Synthesis, enzymic resolution and enantiomeric enhancement of bis(hydroxymethyl)[7]thiaheterohelicenes

Kazuhiko Tanaka,* Hideji Osuga, Hitomi Suzuki, Yuka Shogase and Yoshinori Kitahara

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-01, Japan

Racemic bis(hydroxymethyl)[7]thiaheterohelicene 9 has been prepared in eight steps (33% overall yield) from 2-(hydroxymethyl)benzo[1,2-*b*:4,3-*b*′]dithiophene 1. Lipase (*Pseudomonas cepacia*)-catalyzed transesterification of diol 9 by vinyl acetate in dichloromethane produces optically stable (*P*)-bis(hydroxymethyl)[7]thiaheterohelicene [(*P*)-9] with 98% ee along with the corresponding monoacetate [(*M*)-10] and the diacetate [(*M*)-11]. Hydrolysis of acetates (*M*)-10 and (*M*)-11 by aq. NaOH gives (*M*)-9 in 77% and 94% ee, respectively. In contrast, the enzymic resolution of diol 9 with *Candida antarctica* afforded diol (*M*)-9 in 92% ee. Column chromatography of optically enriched helicenediol 9 on silica gel shows an enantiomeric enhancement. A possible cause of the phenomenon is discussed.

Introduction

Helicenes containing more than six benzene rings ([6]carbohelicenes) or seven aromatic heterocycles such as thiophenes ([7]heterohelicenes) are very stable toward acids, bases and relatively high temperatures because of their rigid helical frameworks. For this reason, chiral functionalized helicenes are promising candidates for chiral ligands and auxiliaries in asymmetric syntheses.[1] The syntheses of optically active helicenes, however, requires repeated recrystallizations of the diastereomeric charge-transfer complex derived from racemic helicenes and optically active reagents like 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminooxy)propionic acid,[2,3] crystal selection of conglomerates,[4–7] recrystallization from chiral solvent,[8] or separation by high-performance liquid chromatography (HPLC) using a chiral column.[9,10]

We have recently reported the synthesis and enzymic resolution of racemic 2,13-bis(hydroxymethyl)dithieno[3,2-*e*:3′,2′-*e*′]benzo[1,2-*b*:4,3-*b*′]bis[1]benzothiophene [(*PM*)-helicenediol].[11] We now report a full account of the synthesis of the optically active helicenediols and the first enantiomeric enhancement of the partially resolved helical molecules by column chromatography on an achiral phase.

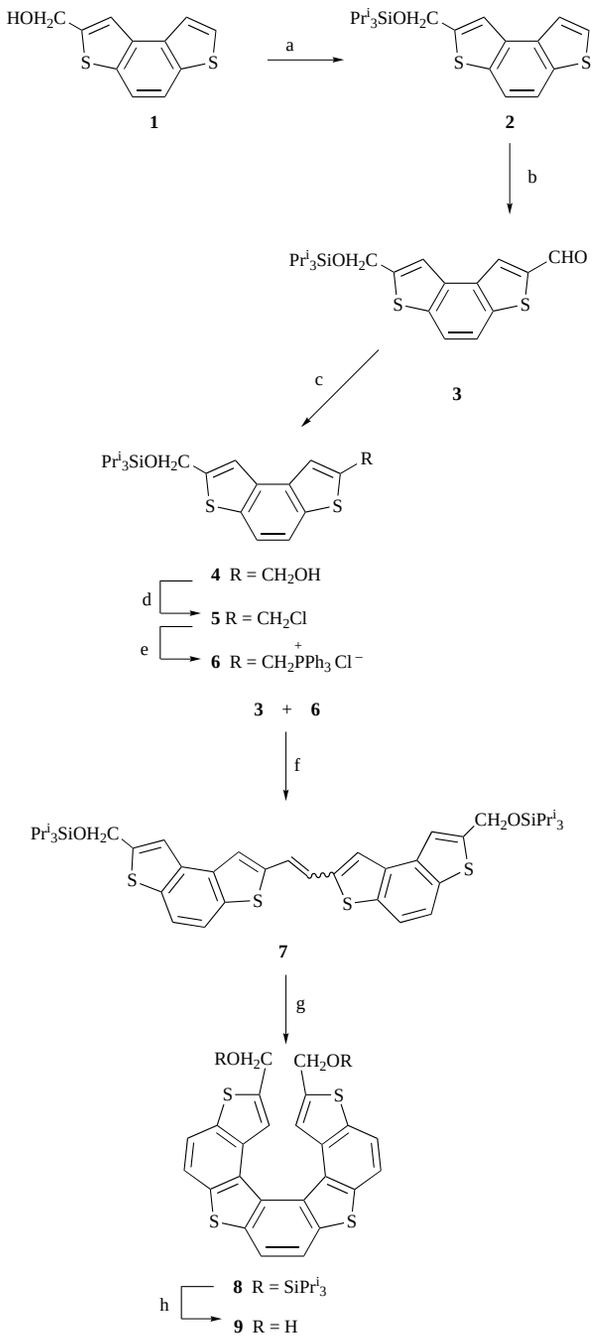
Results and discussion

Synthesis

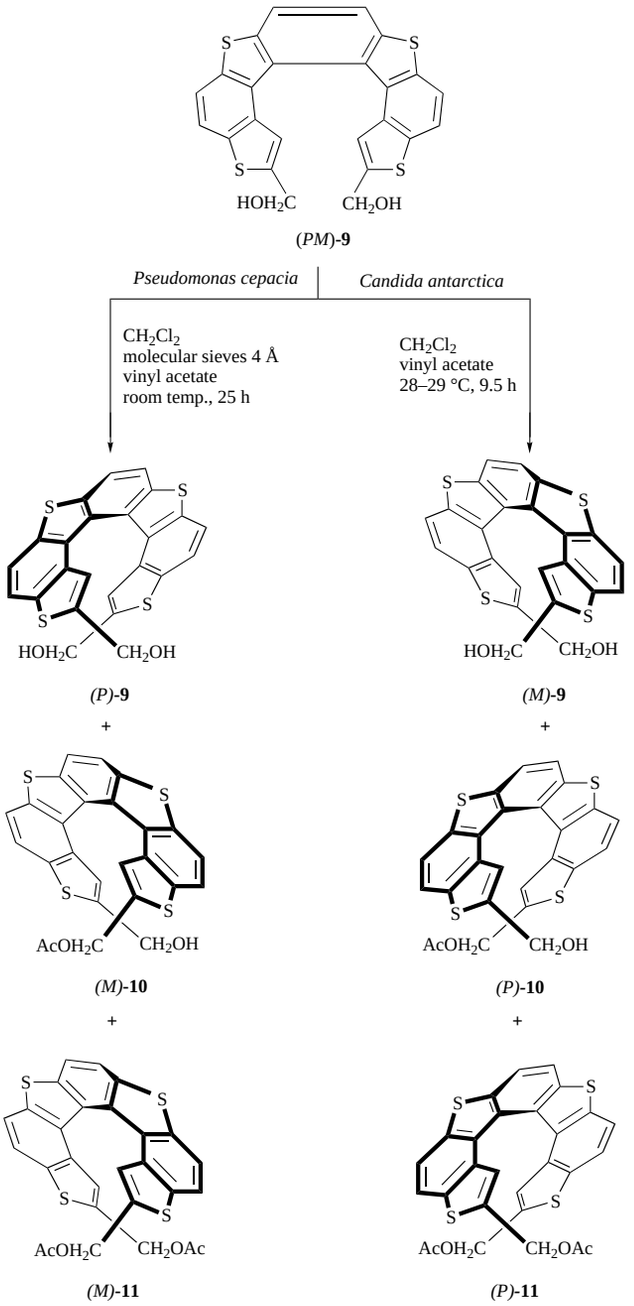
Our starting material for the synthesis of (*PM*)-helicenediol was 2-(hydroxymethyl)benzo[1,2-*b*:4,3-*b*′]dithiophene **1**, the hydroxy group of which was converted into the silyl ether **2** (95%) using triisopropylsilyl triflate[12] and 2,6-dimethylpyridine (2,6-lutidine) in dichloromethane (Scheme 1). Treatment of compound **2** with BuLi at −78 °C afforded the 5-lithio species exclusively, which was trapped with dimethylformamide (DMF) to give aldehyde **3** in 94% yield. Phosphonium salt **6** was prepared from the aldehyde in three steps. Thus, reduction of aldehyde **3** was achieved by $NaBH_4$ at room temp. to give 2-(hydroxymethyl)-7-(triisopropylsiloxymethyl)benzodithiophene **4** in 97% yield. Chlorination of the hydroxy group of alcohol **4** and subsequent treatment of the chloride **5** with triphenylphosphine in refluxing benzene gave the corresponding phosphonium salt **6** in 72% overall yield. The Wittig reaction of aldehyde **3** and phosphonium salt **6** in the presence of KOBu^t in EtOH–tetrahydrofuran (THF) afforded the 1,2-diarylethylene **7** in 89% yield. Photocyclization of the olefine **7** was carried out using propylene oxide as HI-trapping reagent,[13] and gave 2,13-bis(triisopropylsiloxymethyl)[7]thiaheterohelicene **8** in 66% yield. Finally, desilylation of compound **8** by tetrabutylammonium fluoride (TBAF)[14] in THF gave the desired racemic 2,13-bis(hydroxymethyl)dithieno[3,2-*e*:3′,2′-*e*′]benzo[1,2-*b*:4,3-*b*′]bis[1]benzothiophene **9** in 90% yield.

Initial attempts to resolve the racemic helicenediol **9** by using (*R*,*R*)-(+)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide[15] or brucine[16] were unsuccessful. However, lipase-catalyzed transesterification was found to be most effective for the kinetic resolution of our helical molecule.[11] Among lipases such as those from *Pseudomonas cepacia* (PCL), *Ps. sp.* (AK), *Rizomucor miehei* (LZ), *Candida antarctica* (CAL) and *Ps. aeruginosa* (LPL) investigated under various conditions, high enantioselectivities were observed with CAL and PCL in dichloromethane. The reaction was terminated after 25–79% conversion by filtration off of the immobilized enzyme. Column chromatography of the reaction mixture gave unchanged helicenediol **9**, monoacetate **10** and diacetate **11** (Scheme 2). The product proportions of compounds **9**, **10** and **11** and the enantiomeric excess (ee) of diol **9** were determined by HPLC. These results are summarized in Table 1. The enantioselectivity of diol **9** was indicated by enantiomeric ratio, *E*.[17,18] It is noteworthy that with CAL, the *E*-value was 20.6 in the absence of molecular sieves 4 Å, but the enantioselectivity significantly decreased to 7.9 with increasing amounts of molecular sieves 4 Å. In contrast, the highest enantioselectivity (*E* 26.6) was obtained with PCL in the presence of molecular sieves 4 Å. By use of the optimized procedure described above, the optical resolution of helicenediol **9** was carried out on both 100-mg and 1-g scales. Thus the transesterification of diol (*PM*)-**9** (101.2 mg) with PCL gave (*P*)-**9** in 98% ee (44.7 mg, 45% yield) along with acetate (*M*)-**10** (37% yield) and diacetate (*M*)-**11** (13% yield). Hydrolysis of acetates (*M*)-**10** and (*M*)-**11** by aq. sodium hydroxide in methanol gave diol (*M*)-**9** in 77% ee and 94% ee, respectively (Scheme 3). The reaction of diol (*PM*)-**9** (1.003 g) with CAL gave (*M*)-**9** in 92% ee (437 mg, 44% yield) together with the corresponding monoacetate (*P*)-**10** in 53% yield and the diacetate (*P*)-**11** in 3% yield. Hydrolysis of acetates (*P*)-**10** and (*P*)-**11** gave diol (*P*)-**9** in 67% ee and 89% ee, respectively.

The optically active helicenediol **9** was stable under these



Scheme 1 *Reagents and conditions:* a, Pr^i_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; b, BuLi, TMEDA, DMF, THF, −78 °C; c, $NaBH_4$, EtOH–THF, room temp.; d, $SOCl_2$, pyridine, benzene, 0 °C; e, Ph_3P, benzene, reflux; f, KOBu^t, EtOH–THF, 0 °C; g, *hv*, I_2, propylene oxide, benzene, room temp.; h, TBAF, THF, 0 °C



Scheme 2

reaction conditions. No racemization was indicated even in refluxing toluene or xylene (commercial mixture) for 100 h, but a slow racemization was observed when the diol was heated at 160 °C in mesitylene. The racemization rate constant (k_r) of (*M*)-**9** was calculated to be 2.71×10^{-7} (s^{-1}) at 160 °C, which is 1/4.8-times slower than that for 2-methyl[7]thiaheterohelicene and 1/7.7-times slower than for the unsubstituted analogue.[19]

Enantiomeric enhancement

Although it is very rare, ee increases when a chiral compound is isolated by chromatography on an achiral phase. This phenomenon is referred to as enantiomeric enhancement or enantiomeric enrichment.[20–28]

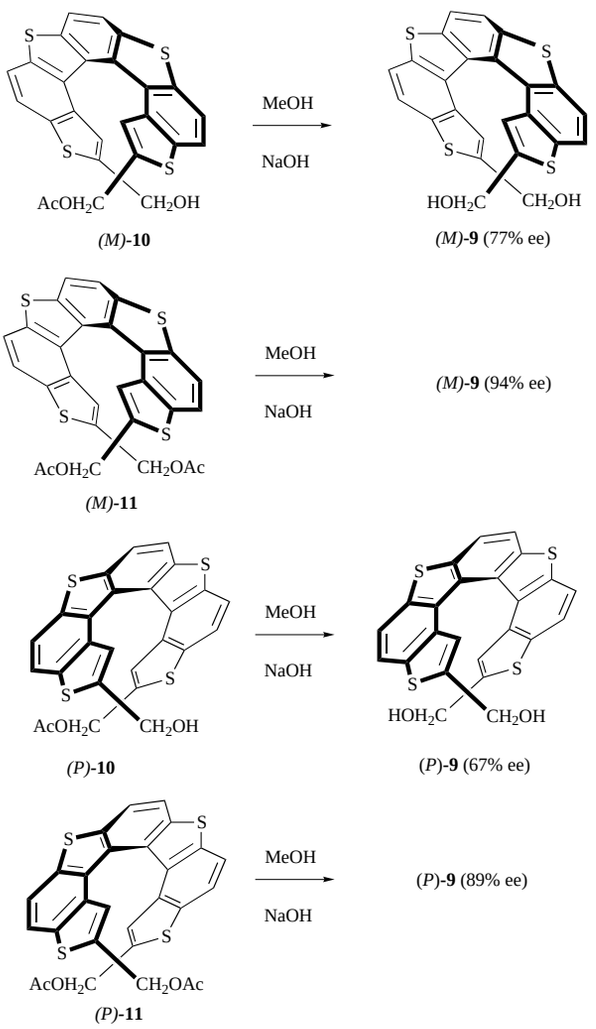
We report here the first example of enantiomeric enhancement by chromatographic separation of helical molecules on an achiral phase. Thus when (*M*)-**9** of 82% ee was purified by column chromatography on silica gel with hexane–ethyl acetate (3 : 1) as eluent, the depletion of ee (69%) occurred in the first fraction, and the enhancement of ee (89%) was observed in the last fraction (Fig. 1). In order to check the reproducibility of this enhancement, the chromatographic separation of the (*P*)-enantiomer with 92% ee was carried out under the same reaction conditions as those described for (*M*)-**9**. The highest ee (95% ee) was again obtained in the last fraction and the depletion (90% ee) was observed in the first fraction. However, no appreciable enantiomeric enhancement was observed in the cases of (*M*)- and (*P*)-helicenediols with less than 50% ee. These results are summarized in Table 2.

The observed enantiomeric enrichment can be explained by assuming diastereomeric associations between two enantiomers by intermolecular hydrogen bonding. If heterochiral-association (*PM*- and *MP*-dimers) is favoured over homochiral-association (*PP*- and *MM*-dimers), (*P*)- or (*M*)-enantiomers would preferentially interact with the stationary phase (SiO_2) *via* hydrogen bonds. Such a situation would lead to a difference in chromatographic mobilities, whereby the more mobile

Table 1 Lipase-catalyzed transesterification of racemic helicenediol **9** in organic solvents[a]

Enzyme (mg)	Solvent	MS 4 Å (mg)	Time (*t*/h)	*P*-**9**:*M*-**9**:**10**:**11**	Ee (%) of **9**[b]	Convn. (%)[b]	*E*-value
AK (5)	benzene + CH_2Cl_2	20	24	44:15:36:5	49	41	9.3
AK (10)	isopropenyl acetate	50	25	42:19:34:5	38	39	5.6
CAL (5)	THF	20	24	17:40:42:2	40	44	4.5
CAL (5)	Pr^i_2O + CH_2Cl_2	30	1	10:40:42:8	60	50	7.2
CAL (5)	AcOEt	30	24	13:41:43:2	52	45	7.4
CAL (5)	benzene + CH_2Cl_2	50	0.5	18:41:39:2	39	41	5.2
CAL (5)	CH_2Cl_2	0	3	17:47:35:0.6	47	36	17.7
CAL (5)	CH_2Cl_2	0	7	0.7:40:56:3	97	59	20.6
CAL (5)	CH_2Cl_2	20	8	4:42:53:2	83	55	13.2
CAL (5)	CH_2Cl_2	40	7	0.3:25.5:69.5:4.7	98	74	7.9
PCL (5)	benzene + CH_2Cl_2	50	5	47:29:23:1	24	24	9.3
PCL (30)	CH_2Cl_2	0	14	46:21:31:2	37	33	10.1
PCL (30)	CH_2Cl_2	10	14	47:17:35:2	47	37	14.3
PCL (30)	CH_2Cl_2	20	14	45:1.8:46:8	92	54	26.6
LZ (5)	benzene + CH_2Cl_2	20	1	16:6:65:13	45	78	1.8
LZ (5)	isopropenyl acetate	30	18	31:19:45:6	24	51	2.0
LPL (5)	benzene + CH_2Cl_2	20	24	37:23:37:3	23	40	2.5
LPL (50)	isopropenyl acetate	50	8	45:21:31:4	36	35	7.1

[a] Racemic helicenediol (2 mg) and 40 μl of vinyl acetate in 2 cm^3 of solvent at 30 °C. [b] Determined by HPLC using Sumichiral OA2000 (100:1, 1,2-dichloroethane–ethanol).



Scheme 3

heterochiral dimers would elute faster than the less mobile enantiomers, with the enantiomeric enrichment being observed at the end of the elution in our case. These phenomena are very similar to the self-amplification observed by Charles and Gil-Av.[21]

In order to confirm the hypothesis, we used hexane–ethanol (5:1) as a mobile phase. Under these conditions, no enhancement was observed because intermolecular hydrogen bonding between heterochiral dimers was interrupted by ethanol molecules. Recrystallization of racemic helicenediol **9** from ethanol yielded the crystalline inclusion complex as supported by X-ray crystallography,[11] where the host molecules of same helicity are aligned in a stacking column along the crystallographic *b* direction by intermolecular hydrogen bonds. These results indicate that the association between ethanol molecules and enantiomers is preferred over the heterochiral-association. We also found that recrystallization of diol (*P*)-**9** of 69% ee from hexane–ethyl acetate (3:1) gave racemic crystals of diol **9**, but the ee of the filtrate increased to 97%. This means that heterochiral association of helicenediols is favoured over the homochiral association.

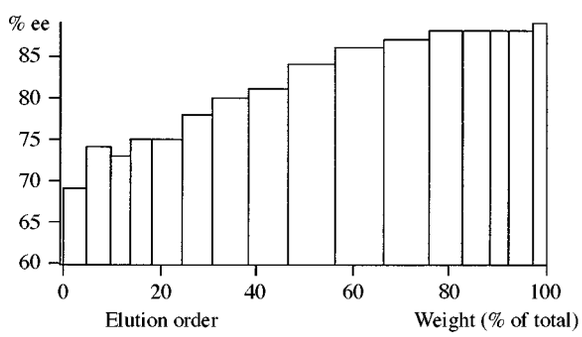


Fig. 1 Chromatography of (*M*)-helicenediol of 82.0% ee

Conclusions

We have prepared racemic bis(hydroxymethyl)[7]heterohelicene **9** in eight steps from readily available 2-(hydroxymethyl)-benzodithiophene. The overall yield of diol **9** from compound **1** was 33%. The enzymic resolution of the racemate gave either (*P*)- or (*M*)-helicenediols in 95–98% ee. A single crystallization of the helicenediols leads to essentially 100% ee. The first enantiomeric enhancement of helical molecules in the chromatographic separation can be explained by assuming heterochiral association to be more favourable than homochiral association in an achiral stationary phase.

Experimental

Mps were determined on a Yanagimoto hotstage apparatus and

Table 2 Enantiomeric enhancement of helicenediols **9**

Helicenediol	ee (%) of sample	ee (%) of first fraction	ee (%) of last fraction
(*M*)-**9**	66	55	77
(*M*)-**9**	82	69	89
(*P*)-**9**	92	90	95
(*P*)-**9**	67	64	72
(*P*)-**9**	50	50	50
(*P*)-**9**	42	42	42
(*P*)-**9**	20	20	20

are not corrected. IR spectra were recorded on a SHIMADZU FT IR DR8000/8100 infrared spectrometer. NMR spectra were obtained with a Varian Gemini 200 (200 MHz) spectrometer for samples in $CDCl_3$ solution with tetramethylsilane as internal standard, and *J*-values are given in Hz. Fast-atom bombardment mass spectra (FAB-MS) were recorded on a JEOL-JMS HS110 mass spectrometer. Optical rotations were measured in 1 dm path length cells of 10 cm^3 volume on a JASCO Model DIP181 polarimeter; $[a]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. THF was distilled under argon from sodium benzophenone ketyl immediately before use. Dichloromethane and benzene were distilled from calcium hydride and stored over molecular sieves 4 Å. Dichloromethane for lipase-catalyzed transesterification was distilled from calcium hydride after being washed by water and was dried over anhydrous calcium chloride, and stored over molecular sieves 4 Å. All photocyclizations were accomplished in an ice–water-cooled Pyrex photoreactor using a 200 W or 400 W high-pressure mercury lamp. Silica gel (Wakogel C-200) of the size 100–200 mesh was used for column chromatography. HPLC analysis was carried out with an Hitachi instrument equipped with UV detector L4000, using Sumichiral OA2000 or OA2000I.

2-(Triisopropylsiloxymethyl)benzo[1,2-*b*:4,3-*b*′]dithiophene 2

To a stirred solution of 2-(hydroxymethyl)benzo[1,2-*b*:4,3-*b*′]-dithiophene **1** (7.56 g, 34.31 mmol) in dichloromethane (115 cm^3) were added 2,6-lutidine (9.19 g, 85.78 mmol) and triisopropylsilyl triflate (11.04 g, 36.03 mmol) at 0 °C under argon. The ice-bath was removed and the solution was stirred at room temp. for 4 h. The reaction was quenched by 5% hydrochloric acid (400 cm^3) and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was crystallized from hexane to give *siloxane* **2** (11.51 g, 89%) as an off-white solid. The filtrate was concentrated and chromatographed on silica gel (hexane) to give more siloxane **2** (0.78 g, 6%) as a solid. The total yield of title compound **2** was 95% (Found: C, 63.80; H, 7.50. $C_{20}H_{28}OS_2Si$ requires C, 63.78; H, 7.49%); mp 50–51 °C; $\delta_H(CDCl_3)$ 1.08–1.29 (21 H, m, 3 × Me_2CH), 5.13 (2 H, d, *J* 1.1, CH_2), 7.51 (1 H, t, *J* 1.0, 1-H), 7.51 (1 H, d, *J* 5.3, 8-H), 7.64 (1 H, d, *J* 5.5, 7-H) and 7.72 (1 H, d, *J* 9.3) and 7.77 (1 H, d, *J* 8.1) (together 4- and 5-H); ν_{max}(KBr)/cm^{-1} 2959, 2940 and 2863.

2-Formyl-7-(triisopropylsiloxymethyl)benzo[1,2-*b*:4,3-*b*′]-dithiophene 3

To a stirred solution of compound **2** (18.45 g, 48.99 mmol) in THF (240 cm^3) were added *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (14.42 g, 124.0 mmol) and BuLi (37.2 cm^3 of 1.58 M solution in hexane) at −78 °C under argon and this mixture was stirred for 5 h. To the resulting green solution was added a solution of DMF (7.16 g, 97.94 mmol) in THF (9.5 cm^3) at −78 °C. The reaction mixture was allowed to warm to room temp. during 16 h. The reaction was quenched by saturated aq. ammonium chloride and 5% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate and concentrated. The crude product was purified by silica gel column chromatography (10:1, hexane–ethyl acetate) to give *aldehyde* **3** (18.73 g, 94%) as a light orange solid (Found: C, 62.39; H, 7.00. $C_{21}H_{28}O_2S_2Si$ requires C, 62.33; H, 6.97%); mp 56–57 °C; $\delta_H(CDCl_3)$ 1.1–1.22 (21 H, m, 3 × Me_2CH), 5.16 (2 H, d, *J* 1.1, CH_2), 7.56 (1 H, d, *J* 1.1, 8-H), 7.74 (1 H, d, *J* 8.7) and 7.89 (1 H, d, *J* 8.8) (together 4- and 5-H), 8.30 (1 H, s, 1-H) and 10.14 (1 H, s, CHO); ν_{max}(KBr)/cm^{-1} 2942, 2863, 1676 (C=O), 1055, 882, 787, 658 and 490.

2-(Hydroxymethyl)-7-(triisopropylsiloxymethyl)benzo-[1,2-*b*:4,3-*b*′]dithiophene 4

To a stirred solution of aldehyde **3** (15.04 g, 37.17 mmol) in a mixture of ethanol (72 cm^3) and THF (58 cm^3) was added sodium borohydride (4.22 g, 111.50 mmol) at 0 °C. The resulting yellow solution was stirred for 2 h at room temp. Diethyl ether (100 cm^3) was added and then saturated aq. citric acid was added to decompose remaining sodium borohydride. The reaction mixture was diluted with water and extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was recrystallized from hexane to give the *title alcohol* **4** (13.65 g, 90%) as a solid. From the filtrate, which was concentrated, and then chromatographed on silica gel (3:1, hexane–ethyl acetate), title compound **4** was obtained (0.98 g, 7%). The total yield of compound **4** was 97% (Found: C, 61.97; H, 7.57. $C_{21}H_{30}O_2S_2Si$ requires C, 62.02; H, 7.44%); mp 97–99 °C; $\delta_H(CDCl_3)$ 1.08–1.30 (21 H, m, 3 × Me_2CH), 1.96 (1 H, t, *J* 6.0, OH), 5.00 (2 H, d, *J* 6.0, CH_2OSi), 5.13 (2 H, d, *J* 1.1, CH_2O), 7.46 (1 H, q, *J* 1.1, 8-H), 7.54 (1 H, q, *J* 0.74, 1-H) and 7.68 (1 H, d, *J* 8.6) and 7.74 (1 H, d, *J* 8.6) (together 4- and 5-H).

2-(Chloromethyl)-7-(triisopropylsiloxymethyl)benzo-[1,2-*b*:4,3-*b*′]dithiophene 5

To a stirred solution of alcohol **4** (18.09 g, 44.48 mmol) in benzene (250 cm^3) were added pyridine (3.69 g, 46.70 mmol) and thionyl dichloride (5.57 g, 46.70 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to room temp. and was stirred overnight. The reaction mixture was then diluted with benzene and the solution was poured into water. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to give the crude chloride **5** as a yellow-brown oil. Since chloride **5** was unstable at room temp. it was used for the next step without purification; $\delta_H(CDCl_3)$ 1.00–1.28 (21 H, m, 3 × Me_2CH), 4.94 (2 H, d, *J* 0.73, CH_2Cl), 5.13 (2 H, d, *J* 1.1, CH_2O), 7.46 (1 H, d, *J* 1.1, 8-H), 7.61 (1 H, d, *J* 0.7, 1-H) and 7.67 (1 H, d, *J* 8.7) and 7.75 (1 H, d, *J* 9.0) (together 4- and 5-H).

({7-(Triisopropylsiloxymethyl)benzo[1,2-*b*:4,3-*b*′]dithiophenyl-2-yl}methyl)triphenylphosphonium chloride 6

A solution of the above chloride **5** and triphenylphosphine (17.50 g, 66.72 mmol) in benzene (100 cm^3) was heated under reflux for 20 h. Benzene was removed by evaporation and the residue was washed with diethyl ether to give the salt **6** (18.19 g, 59%) as an off-white solid. From the filtrate, which was concentrated, and refluxed in dry toluene for 6 h, more salt **6** was isolated (4.00 g, 13%). The total yield of the salt **6** was 72%. An analytical sample was obtained by silica gel column chromatography (10:1, dichloromethane–methanol); mp 159–161 °C; $\delta_H(CDCl_3)$ 1.08–1.29 (21 H, m, 3 × Me_2CH), 5.07 (2 H, d, *J* 1.1, CH_2O), 6.09 (2 H, d, *J* 14.2, CH_2P) and 7.37–7.89 (19 H, m, 19 × ArH); ν_{max}(KBr)/cm^{-1} 2944, 2867, 1439, 1132 and 507.

2-(Triisopropylsiloxymethyl)-7-({7-(triisopropylsiloxymethyl)-benzo[1,2-*b*:4,3-*b*′]dithiophenyl-2-yl}ethenyl)benzo-[1,2-*b*:4,3-*b*′]dithiophene 7

The aldehyde **3** (10.71 g, 26.46 mmol) and the phosphonium salt **6** (18.19 g, 26.46 mmol) were dissolved to a mixture of THF (90 cm^3) and ethanol (380 cm^3). To the solution was added a solution of potassium *tert*-butoxide (4.45 g, 39.69 mmol) in ethanol (80 cm^3) at room temp. The resulting yellow suspension was stirred for 16 h. The reaction was quenched by water and 10% hydrochloric acid, and the precipitates were removed by filtration. The residue was washed with ethanol and then with hexane, and dried *in vacuo* to give the *coupling product* **7** as a yellow powder (17.69 g, 86%) (Found: C, 64.82; H, 7.42. $C_{42}H_{56}O_2S_4Si_2$ requires C, 64.90; H, 7.26%); mp 197–199 °C; $\delta_H(CDCl_3)$ 1.09–1.29 (42 H, m, 6 × Me_2CH), 5.14 (4 H, d, *J* 1.1. 2 × CH_2), 7.30 (2 H, s, 2 × CH=), 7.48 (2 H, d, *J* 1.1, 2 × 1-H), 7.61 (2 H, s, 2 × 8-H) and 7.66 (2 H, d, *J* 9.0) and 7.74 (2 H, d, *J* 9.0) (together 2 × 4-, 2 × 5-H); ν_{max}(KBr)/cm^{-1} 2942, 2865 and 995.

2,13-Bis(triisopropylsiloxymethyl)dithieno[3,2-*e*:3′,2′-*e*′]-benzo[1,2-*b*:4,3-*b*′]bis[1]benzothiophene 8

The olefin **7** (2.00 g, 2.57 mmol) was dissolved in benzene (1.7 dm^3), and argon gas was bubbled into the solution for 30 min before photo-irradiation. The photoreactor was cooled to 10 °C by an ice–water-bath. Iodine (1.44 g, 5.65 mmol) and propylene oxide (36.0 cm^3, 51.45 mol) were added and then the solution was irradiated for 10 h under argon. The reaction mixture was washed successively with aq. sodium thiosulfate and aq. sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated. These procedures were repeated four times. The combined crude product obtained from 2.00 g × 5 of substrate **7** (12.87 mmol) was purified by silica gel column chromatography (100 : 1, hexane–ethyl acetate) to give *title heptacycle* **8** (6.58 g, 66%) as a pale yellow solid (Found: C, 65.43; H, 7.07. $C_{42}H_{54}O_2S_4Si_2$ requires C, 65.06; H, 7.02%); mp 164–167 °C; $\delta_H(CDCl_3)$ 0.93–1.13 (42 H, m, 6 × Me_2CH), 4.53 (2 H, dd, *J* 1.1 and 13.4, CH_2), 4.60 (2 H, dd, *J* 1.1 and 13.5, CH_2), 6.56 (2 H, t, *J* 1.1, 1- and 14-H), 7.88 (2 H, d, *J* 8.6) and 7.97 (2 H, d, *J* 9.0) (together 4-, 5-, 10- and 11-H) and 7.99 (2 H, s, 7- and 8-H); ν_{max}(KBr)/cm^{-1} 2942, 2865, 1134, 1092, 1067 and 735.

2,13-Bis(hydroxymethyl)dithieno[3,2-*e*:3′,2′-*e*′]benzo[1,2-*b*:4,3-*b*′]bis[1]benzothiophene 9

To a solution of compound **8** (6.68 g, 8.62 mmol) in THF (150 cm^3) was added a solution of TBAF (18.1 cm^3 of 1 M solution in THF) at 0 °C. The solution was stirred at 0 °C for 4 h and at room temp. for 2 h. The reaction was quenched by brine, and ethyl acetate was added to separate the organic layer. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified by silica gel column chromatography (2 : 1, hexane–ethyl acetate) and recrystallized from ethanol to give *title diol* **9** (3.95 g, 90%) as a yellow solid [Found: C, 61.46; H, 3.76. $C_{26}H_{20}O_3S_4$ (**9** + C_2H_5OH) requires: C, 61.39; H, 3.96%]; mp 179–181 °C; $\delta_H(CDCl_3)$ 1.24 (3 H, t, *J* 8.0, Me of ethanol), 1.72 (2 H, m, OH), 3.73 (2 H, q, *J* 8.0, CH_2 of ethanol), 4.27 (2 H, d, *J* 12.8, CH_2), 4.46 (2 H, d, *J* 12.8, CH_2), 6.59 (2 H, s, 1- and 14-H), 7.97–8.02 (4 H, d, *J* 8.0, 4-, 5-, 10- and 11-H) and 8.06 (2 H, s, 7- and 8-H).

(*P*)-(+)-2,13-Bis(hydroxymethyl)dithieno[3,2-*e*:3′,2′-*e*′]-benzo[1,2-*b*:4,3-*b*′]bis[1]benzothiophene (*P*)-9

To a solution of racemate (*PM*)-**9** (101 mg, 0.219 mmol) in dichloromethane (100 cm^3) were added molecular sieves 4 Å (4.37 g), PCL (2.99 g, 60 units mg^{-1}, Amano), and vinyl acetate (2.0 cm^3, 21.7 mmol), and the mixture was stirred at 30 °C. The reaction was terminated close to the 50% esterification point (*ca.* 25 h) by filtration off of lipase. Evaporation of the mixture followed by silica gel chromatography gave diol (*P*)-**9** (44 mg, 44%) in 98% ee {$[\alpha]_D$ +1973 (*c* 0.055 in $CHCl_3$)} along with acetate (*M*)-**10** (41 mg, 37%) and diacetate (*M*)-**11** (15 mg, 13%). Hydrolysis of acetate (*M*)-**10** in methanol (10 cm^3) with 0.1 M aq. sodium hydroxide gave diol (*M*)-**9** (36 mg) in 77% ee. In a similar way, hydrolysis of diacetate (*M*)-**11** led to diol (*M*)-**9** (12 mg) in 94% ee.

(*M*)-(−)-2,13-Bis(hydroxymethyl)dithieno[3,2-*e*:3′,2′-*e*′]-benzo[1,2-*b*:4,3-*b*′]bis[1]benzothiophene (*M*)-9

To a solution of racemate (*PM*)-**9** (1.00 g, 0.217 mmol) in dichloromethane (800 cm^3) were added CAL (2.50 g, 70 units mg^{-1}, Novo) and vinyl acetate (20.0 cm^3, 217 mmol), and the mixture was stirred at 30 °C. The reaction was terminated close to the 50% esterification point (9.5 h) by filtration off of lipase. Evaporation of the mixture followed by silica gel chromatography gave diol (*M*)-**9** (440 mg, 44%) in 92% ee {$[\alpha]_D$ −1965 (*c* 0.050 in $CHCl_3$)} along with acetate (*P*)-**10** (578 mg, 53%) and diacetate (*P*)-**11** (34 mg, 3%). Hydrolysis of acetate (*P*)-**10** gave diol (*P*)-**9** in 67% ee, and diacetate (*P*)-**11** gave diol (*P*)-**9** in 89% ee.

Thermal racemization of compound 9

(*M*)-Helicenediol **9** (5 mg) of 95% ee was dissolved in 20 cm^3 of mesitylene, then the solution was heated under argon. Every 24 h, 0.4 cm^3 of the reaction was withdrawn *via* a syringe as a sample for HPLC analysis.

Enantiomeric enhancement

Chromatography was carried out on a column packed with silica gel (18 mm diameter, 20 cm height) by elution with hexane–ethyl acetate (3 : 1). A dichloromethane solution of helicenediol **9** was chromatographed and fractions of 20 cm^3 volume were collected in test tubes. The ees were determined by HPLC by using methyl *m*-hydroxybenzoate as an internal standard.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research and by Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports and Culture. H. O. thanks JSPS for fellowships (Nos. 6-3089 and 9-2575).

References

1 M. T. Reetz, E. W. Beuttenmüller and R. Goddard, *Tetrahedron Lett.*, 1997, **38**, 3211.
2 M. S. Newman, W. B. Lutz and D. Lednicer, *J. Am. Chem. Soc.*, 1955, **77**, 3420.
3 M. S. Newman and D. J. Lednicer, *J. Am. Chem. Soc.*, 1956, **78**, 4765.
4 H. Wynberg and M. B. Groen, *J. Am. Chem. Soc.*, 1968, **90**, 5339.
5 Y. H. Kim, A. Balan, A. Tishbee and E. Gil-Av, *J. Chem. Soc., Chem. Commun.*, 1982, 1336.
6 R. H. Martin, M. Flammang-Barbieux, J. P. Cosyn and M. Gelbcke, *Tetrahedron Lett.*, 1968, 3507.
7 H. Wynberg, M. B. Groen and H. Schadenberg, *J. Org. Chem.*, 1971, **36**, 2797.
8 H. Wynberg and M. B. Groen, *J. Am. Chem. Soc.*, 1970, **92**, 6664.
9 F. Mikes, G. Boshart and E. Gil-Av, *J. Chromatogr.*, 1976, **122**, 205.
10 H. Numan, R. Helder and H. Wynberg, *Recl. Trav. Chim. Pays-Bas*, 1976, **95**, 211.
11 K. Tanaka, Y. Shogase, H. Osuga, H. Suzuki and K. Nakamura, *Tetrahedron Lett.*, 1995, **36**, 1675.
12 E. J. Corey, H. Cho, C. Rücker and D. H. Hua, *Tetrahedron Lett.*, 1981, **22**, 3455.
13 L. Liu, B. Yang, T. J. Katz and M. K. Poindexter, *J. Org. Chem.*, 1991, **56**, 3769.

14 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
15 F. Toda and K. Tanaka, *J. Org. Chem.*, 1988, **53**, 3607.
16 F. Toda, K. Tanaka and H. Ueda, *Tetrahedron Lett.*, 1981, **22**, 4669.
17 C.-S. Chen, Y. Fugimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294.
18 V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.
19 K. Yamada, H. Nakagawa and H. Kawazura, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2429.
20 K. C. Cundy and P. A. Crooks, *J. Chromatogr.*, 1983, **281**, 17.
21 R. Charles and E. Gil-Av, *J. Chromatogr.*, 1984, **298**, 516.
22 W.-L. Tsai, K. Hermann, E. Hug, B. Rohde and A. S. Dreiding, *Helv. Chim. Acta*, 1985, **68**, 2238.
23 A. Dobashi, Y. Motoyama, K. Kinoshita and S. Hara, *Anal. Chem.*, 1987, **59**, 2209.
24 R. Matusch and C. Coors, *Angew. Chem.*, *Int. Ed. Engl.*, 1989, **28**, 626.
25 R. M. Carman and K. D. Klika, *Aust. J. Chem.*, 1991, **44**, 895.
26 P. Diter, S. Taudien, O. Samuel and H. Kagan, *J. Org. Chem.*, 1994, **59**, 370.
27 E. Loza, D. Lola, A. Kemme and J. Freimanis, *J. Chromatogr.*, 1995, **708**, 231.
28 M. Nakajima, K. Kanayama, I. Miyoshi and S. Hashimoto, *Tetrahedron Lett.*, 1995, **36**, 9519.

Paper 7/07196E
Received 6*th October* 1997
Accepted 25*th November* 1997