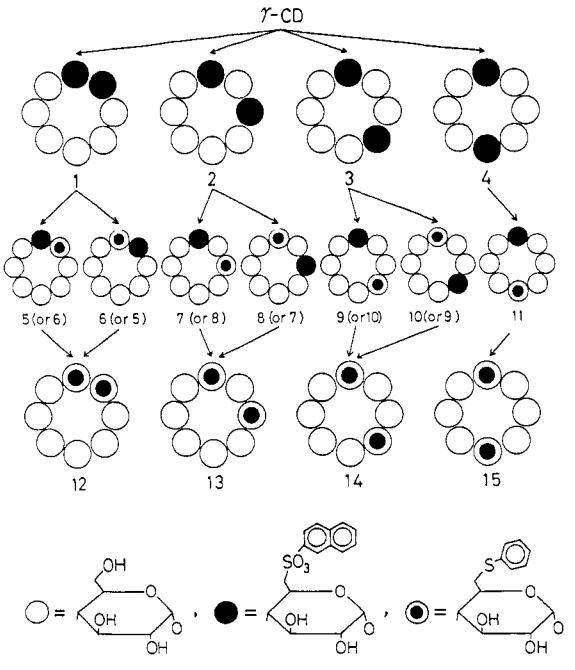
Regioisomers of $6^A,6^X$-bis(anthracene-9-carbonyl)-γ-cyclodextrins were prepared by reactions of sodium 9-anthracenecarboxylate with regioisomers of $6^A,6^X$-bis(2-naphthylsulfonyl)-γ-cyclodextrins. The anthracene moieties of the bis(anthracene) regioisomers undergo photodimerization in a 10% ethylene glycol aqueous solution, affording a trans photodimer for $6^A,6^C$, $6^A,6^D$, and $6^A,6^E$ regioisomers and a cis photodimer for $6^A,6^B$ regioisomer. The photodimers of $6^A,6^D$ and $6^A,6^E$ regioisomers were stable, but those of $6^A,6^B$ and $6^A,6^C$ regioisomers were unstable and return toward the original anthracene monomers with half-lives of 12.5 and 275 min for $6^A,6^B$ and $6^A,6^C$ regioisomers, respectively. The dissociation of the photodimers is suggested to be due to the inherent property of cis photodimer for $6^A,6^B$ regioisomer and the strain-rich nature of trans photodimer for $6^A,6^C$ regioisomer.

Cyclodextrins are naturally occurring cyclic oligosaccharides and are known to form inclusion complexes with a variety of organic molecules in aqueous solution.[1] They are composed of six or more α-1,4-linked glucose units and called α-, β-, γ-cyclodextrins for six-, seven-, and eight-unit substances, respectively. The stoichiometry of complex formation is usually 1:1, but γ-cyclodextrin has been shown to form 1:2 host–guest complexes because of its larger cavity size.[2,3] This property of γ-cyclodextrin enables it to be used as a molecular flask, in which two species can meet and react as shown by facilitated formation of excimers,[3] charge transfer complexes,[4] and dimers.[5] In connection with this unique property of γ-cyclodextrin, host–guest complexation of some modified γ-cyclodextrins bearing one or two aromatic moieties has been studied.[6,7] In this study, we have attempted regulation of product stereochemistry, using regioisomers of disubstituted γ-cyclodextrins as templates, in which two

Scheme I



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