First Total Synthesis of (−)-Ichthyothereol and Its Acetate

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Received May 2, 2001

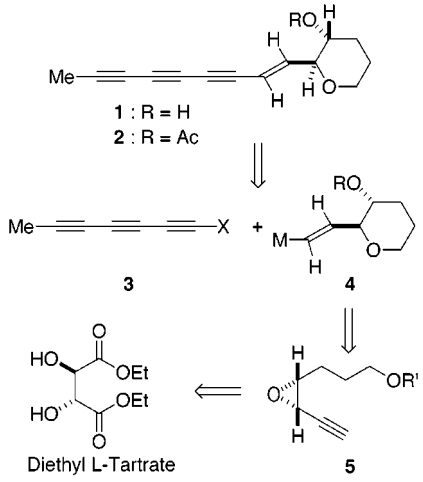
The first and stereoselective total syntheses of (−)-ichthyothereol (**1**) and its acetate ((+)-**2**) were achieved by incorporation of the two chiral centers of diethyl L-tartrate. The starting diethyl L-tartrate was converted into *trans*-2-ethynyl-3-hydroxytetrahydropyran **14** in a stereoselective manner via the endo mode cyclization of the epoxy−alkyne derivative **12**. The alcohol **12** was then transformed into (*E*)-iodoolefin derivative **15**, which was exposed to a coupling reaction with 1-tributylstannyl-1,3,5-heptyne (**19**), derived from the corresponding 1-trimethylsilyl-1,3,5-heptyne (**18**), under Stille conditions to produce the all-carbon framework of the target natural products. Chemical modification of the coupled product **20** under conventional conditions completed the first total synthesis of (−)-ichthyothereol (**1**) and its acetate ((+)-**2**).

Introduction

In 1965, (−)-ichthyothereol (**1**) and its acetate (**2**)[1,2] were isolated from the leaves and flowers of *Dahlia coccinea* as well as from the leaves of *Ichthyother terminals*, the latter of which have long been known to be used as a fish poison by the natives of the Lower Amazon Basin.[1,3] The crude extracts of the leaves of *I. terminals* had been found to be extremely poisonous not only to fish but also to mammals.[3] The effects in dogs were typically convulsant, similar to those of picrotoxin, indicating bulbar action. Minute quantities of either ichthyothereol (**1**) or its acetate (**2**) were extremely toxic to the fish *Lebistes reticulatus*, confirming that these triyne derivatives should be at least in part responsible for the toxicity of the leaves of *I. terminals*.[1,3] These two compounds were also shown to kill mice[1] when injected intraperitoneally in doses of 1 mg in olive oil. The gross structure[1,3] including the relative stereochemistry of compounds **1** and **2** was determined by ^{1}H NMR analysis. The absolute configuration of two chiral centers of **1** and **2** was first tentatively deduced on the basis of the optical rotatory dispersion curve[1] of the substituted tetrahydropyran-3-one derivatives prepared by oxidation of perhydroichthyothereol. Finally, the absolute configuration of **1** and **2** was unambiguously established by chemical transformation of **1** into the (−)-bis(2,4-dinitrobenzoate) of *trans*-3-hydroxy-2-hydroxymethyltetahydropyran.[4]

Surprisingly, no publication dealing with the total synthesis of toxic ichthyothereol (**1**) and/or its acetate (**2**) has so far been available notwithstanding the fact that more than 30 years have now elapsed since their first isolation in 1965. In this paper, we describe the first total synthesis of (−)-ichthyothereol (**l**) and its acetate (**2**) starting from L-tartrate in a highly stereoselective manner.

Scheme 1



Our retrosynthetic analysis is outlined in Scheme 1. The first carbon−carbon bond disconnection of **1** would be made between the triyne moiety and the (*E*)-olefin part leading to the triyne species **3** and the *trans*-3-hydroxy-2-vinyltetrahydropyran derivative **4**. The latter should be prepared from the optically active *cis*-epoxide **5** through the dicobalt octacarbonyl [$Co_2(CO)_8$]-mediated endo mode cyclization[5] of the *cis*-epoxy−alkyne species

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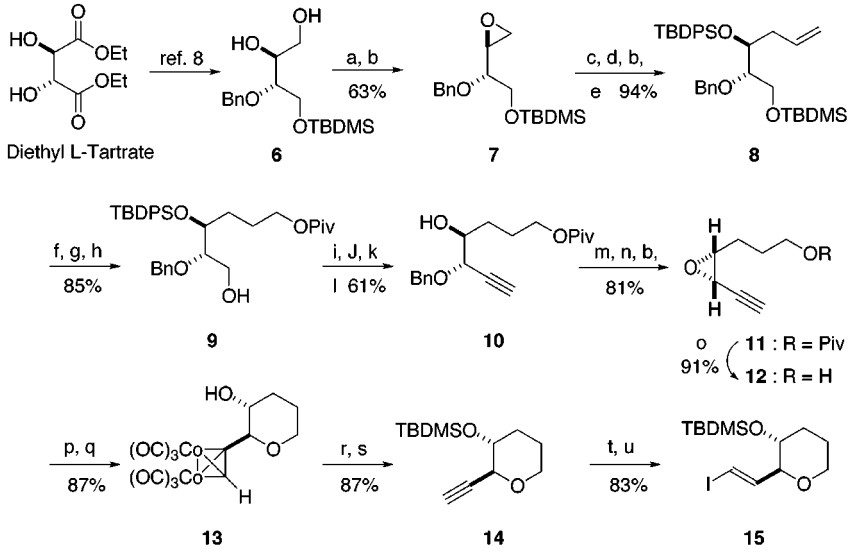
10.1021/jo0104532 CCC: $20.00
Published on Web 07/25/2001

Scheme 2[a]



[a] Reaction conditions: (a) TsCl, pyridine, 0 °C; (b) K_2CO_3, MeOH, rt; (c) TMS-≡, ^{n}BuLi,BF_3·OEt_2, THF, −78 °C; (d) TBDPSCl, imidazole, DMF, rt; (e) Lindlar cataltst, H_2, rt; (f) BH_3·THF, then H_2O_2, NaOH, 0 °C; (g) PivCl, DMAP, CH_2Cl_2, 0 °C; (h) PPTS, MeOH, rt; (i) Swern oxidation, −78 °C; (j) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (k) EtMgBr, THF, −20 °C; (l) TBAF, THF, rt; (m) TsCl, DMAP, CH_2Cl_2, rt; (n) BBr_3, CH_2Cl_2, −78 °C; (o) DIBAL-H, epoxypropane, CH_2Cl_2, −78 °C; (p) $Co_2(CO)_8$, CH_2Cl_2, rt; (q) BF_3·OEt_2, −78 °C; (r) CAN, MeOH, rt; (s) TBDMSCl, imidazole, DMF, rt; (t) Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, −78 °C; (u) I_2, CH_2Cl_2, rt.

5, which would be obtained by taking advantage of the two contiguous chiral centers of diethyl L-tartrate. Thus, diethyl L-tartrate became the starting material for this program. The triyne counterpart **3** (X = $SnBu_3$) for the coupling reaction would be anticipated to be obtained from hex-1,4-diyn-3-one by combination of Tykwinski's triyne synthesis[6] and transformation of the silyl group to a stannyl one by Buchwald's procedure.[7]

Results and Discussion

(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-[(*E*)-2-iodovinyl]-tetrahydropyran (**15**), the key compound of the coupling reaction for construction of the carbon framework of **1** and **2**, was prepared as depicted in Scheme 2. Diol **6** was easily obtained from diethyl L-tartrate according to Saito's procedure.[8] Activation of the primary hydroxy group of **6** by tosylation was followed by base treatment, affording epoxide **7** in 63% yield. Transformation of **7** into vinyl derivative **8** was realized as follows. Addition of the acetylide, prepared from trimethylsilylacetylene and *n*-BuLi, to **7** in the presence of BF_3·OEt_2 [9] furnished the homopropynyl alcohol, which was protected with a *tert*-butyldiphenyl (TBDPS) group, and then the terminal trimethylsilyl (TMS) group was removed. The resulting alkyne derivative was half-hydrogenated over a Lindlar catalyst to give **8** in 94% overall yield. Upon successive exposure to BH_3·THF and hydrogen peroxide, compound **8** underwent hydroboration−oxidation to produce the primary alcohol. Protection of the primary hydroxy moiety with a pivaloyl group and desilylation under acidic conditions provided **9** in 85% yield. Compound **9** was oxidized under Swern conditions to give the labile aldehyde, which was subsequently exposed to Corey's dibromoolefination conditions[10] and ethylmagnesium bromide[11] to produce, after *n*-tetrabutylammonium fluoride (TBAF) treatment, the alkyne derivative **10** in 61% yield. Treatment of **10** with tosyl chloride (TsCl) at room temperature and debenzylation with BBr_3 at −78 °C afforded the hydroxy compound, epoxidation of which was then accomplished by exposure to K_2CO_3 in MeOH, yielding the epoxy derivative **11** in 81% overall yield.

Conversion of **11** into **12** was somewhat troublesome. Treatment of **11** with ethylmagnesium bromide or methylmagnesium bromide in several kinds of solvents gave an intractable mixture including the desired **12**. A similar behavior was observed on exposure of **11** to methyllithium. When 2 equiv of diisobutylaluminum hydride (DIBAL-H) in THF was employed, **11** gave a rather clear mixture mainly consisting of **12** and the epoxy ring-opened products arising from **12** along with the starting **11**. We envisaged that DIBAL-H might have reacted with the pivaloyl group faster than with the epoxy moiety of **11,** leading to the production of **12**. However, **12** seems susceptible to further reduction by DIBAL-H. Thus, the addition of another epoxy compound in the reaction mixture would avoid the over-reaction of **12**. The epoxy derivative that would be used for the above purpose must be one with less steric hindrance compared to the epoxy moiety of **11** and **12**. In other words, epoxy derivatives more reactive than **11** and **12** toward DIBAL-H would be favorable for this aim. Therefore, we selected propylene oxide as a scavenger of excess of DIBAL-H. As a result, reaction of **11** with DIBAL-H (5.0 equiv) in the presence of excess propylene oxide (20 equiv)[12] at −78 °C proceeded very clearly to provide **12** as the sole isolable product in 91% yield. The substrate for the endo mode cyclization was thus obtained. According to the procedure[5] for the endo mode cyclization of the racemic epoxy−alkyne derivatives, **12** was converted to the corresponding dicobalthexacarbonyl species, which was then

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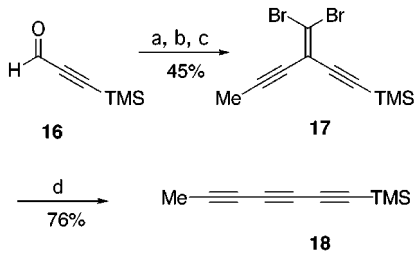
(11) *n*-BuLi was found to be ineffective in this case.
(12) An excess of propylene oxide (bp 34 °C) can be easily removed by evaporation.

Scheme 3[a]



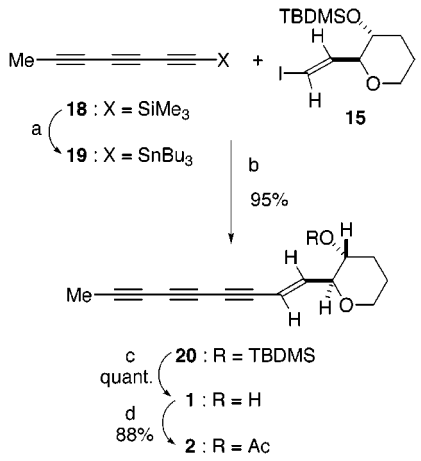
[a] Reaction conditions: (a) Me-≡-MgBr, THF, 0 °C; (b) MnO_2, CH_2Cl_2, rt; (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (d) *n*-BuLi, hexane, −78 °C.

treated with a catalytic amount of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C to leave the *trans*-tetrahydropyran derivative **13**[5d] in 87% yield. Demetalation of **13** with cerium ammoniun nitrate (CAN) was followed by protection of the secondary hydroxy functionality with a silyl group to afford **14**[13] in 87% yield. Upon consecutive treatment with *n*-butyltin hydride in the presence of a palladium catalyst at −78 °C and iodine at room temperature, **14** undertook hydrostannylation,[14] followed by a tributylstannyl moiety−iodine exchange reaction[15] leading to the (*E*)-iodovinyl derivative **15** in 83% yield.

Our endeavors were then directed toward the preparation of counterpart **18** for the coupling reaction (Scheme 3). Trimethylsilylpropynal (**16**) was reacted with propynylmagnesium bromide to give the alcohol, which was subsequently oxidized with manganese dioxide. The resulting diynone derivative was then converted into the dibromoolefin **17** in 45% overall yield under standard conditions.[10] By taking advantage of the method developed by Tykwinski,[6] **17** was exposed to *n*-BuLi in hexane at −78 °C furnishing 1-trimethylsilyl-1,3,5-heptatriyne (**18**) in 76% yield.

With ready access to **18**, we were ready to consider the completion of the construction of the carbon skeleton of **1** and **2** by the palladium-catalyzed coupling reaction under Stille conditions. Transmetalation of the silyl group of **18** to the corresponding stannyl one was realized by Buchwald's procedure.[7] Treatment of **18** with bis(tributyltin)oxide in THF in the presence of a catalytic amount of TBAF at 60 °C for 2.5 h provided the crude stannyl derivative **19**, the Stille coupling of which with **15** in the standard fashion (5 mol % of $Pd_2(PPh_3)_2$ in THF at room temperature)[16] proceeded without difficulty to produce the coupling product **20** in 95% yield (Scheme 4). The final phase of this program is simple chemical modifications of **20**. Desilylation of **20** with TBAF in THF at room temperature afforded (−)-ichthyothereol (**1**) in a quantitative yield. Acetylation of (−)-**1** by conventional means provided (+)-**2** in 88% yield. The synthetic (−)-**1** and (+)-**2** were identical with the natural (−)-ichtyothereol and its acetate, (+)-**2**, respectively, by comparison with their spectral as well as physical data.

Scheme 4[a]



[a] Reaction conditions: (a) $(Bu_3Sn)_2O$, catalytic TBAF, THF, 60 °C; (b) 5 mol % of $PdCl_2(PPh_3)_2$, rt; (c) TBAF, THF, rt; (d) Ac_2O, DMAP, CH_2Cl_2, rt.

In summary, we have completed the first total synthesis of (−)-ichthyothereol and its acetate by a palladium-catalyzed coupling reaction between the iodoolefin **15** and the triyne derivative **19**. The iodoolefin **15** was prepared from commercially available diethyl L-tartrate through the $Co_2(CO)_8$-mediated endo mode cyclization of the optically active epoxy−alkyne derivative **12** in a highly stereoselective manner. Further studies on the preparation of the analogues of **1** and **2** using the procedure described here as well as on the examination of their biological activities are now in progress.

Experimental Section

Melting points are uncorrected. IR spectra were measured in $CHCl_3$. ^1H NMR spectra were taken in $CDCl_3$. $CHCl_3$ (7.26 ppm) was used as an internal standard for silyl compounds. ^{13}C NMR spectra were recorded in $CDCl_3$ with $CHCl_3$ (77.00 ppm) as an internal standard. Commercially available dry CH_2Cl_2 and THF were employed for reactions. Et_3N and $^iPr_2NH$ were distilled from CaH_2 prior to use. All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Silica gel (silica gel 60, 230−400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

(2*S*,3*S*)-2-Benzyloxy-3,4-epoxy-1-(*tert*-butyldimethylsiloxy)butane ((−)-7). A solution of TsCl (620 mg, 3.00 mmol) in pyridine (4 mL) was added to a solution of diol **6** (890 mg, 2.73 mmol) in pyridine (5.00 mL) at 0 °C. After stirring for 8 h, the solution was concentrated and the residue was diluted with Et_2O. The Et_2O solution was washed with water and brine, dried, and concentrated to leave the crude tosylate. The crude tosylate was used directly for the next reaction. To a solution of the residue in MeOH (15.0 mL) was added K_2CO_3 (530 mg 3.82 mmol), and the reaction mixture was stirred for 1 h. MeOH was evaporated off, and the residue was taken up in AcOEt, which was washed with saturated aqueous NH_4Cl, water, and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (10:1) afforded (−)-**7** (532 mg, 63%) as a colorless oil: $[\alpha]_D^{25}$ −7.3 (*c* 0.50, $CHCl_3$); ^1H NMR δ 7.29−7.22 (m, 5H), 4.82, 4.65 (AB-q, 2H, J = 11.9 Hz), 3.81−3.67 (m, 2H), 3.20 (dt, 1H, J = 6.6, 5.6 Hz), 3.08 (ddd, 1H, J = 6.6, 3.9, 2.6, Hz), 2.80 (dd, 1H, J = 4.9, 3.9 Hz), 2.63 (dd, 1H, J = 4.9, 2.6 Hz), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 138.37, 128.25, 127.69, 127.49, 80.68, 71.99, 63.38, 53.25, 43.38, 25.77, 18.15, −5.51, −5.57; MS *m*/*z* 308 (M^+, 0.1). Anal. Calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15. Found: C, 65.94; H, 9.25.

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(15) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438, and references therein.

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(2*S*,3*S*)-2-Benzyloxy-1-(*tert*-butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)hex-5-ene ((−)-8). A solution of *n*-BuLi in hexane (1.14 M, 10.0 mL, 11.4 mmol) was added to a solution of (trimethylsilyl)acetylene (1.60 mL, 11.4 mmol) in THF (30.0 mL) at −78 °C. After being stirred for 10 min, BF_3·OEt_2 in THF (1.00 M, 11.4 mL, 11.4 mmol) was added to the reaction mixture and stirring was continued for 10 min at the same temperature. A solution of (−)-**7** (1.39 g, 4.54 mmol) in THF (15.0 mL) was then added to the reaction mixture, which was further stirred for 5 min, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to give the crude alcohol. The crude alcohol was taken up in DMF (3.50 mL), to which imidazole (1.23 g, 18.2 mmol) and TBDPSCl (2.36 mL, 9.08 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 4.5 h, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to afford the crude TBDPS-protected product. To the solution of the crude product thus obtained in MeOH (30.0 mL) was added K_2CO_3 (1.25 g, 9.08 mmol), and the reaction mixture was stirred for 1 h. MeOH was evaporated off, and the residue was taken up in AcOEt, which was washed with saturated aqueous NH_4Cl, water, and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to provide the terminal alkyne derivative. A solution of this alkyne and pyridine (2.75 mL, 34.1 mmol) in AcOEt (45.0 mL) was hydrogenated for 4.5 h under a hydrogen atmosphere in the presence of Pd−$BaCO_3$ (260 mg) at room temperature. The catalyst was filtered off, and the filtrate was concentrated to dryness. Chromatography of the residual oil with hexane-AcOEt (100:1) afforded (−)-**8** (2.44 g, 94%) as a colorless oil: $[\alpha]_D^{24}$ −3.4 (*c* 0.50, $CHCl_3$); IR 1639 cm^{-1}; ^1H NMR δ 7.69−7.66 (m, 4H), 7.40−7.21 (m, 11H), 5.67−5.51 (m, 1H), 4.88−4.81 (m, 2H), 4.56, 4.37 (AB-q, 2H, J = 11.9 Hz), 3.97−3.87 (m, 2H), 3.78 (dd, 1H, J = 10.7, 7.1 Hz), 3.46−3.41 (m, 1H), 2.46−2.35 (m, 1H), 2.15−2.03 (m, 1H), 1.04 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 139.23, 136.08, 135.98, 135.53, 134.16, 133.93, 129.58, 129.52, 128.07, 127.49, 127.39, 127.13, 116.69, 82.19, 72.99, 72.63, 63.36, 37.06, 27.05, 25.90, 19.41, 18.19, −5.35, −5.46; FABMS *m*/*z* 575 (M^+ + 1, 0.1). Anal. Calcd for $C_{35}H_{50}O_3Si$: C, 73.12; H, 8.77. Found: C, 73.01; H, 8.89.

(2*S*,3*S*)-2-Benzyloxy-3-(*tert*-butyldiphenylsiloxy)-6-(pivaloyloxy)hexan-1-ol ((−)-9). To a solution of (−)-**8** (510 mg, 0.89 mmol) in THF (9.00 mL) was added BH_3·THF complex in THF (0.90 M, 1.50 mL, 1.33 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. Then 5% aqueous NaOH (5.50 mL) and 30% aqueous H_2O_2 (5.50 mL) were successively added to the reaction mixture, and stirring was continued for an additional hour at room temperature. The mixture was extracted with AcOEt, which was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to give the alcohol. Pivaloyl chloride (0.22 mL, 1.78 mmol) was added to a mixture of the alcohol, Et_3N (0.50 mL, 3.56 mmol), and DMAP (22.0 mg, 0.18 mmol) in CH_2Cl_2 (9.00 mL) at 0 °C. After being stirred for 4 h at room temperature, the reaction was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to leave the acylated product. To the residue in MeOH (6.00 mL) was added PPTS (25.0 mg, 0.01 mmol) at room temperature, and the reaction mixture was stirred for 24 h. MeOH was evaporated off, and the residue was taken up in AcOEt, which was washed with saturated aqueous $NaHCO_3$, water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded (−)-**9** (426 mg, 85%) as a colorless oil: $[\alpha]_D^{26}$ −12.2 (*c* 0.50, $CHCl_3$); IR 3582, 3520, 1719 cm^{-1}; ^1H NMR δ 7.61−7.57 (m, 4H), 7.38−7.30 (m, 6H), 7.28−7.18 (m, 3H), 7.07−7.04 (m, 2H), 4.19 (s, 2H), 3.84−3.72 (m, 4H), 3.63 (dd, 1H, J = 11.6, 6.9 Hz), 3.45−3.39 (m, 1H), 2.01−1.91 (s, 1H), 1.62−1.20 (m, 4H), 1.07 (s, 9H), 0.99 (s, 9H); ^{13}C NMR δ 178.36, 138.24, 135.97, 135.93, 133.61, 133.45, 129.88, 129.82, 128.34, 127.71, 127.65, 127.62, 127.59, 81.65, 77.20, 72.27, 64.05, 61.28, 38.64, 28.33, 27.13, 27.02, 25.27, 19.31; FABMS *m*/*z* 561 (M^+, 4.7). Anal. Calcd for $C_{34}H_{46}O_5Si$: C, 72.56; H,8.24. Found: C, 72.28; H, 8.37.

(3*S*,4*S*)-3-Benzyloxy-6-(pivaloyloxy)-1-heptyn-4-ol ((+)-10). A solution of DMSO (0.18 mL, 2.53 mmol) in CH_2Cl_2 (6.00 mL) was added to a solution of oxalyl chloride (0.11 mL, 1.27 mmol) in CH_2Cl_2 (4.00 mL) at −78 °C over a period of 5 min. After the mixture was stirred for 15 min, a solution of the alcohol (−)-**9** (650 mg, 1.15 mmol) in CH_2Cl_2 (4.00 mL) was added to the CH_2Cl_2 solution, and the reaction mixture was stirred at the same temperature for an additional 1 h. Et_3N (0.80 mL 5.75 mmol) was then added to the reaction mixture, which was gradually warmed to room temperature and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and brine, dried, and concentrated to leave the crude aldehyde. The crude aldehyde was used directly for the next reaction. To a solution of PPh_3 (1.80 g, 6.90 mmol) in CH_2Cl_2 (4.00 mL) was added CBr_4 (1.14 g, 3.45 mmol) in CH_2Cl_2 (4.00 mL) at 0 °C, and the reaction mixture was stirred for 30 min. A solution of crude aldehyde in CH_2Cl_2 (6.00 mL) was then added to a solution of the ylide in CH_2Cl_2 solution thus adjusted 0 °C, and stirring was continued for 5 min at the same temperature. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and the CH_2Cl_2 solution was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (5:1) to give the dibromoolefin derivative. To a solution of the dibromoolefin derivative in THF (12.0 mL) was added EtMgBr in THF (0.96 M, 5.99 mL, 5.75 mmol) at −20 °C, and the reaction mixture was stirred for 10 min at the same temperature. The reaction mixture was quenched by addition of water and extracted with Et_2O, which was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (5:1) to afford the alkyne derivative. To a solution of residue in THF (12.0 mL) was added TBAF in THF (1.00 M, 1.60 mL, 1.60 mmol), and the reaction mixture was stirred for 12 h at room temperature, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residual oil was chromatographed with hexane−AcOEt (6:1) to afford (+)-**10** (224 mg, 61%) as a colorless oil: $[\alpha]_D^{24}$ +68.8 (*c* 0.5, $CHCl_3$); IR 3578, 3304, 2116, 1717 cm^{-1}; ^1H NMR δ 7.36−7.33 (m, 5H), 4.86, 4.52 (AB-q, 2H, J = 11.6 Hz), 4.09 (t, 2H, J = 6.1 Hz), 3.93 (dd, 1H, J = 7.3, 2.0 Hz), 3.77−3.70 (m, 1H), 2.55 (br s, 1H), 2.53 (d, 1H, J = 2.0 Hz), 1.90−1.47 (m,4H), 1.19 (s, 9H); ^{13}C NMR δ 178.47, 137.05, 128.45, 128.12, 127.98, 79.88, 75.90, 73.92, 72.63, 70.96, 64.03, 38.67, 28.59, 27.14, 24.69; MS *m*/*z* 318 (M^+, 0.8). HRMS calcd for $C_{19}H_{26}O_4$ 318.1841, found 318.1818.

(3*S*,4*R*)-3,4-Epoxy-6-(pivaloyloxy)hept-1-yne ((+)-11). TsCl (9.20 g, 48.1 mmol) was added to a solution of (+)-**10** (1.53 g, 4.81 mmol), Et_3N (13.7 mL, 96.2 mmol), and DMAP (580 mg, 4.81 mmol) in CH_2Cl_2 at 0 °C. After being stirred for 24 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to afford the crude tosylate. To a solution of crude tosylate in CH_2Cl_2 (48 mL) was added BBr_3 in CH_2Cl_2 solution (1.00 M, 4.81 mL, 4.81 mmol) at −78 °C. The mixture was stirred for 5 min, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to leave the crude alcohol. The crude alcohol was used directly for the next reaction. A suspension of the crude alcohol and K_2CO_3 (1.33 mg, 9.62 mmol) in MeOH (48.0 mL) was stirred at room temperature for 30 min. MeOH was evaporated off, and the residue was taken up in AcOEt, which was washed

with saturated aqueous NH_4Cl, water, and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (30:1) afforded (+)-**11** (820 mg, 81%) as a colorless oil: $[\alpha]_D^{27}$ +26.0 (*c* 0.50, $CHCl_3$); IR 3306, 2125, 1722 cm^{-1}; ^1H NMR δ 4.10−4.04 (m, 2H), 3.37 (dd, 1H, J = 4.1, 1.7 Hz), 3.01 (td, 1H, J = 5.6, 4.1 Hz), 2.32, (d, 1H, J = 1.7 Hz), 1.82−1.72 (m, 4H), 1.14 (s, 9H); ^{13}C NMR δ 178.20, 78.51, 73.68, 63.52, 56.95, 44.55, 38.55, 27.01, 25.88, 24.98; FABMS *m*/*z* 211 (M^+ + 1, 5.1). FABHRMS calcd for $C_{12}H_{18}O_3$ 211.1334, found 211.1343.

(3*S*,4*R*)-3,4-Epoxy-1-heptyn-7-ol ((+)-12). A solution of DIBAL-H in hexane (1.00 M, 3.88 mL, 3.88 mmol) was added to a solution of (+)-**11** (163 mg, 0.78 mmol) and propyleneoxide (1.08 mL, 15.5 mmol) in CH_2Cl_2 (15.0 mL) at −78 °C. The mixture was stirred for 5 min, quenched by addition of saturated aqueous Na_2SO_4, and filtered through Celite. The filtrate was concentrated to leave the residual oil which was chromatographed with hexane−AcOEt (1:1) to afford (+)-**12** (89.0 mg, 91%) as a colorless oil: $[\alpha]_D^{27}$ +54.6 (*c* 0.20, $CHCl_3$). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.25; H, 8.01. Spectral data of racemic **12** were already reported in ref 5d.

Hexacarbonyl-μ-[η^4-(2*R*,3*R*)-2-ethynyl-3-hydroxytetrahydropyran]dicobalt(Co−Co) (13). Compound **13** (93.0 mg, 87%) was obtained from (+)-**12** (33.0 mg, 0.26 mmol) according to the procedure described in ref 5d. Compound **13** was a reddish needle: mp 58−61 °C (hexane). Anal. Calcd for $C_{13}H_{10}Co_2O_8$: C, 37.89; H, 2.46. Found: C, 37.93; H, 2.45. Specific rotation could not be determined because demetalation occurred during measurement. Spectral data of racemic **13** were already reported in ref 5d.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethynyltetrahydropyran ((−)-14). To a solution of **13** (244 mg, 0.59 mmol) in MeOH (6.00 mL) was added CAN (1.62 g, 2.96 mmol) at 0 °C. After being stirred for 30 min, the reaction mixture was concentrated, diluted with water, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to dryness. The residue was dissolved in DMF (0.30 mL), to which imidazole (120 mg, 1.77 mmol) and TBDMSCl (134 mg, 0.89 mmol) were added. The reaction mixture was stirred at room temperature for 5 h, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (50:1) to afford (−) **14** (123 mg, 87%) as a colorless oil: $[\alpha]_D^{24}$ −34.9 (*c* 0.50, $CHCl_3$); IR 3308, 2125 cm^{-1}; ^1H NMR δ 3.93−3.84 (m, 2H), 3.59 (ddd, 1H, J = 8.9, 7.8, 4.2 Hz), 3.37 (ddd, 1H, J = 11.5, 9.8, 2.9 Hz), 2.41 (d, 1H, J = 2.3 Hz), 2.07−1.98 (m, 1H), 1.74−1.37 (m, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 82.03, 73.68, 72.76, 70.24, 66.70, 32.08, 25.73, 23.96, 17.99, −4.51, −4.63; MS *m*/*z* 240 (M^+, 0.1). HRMS calcd for $C_{13}H_{24}O_2Si$ 240.1546, found 240.1523.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-[(*E*)-2-iodovinyl]-tetrahydropyran ((−)-15). To a solution of (−)-**14** (67.0 mg, 0.28 mmol) and $PdCl_2(PPh_3)_2$ (3.90 mg, 0.56 × 10^{-2} mmol) in THF (5.60 mL) was added tributyltin hydride (0.19 mL, 0.70 mmol) at −30 °C, and the reaction mixture was gradually warmed to 0 °C over a period of 3 h. THF was evaporated off, and the residue was used directry for the next reaction. To a solution of the crude stanylated product in CH_2Cl_2 (5.60 mL) was added iodine (140 mg, 0.56 mmol) at room temperature. After being stirred for 1 h, THF was evaporated off and the residue was chromatographed with hexanes−Et_2O (85:1) to afford (−)-**15** (86.0 mg, 83%) as a pale yellow oil: $[\alpha]_D^{24}$ −33.2 (*c* 0.50, $CHCl_3$); IR 1614 cm^{-1}; ^1H NMR δ 6.63 (dd, 1H, J = 14.5, 5.9 Hz), 6.36 (dd, 1H, J = 14.5, 1.0 Hz), 3.96−3.88 (m, 1H), 3.48 (ddd, 1H, J = 8.8, 5.9, 1.0 Hz), 3.38−3.27 (m, 2H), 2.04−1.98 (m, 1H), 1.69−1.62 (m, 1H), 1.50−1.41 (m, 1H), 0.88 (s, 9H), 0.66 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ 144.62, 84.55, 78.58, 70.95, 67.57, 33.50, 25.72, 25.33, 17.92, −4.36, −4.64; FABMS *m*/*z* 369 (M^+ + 1, 2.3). FABHRMS calcd for $C_{13}H_{26}O_2SiI$ 369.0746, found 369.0739.

3-(Dibromomethylidene)-1-trimethylsilylhex-1,4-diyne (17). To a solution of **16** (1.00 g, 7.94 mmol) in THF (60.0 mL) was added 1-propynylmagnesium bromide in THF (0.50 M, 17.5 mL, 8.73 mmol) at 0 °C, and the reaction mixture was stirred for 10 min, quenched by addition of water, extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to give the crude alcohol. A mixture of crude alcohol and chemical manganese dioxide[17] (7.06 g, 79.4 mmol) in CH_2Cl_2 (40.0 mL) was stirred at room temperature for 24 h. The mixture was filtered off, and the filtrate was concentrated to leave the diynone derivative. To a solution of PPh_3 (8.30 g, 31.8 mmol) in CH_2Cl_2 (20.0 mL) was added CBr_4 (5.27 g, 15.9 mmol) in CH_2Cl_2 (5.00 mL) at 0 °C, and the reaction mixture was stirred for 5 min. A solution of the diynone derivative in CH_2Cl_2 was then added to a solution of the ylide in CH_2Cl_2 solution thus adjusted at 0 °C, and stirring was continued for 5 h at the same temperature. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and the CH_2Cl_2 layer was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane afforded **17** (1.14 g, 45%) as a colorless oil: IR 2230, 2147 cm^{-1}; ^1H NMR δ 1.99 (s, 3H), 0.22 (s, 9H); ^{13}C NMR δ 114.41, 107.78, 101.76, 100.69, 93.85, 76.60, 4.82, −0.44; MS *m*/*z* 320 (M^+, 100). HRMS calcd for $C_{10}H_{12}Br_2Si$ 319.9054, found 319.9081.

1-Trimethylsilylhept-1,3,5-triyne (18). To a solution of **17** (500 mg, 1.56 mmol) in hexane was added a solution of *n*-BuLi in hexane (1.36 M, 1.15 mL, 1.56 mmol) at −78 °C, and the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was gradually warmed to 0 °C, quenched by addition of saturated aqueous NH_4Cl, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane afforded **18** (190 mg, 76%) as colorless needles: mp 53.5−54 °C (hexane); IR 2218, 2168, 2081 cm^{-1}; ^1H NMR δ 1.96 (s, 3H), 0.19 (s, 9H); ^{13}C NMR δ 88.32, 85.21, 76.55, 64.74, 62.56, 59.33, 4.51, −0.52; MS *m*/*z* 160 (M^+, 22.9). Anal. Calcd for $C_{10}H_{12}Si$: C, 74.93; H, 7.55. Found: C, 74.76; H, 7.75.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-[(*1E*)-non-3,5,7-triyn-1-enyl]tetrahydropyran ((−)-20). To a solution of **18** (86.0 mg, 0.54 mmol) and $(Bu_3Sn)_2O$ (0.14 mL, 0.27 mmol) in THF (5.40 mL) was added TBAF in THF (1.00 M, 0.01 mL, 0.01 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at 60 °C, at which time the volatiles were removed in vacuo. The residue was diluted with hexane and filtered over Celite. The filtrate was concentrated to give the crude 1-trimethylstannyl-1,3,5-heptatriyne (**19**). Crude **19** was then added to a solution of (−)-**15** (20.0 mg, 0.54 × 10^{-1} mmol) and $PdCl_2(PPh_3)_2$ (1.90 mg, 0.27 × 10^{-2} mmol) in THF (0.50 mL) at room temperature. After being stirred for 24 h, THF was evaporated off and the residue was chromatographed with hexanes−Et_2O (80:1) to afford (−)-**20** (17.0 mg, 95%) as a pale yellow oil: $[\alpha]_D^{26}$ −65.5 (*c* 0.34, $CHCl_3$); IR 2222, 2201 cm^{-1}; ^1H NMR δ 6.45 (dd, 1H, J = 16.1, 5.4 Hz), 5.77 (dd, 1H, J = 16.1, 1.5 Hz), 3.93−3.91 (m, 1H), 3.57 (ddd, 1H, J = 8.8, 5.4, 1.5 Hz), 3.37−3.32 (m, 1H), 3.27 (ddd, 1H J = 10.6, 8.8, 4.5 Hz), 2.04−2.00 (m, 1H), 1.98 (s, 3H), 1.68−1.35 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 146.76, 108.89, 81.91, 77.89, 74.76, 74.13, 71.27, 67.56, 66.88, 64.94, 59.26, 33.69, 25.74, 25.29, 17.93, 4.62, −4.27, −4.69; MS *m*/*z* 328 (M^+, 4.3). HRMS calcd for $C_{20}H_{28}O_2Si$ 328.1858, found 328.1860.

(−)-Ichthyothereol ((−)-1). To a solution of (−)-**20** (17.0 mg, 0.52 × 10^{-1} mmol) in THF (0.50 mL) was added TBAF in THF (1.00 M THF, 0.06 mL, 0.06 mmol) at room temperature. After being stirred for 2 h, THF was evaporated off and the residue was chromatographed with hexanes−Et_2O (2:1) to afford (−)-**1** (11.0 mg, 100%) as white crystals: mp 86−87.5 °C (hexane) (lit.[3] mp 89−90 °C); $[\alpha]_D^{24}$ −40.2 (*c* 0.12, $CHCl_3$) (lit.[3] $[\alpha]_D$ −44); IR 3597, 2224, 2200 cm^{-1}; ^1H NMR δ 6.50 (dd, 1H, J = 16.1, 5.9 Hz), 5.84 (d, 1H, J = 16.1 Hz), 3.96−3.92 (m, 1H), 3.57 (ddd, 1H, J = 9.3, 5.9, 1.5 Hz), 3.58−3.28 (m, 2H), 2.15−2.11 (m, 1H), 1.98 (s, 3H), 1.72−1.67 (m, 3H), 1.50−

(17) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35.

1.40 (m, 1H); ^{13}C NMR δ 145.57, 110.24, 81.92, 78.18, 75.43, 73.59, 70.08, 67.42, 67.29, 64.90, 58.97, 32.42, 25.19, 4.64; MS *m*/*z* 214 (M^+, 26.7). HRMS calcd for $C_{14}H_{14}O_2$ 214.0994, found 214.0990.

(+)-Ichthyothereol Acetate ((+)-2). Ac_2O (0.13×10^{-1} mL, 0.13 mmol) was added to a solution of (−)-**1** (14.0 mg, 0.67×10^{-1} mmol), Et_3N (0.28×10^{-1} mL, 0.20 mmol), and DMAP (0.80 mg, 0.67×10^{-2} mmol) in CH_2Cl_2 (0.67 mL) at 0 °C. After being stirred for 5 min, CH_2Cl_2 was evaporated off and the residue was chromatographed with hexanes−Et_2O (5:1) to afford (−)-**2** (15.0 mg, 88%) as colorless needles: mp 59−61 °C (hexane) (lit.[3] mp 63−65 °C); $[\alpha]_D^{24}$ +6.7 (*c* 0.29, $CHCl_3$) (lit.[3] $[\alpha]_D$ +7); IR 2224, 2202, 1738 cm^{-1}; ^{1}H NMR δ 6.30 (dd, 1H, J = 16.1, 5.4 Hz), 5.79 (dd, 1H, J = 16.1, 1.5 Hz), 4.49 (ddd, 1H, J = 10.8, 9.3, 4.9 Hz), 3.99−3.93 (m, 1H), 3.77 (ddd, 1H, J = 9.3, 5.4, 1.5 Hz), 3.40 (td, 1H, J = 11.2, 3.3 Hz), 2.22−2.18 (m, 1H), 2.04 (s, 3H), 1.98 (s, 3H), 1.76−1.67 (m, 2H); ^{13}C NMR δ 169.83, 144.35, 110.25, 78.74, 78.21, 75.60, 73.46, 71.45, 67.46, 67.36, 64.87, 58.91, 29.24, 24.72, 21.05, 4.62; MS *m*/*z* 256 (M^+, 4.2). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.87; H, 6.35.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **10**, **11**, **14**, **15**, **17**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0104532