Tetrahedron: Asymmetry Vol 4, No. 8, pp. 1843-1856, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Diastereocontrolled Synthesis of Optically Pure Functionalized Heterohelicenes

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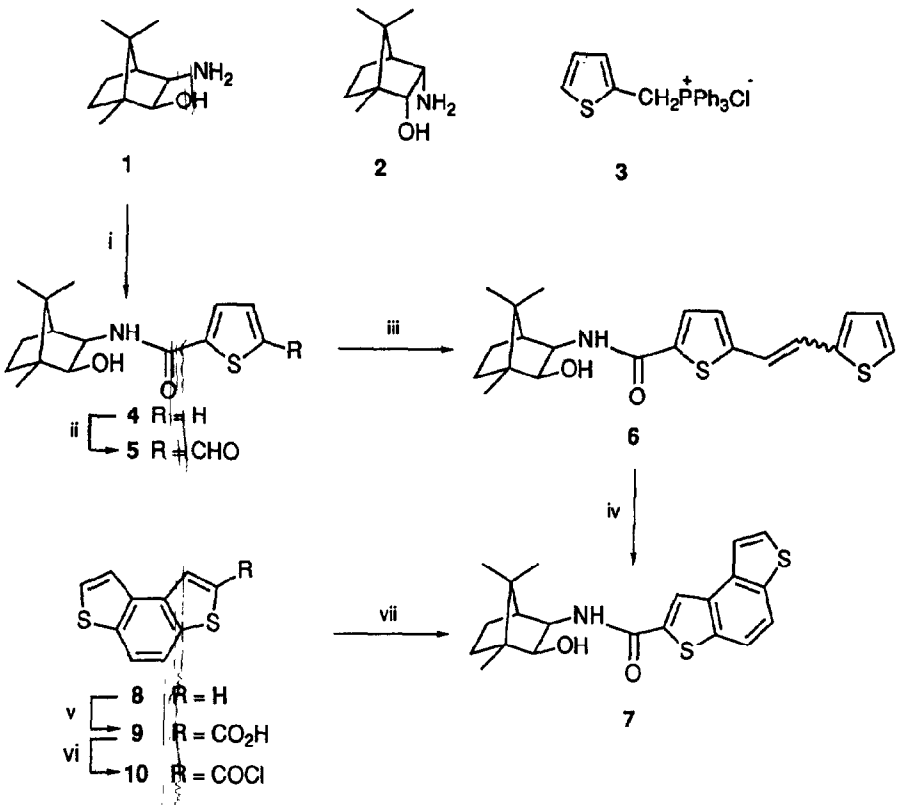
(*Received in UK* 19 *April* 1993; *accepted* 25 *May* 1993)

Abstract: (1*R*,2*S*,3*R*,4*S*)-*exo*-3-Amino-*exo*-2-hydroxybornane (*exo*-amino alcohol) and (1*R*,2*R*,3*S*,4*S*)-*endo*-3-amino-*endo*-2-hydroxybornane (*endo*-amino alcohol) were found to be efficient diastereomeric chiral auxiliaries for the preparation of functionalized optically pure heterohelicenes. The diastereoselectivities in the synthesis of the helicenes via photocyclization were controlled by the use of these chiral auxiliaries and the resulting diastereomers were readily separated by column chromatography. Removal of the chiral auxiliaries gave optically pure (+)-*(P)*- and (-)-*(M)*-[7]heterohelicenes, whose rotational values were +2830 and -2770, respectively.

Introduction

Helical structures are often encountered in natural products such as polyamilose, polypeptides and nucleic acids, which are stabilized through hydrogen bonds, disulfide linkages, hydrophobic interactions, and metal coordination.[1] These compounds possess inherent chirality which is related with the screw sense of helicity, *i.e.* a right-handed helix (*P*) and a left-handed helix (*M*). The artificially prepared helical compounds are known as helicenes,[2] helicates,[3a] and helixanes.[3b] Among them, helicenes have rigid helicity and therefore possess high optical stability.[4] Therefore, functionalized helicenes of high optical purity are of great interest in respect to new chiral ligands, chiral stationary phase or chiral elements.[5] Ever since the first study on hexahelicene and its optical resolution by Newman and Lednicer in 1955,[6] the chemistry of helicenes has attracted a great deal of attention because of their very high rotational values and unique helical structure. In 1968, Wynberg and coworkers began to study the synthesis of a wide variety of heterohelicenes by photocyclization of 1,2-diarylethylene.[7,8] The preparation of optically active helicenes, however, requires laborious methods such as (i) the repeated recrystallizations of diastereomeric π complexes derived from racemic helicenes and optically active compounds like α-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA),[4b,6,9] (ii) crystal picking,[8] or (iii) microscale separation by chiral column of high performance liquid chromatography (HPLC).[10] Although photosynthesis by circularly polarized light[11] or in chiral solvents[12] is a very attractive method for chiral helicenes, the enantioselectivities are very low, ranging from 0 to 3.0 %. Asymmetric synthesis using a chiral auxiliary such as a menthyl ester has been developed.[13] However, the diastereoselectivities of photocyclization are low to moderate and the diastereoisomers could not be isolated.

In a preliminary communication,[14] we reported that (1*R*,2*S*,3*R*,4*S*)-*exo*-3-amino-*exo*-2-hydroxybornane (**1**) is an efficient chiral auxiliary for the preparation of optically pure functionalized heterohelicenes. In this paper we now wish to report a full account of the synthesis of the heterohelicenes by use of diastereomeric *exo*- and *endo*-bicyclic amino alcohols as chiral auxiliaries, both of which are readily prepared from D-camphor.[15] Our strategies for the synthesis of the optically active heterohelicenes consist of the carboxamide-induced

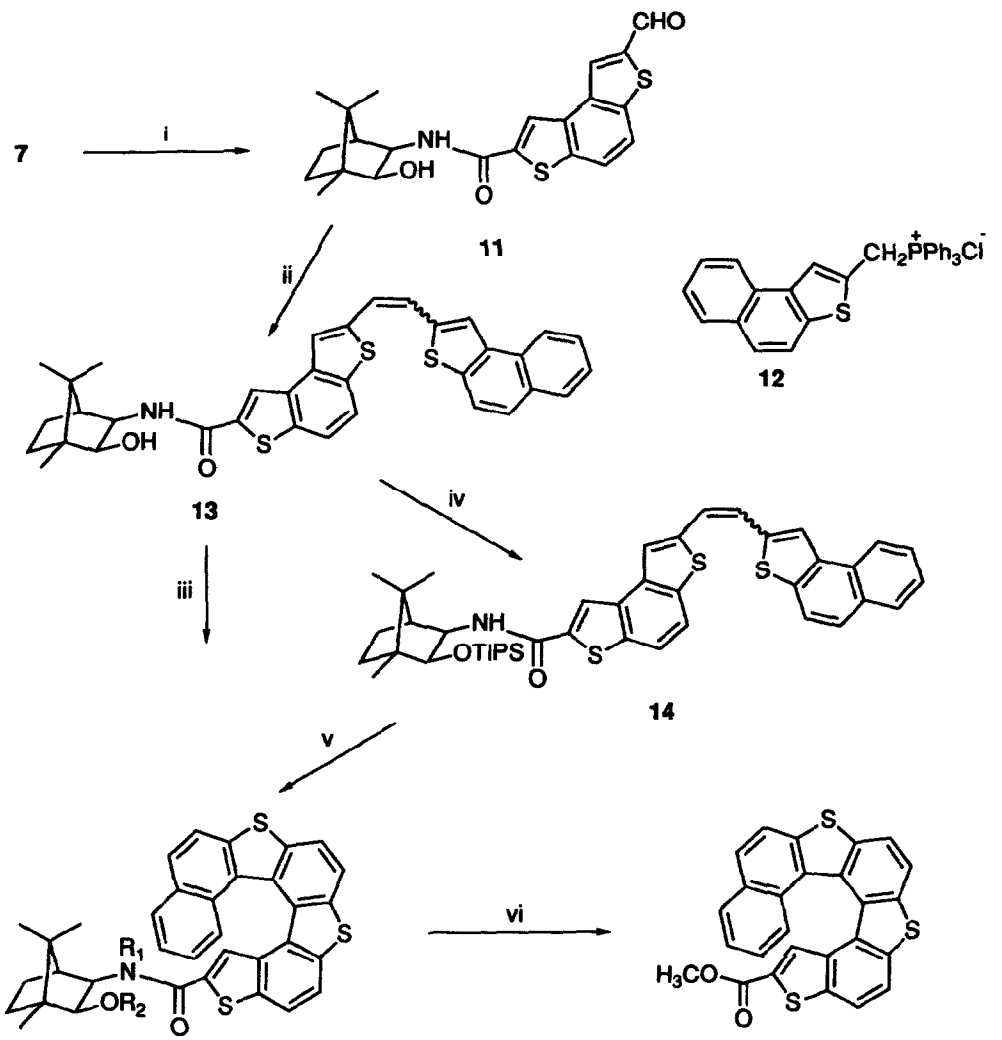


Scheme 1. *Reagents and conditions*: (i) 2-thiophenecarbonyl chloride, CH_2Cl_2, pyridine; (ii) LDA, THF, -15 °C, DMF; (iii) **3**, *t*-BuOK, MeOH, THF; (iv) *hν*, I_2, benzene; (v) *n*-BuLi, ether, room temperature, CO_2 (solid); (vi) $SOCl_2$, benzene; (vii) **1**, pyridine, 4-dimethylaminopyridine (DMAP), CH_2Cl_2

remote lithiation and the diastereoselective photocyclization of dithienylethylenes prepared by Wittig reaction.

Results and discussion

When lithium diisopropylamide (LDA) was treated with amide **4**, prepared from secondary *exo*-amino alcohol **1** and 2-thiophenecarbonyl chloride[15] at -15 °C in tetrahydrofuran (THF), the 5-lithio-species was obtained exclusively[16] and trapped with *N*,*N*-dimethylformamide (DMF) to give 5-formylthiophenecarboxamide (**5**) in 79 % yield. The Wittig reaction of **5** with thienyltriphenylphosphonium chloride (**3**) and subsequent photocyclization of the resulting 1,2-dithienylethylene **6** gave benzodithiophenecarboxamide (**7**) in 54 % yield. The carboxamide **7** was also prepared from *exo*-amino alcohol **1** and 2-benzo[1,2-b:4,3-b']-dithiophenecarbonyl chloride (**10**) derived from benzo[1,2-b:4,3-b']dithiophene (**8**).[17] Alpha-lithiation of the terminal thiophene ring of **7** was carried out under similar conditions to that for the amide **4** and the lithio-species was treated with DMF to afford **11** in 79 % yield. The aldehyde **11** was converted into 1,2-dithienylethylene **13** in 83 % yield by Wittig reaction with 2-naphtho[2,1-b]thienylmethyltriphenyl-



15 (R_1=H, R_2=H)
16 (R_1=H, R_2=TIPS)
17 (R_1=*t*-Boc, R_2=H)
(-)-(*M*)-**18** (R_1=H, R_2=H)
(+)-(*P*)-**18** (R_1=H, R_2=H)

(-)-(*M*)-**19**
(+)-(*P*)-**19**

Scheme 2. *Reagents and conditions*: (i) LDA, THF, -15 °C, DMF; (ii) **12**, *t*-BuOK, MeOH, THF; (iii) *hν*, I_2, propylene oxide, benzene; (iv) (*i*-Pr)$_3$SiOTf, 2,6-lutidine, CH_2Cl_2; (v) (a) *hν*, I_2, propylene oxide, benzene; (b) tetrabutylammonium fluoride, THF; (vi) (a) (*t*-$BuO_2C)_2O$, Et_3N, DMAP, CH_2Cl_2; (b) CH_3ONa, MeOH, THF.

phosphonium chloride (**12**). Photocyclization of **13** in the presence of propylene oxide (excess) and a stoichiometric amount of iodine in bezene (0.60 mM) under argon[18] gave the desired [7]heterohelicene **15** in 57 % yield as a mixture of the diastereoisomers (45:55).[14] The chemical yield of the helicene **15** was improved to 91 %, when the reaction was carried out in more dilute solution of **13** (0.31 mM). The use of the triisopropylsilyl ether **14** prepared from **13** and triisopropylsilyl trifluoromethanesulfonate,[19,20] provided better diastereoselectivity (32:68) in this photocyclization. Desilylation of the corresponding helicene **16** with tetrabutylammonium fluoride in THF gave **15** in 60 % yield.

The separation of diastereoisomers of **15** was readily achieved by column chromatography on silica gel using hexane–ethyl acetate (5:1) as eluent. The optical purity of both diastereomers, (-)-(*M*)-**18** and (+)-(*P*)-**18**, was determined as >99.5 % by HPLC analysis.[14] It is important to note that the hydroxy function on the bicyclic moiety of the amide is crucial for chromatographic separation of the diastereomers **15**, since the diastereomers of the corresponding helicenes **16** having *O*-triisopropylsilyl group were not separable by column chromatography. Removal of the chiral auxiliary from the major diastereomer (-)-(*M*)-**18** was carried out by *N*-*tert*-butoxycarbonylation[21] and subsequent methanolysis[22] of **17** to afford (-)-2-methoxycarbonyl-[7]heterohelicene (-)-(*M*)-**19** in 16 % yield along with the helicenecarboxamide (-)-(*M*)-**18** in 68 % yield. Similarly, (+)-methyl ester **19** was obtained from the minor isomer (+)-(*P*)-**18**. The low yield of the methyl ester **19** was probably due to the steric hindrance of the helicene moiety, since the attack of methoxide anion to carbonyl of the amide moiety is sterically hindered and leading to the formation of the helicenecarboxamide **15**.[23] The optical rotation of (-)-(*M*)-**19** obtained from (-)-(*M*)-**18** was $[\alpha]_D$ -2770 (c 0.053, $CHCl_3$), whose absolute value was good agreement with that of the enantiomer derived from (+)-(*P*)-**18**, $[\alpha]_D$ +2830 (c 0.046, $CHCl_3$) within the experimental error. The CD spectra of the (+)- and (-)-heterohelicenes **19** in chloroform solution are shown in Figure 1. These results indicate that both of the methyl esters **19** obtained from the diastereomers, (-)-(*M*)-**18** and (+)-(*P*)-**18**, are enantiomerically pure.

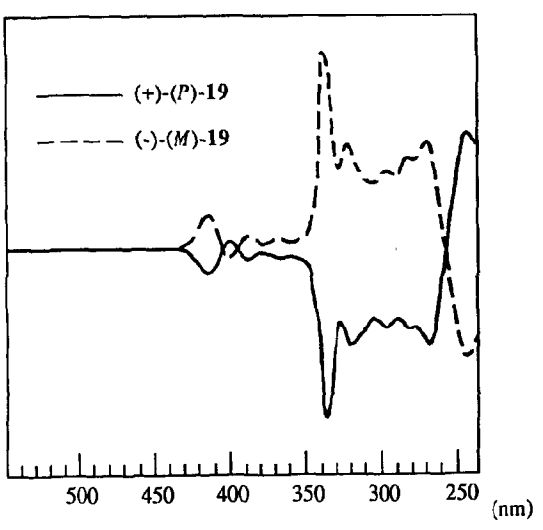
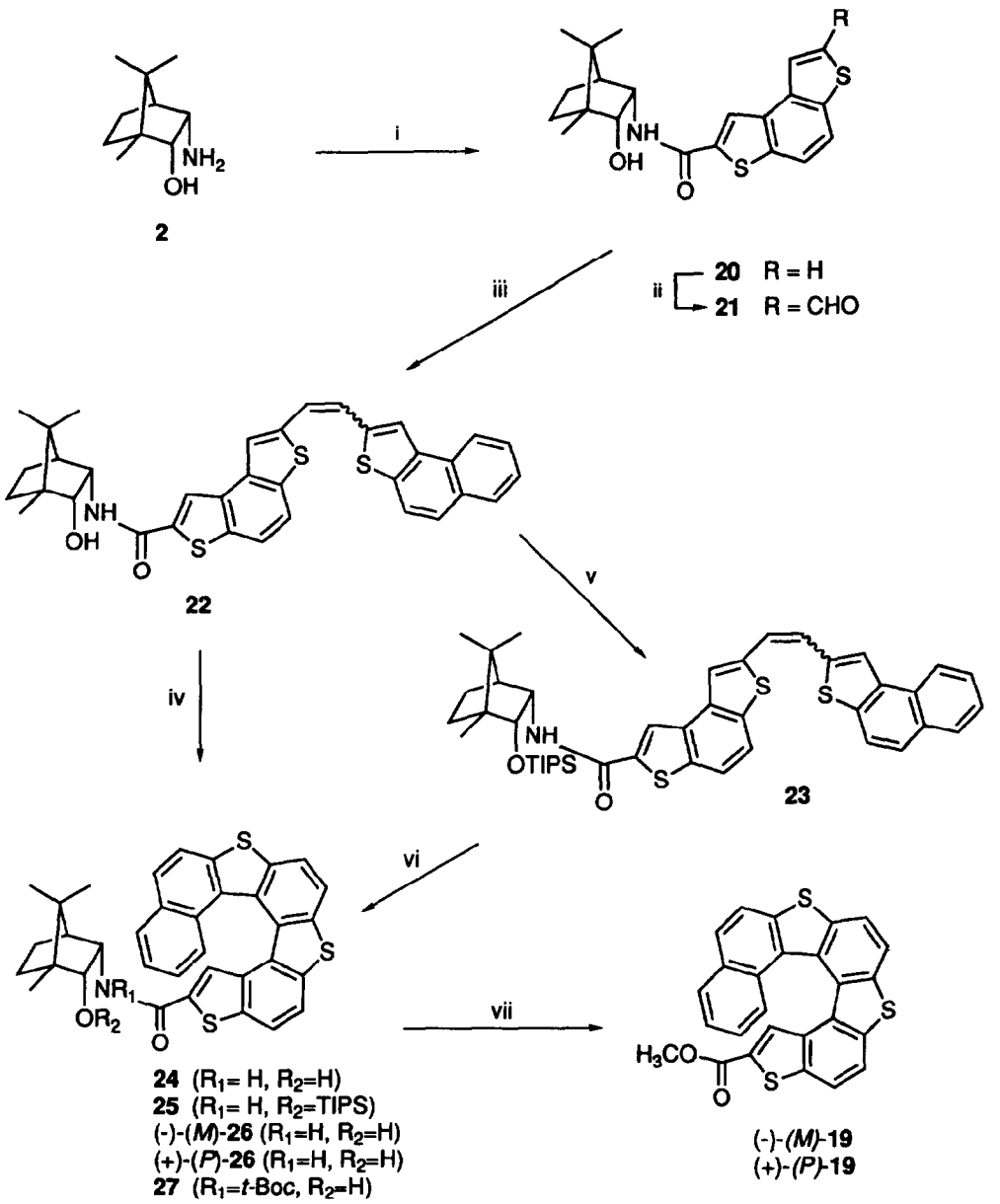


Figure 1. CD spectra of the enantiomers of the methyl ester **19** in chloroform.



Scheme 3. *Reagents and conditions*: (i) **10**, pyridine, DMAP, CH_2Cl_2; (ii) LDA, THF, -15 °C, DMF; (iii) *t*-BuOK, MeOH, THF; (iv) *hν*, I_2, propylene oxide, benzene; (v) $(i\text{-Pr})_3SiOTf$, 2,6-lutidine, CH_2Cl_2; (vi) (a) *hν*, I_2, propylene oxide, benzene; (b) tetrabutylammonium fluoride, THF; (vii) (a) $(t\text{-}BuO_2C)_2O$, Et_3N, DMAP, CH_2Cl_2; (b) CH_3ONa, MeOH, THF.

The synthesis of the heterohelicenes was next carried out using *endo*-amino alcohol **2** as a chiral auxiliary. The carboxamide **20** was prepared from *endo*-amino alcohol **2** and 2-benzo[1,2-b:4,3-b']dithiophenecarbonyl chloride (**10**). Alpha-lithiation of the terminal thiophene ring of **20** was carried out under similar conditions to those for the amide **7** and the lithio-species was treated with DMF to afford **21** in 82 % yield. The aldehyde **21** was converted into 1,2-dithienylethylene **22** in 81 % yield by the Wittig reaction with 2-naphtho[2,1-b]-thienylmethyltriphenylphosphonium chloride (**12**). Although the photocyclization of olefin **22** showed no diastereoselectivity (50:50), the use of triisopropylsilyl ether **23** prepared from **22** increased the diastereoselectivity (75:25). Separation of the diastereoisomers **24** was performed by column chromatography on silica gel (hexane–ethyl acetate 10:1) or by recrystallization from ethyl acetate. Removal of chiral auxiliary from the major diastereomer (+)-(*P*)-**26** gave (+)-methyl ester **19**. These results indicate that the diastereoselectivity is controlled by the use of the diastereomeric chiral auxiliaries, *i.e. exo*-amino alcohol and its *endo*-isomer.

In order to examine whether racemization or kinetic resolution take place during the removal of chiral auxiliary, the carboxamide **24** (74.6:25.4 ratio of the diastereoisomers) was converted into *N*-Boc derivative **27**. Methanolysis of **27** gave methyl ester **19** along with carboxamide **24** (61 %). The ratio of the diastereoisomers **24** was determined as 74.1:25.9 by HPLC, indicating neither racemization nor kinetic resolution took place. The absolute configuration of the major diastereomer (+)-**26**, prepared in the photocyclization of *endo*-amino alcohol derivative **22** was determined by X-ray crystallography.[24]

The result indicates that the configuration of the helicene (+)-**26** is *P*, a right-handed helicity which agrees with the fact that the dextrorotatory helicenes have the right-handed helicity and the levorotatory helicenes have the left-handed helicity.[25]

In conclusion, we have developed an efficient synthetic method for optically pure functionalized heterohelicenes, which would provide a wide variety of derivatives of optically pure heterohelicenes. The method which provides both enantiomers of helicenes by using chiral auxiliaries derived from a single chiral pool, D-camphor, would be most attractive and desirable from a synthetic viewpoint. The synthesis of optically pure bifunctionalized heterohelicenes which are more effective for chiral auxiliaries or chiral ligands are in progress and will be reported in due course.

Experimental

General. THF was distilled under argon atmosphere from sodium benzophenone ketyl immediately before use. Ether, dichloromethane and benzene were distilled from calcium hydride and stored over 4Å molecular sieves. The hexane solution of *n*-butyllithium (Kanto Chemicals) was titrated using diphenylacetic acid.[26] Melting points were determined on a Yanagimoto hotstage apparatus and are not corrected. IR spectra were recorded on a SHIMADZU FT IR DR 8000/8100 infrared spectrometer. NMR spectra were obtained with a Varian Gemini-200 (200 MHz) spectrometer in $CDCl_3$ or CD_3SOCD_3 solution with tetramethylsilane as an internal standard. *J* values are given in Hz. Optical rotations were measured in 1dm path length cells of $10cm^3$ on a JASCO Model DIP-181 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}. The CD spectra were recorded in chloroform at room temperature on a JASCO model J-500 recording spectropolarimeter. All photo-cyclizations were accomplished in a water-cooled Pyrex photoreactor using a 200-W high-pressure mercury lamp. Thin layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100-200 mesh was used for column chromatography. Elemental analysis were

performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University.

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-formylthiophene-2-carboxamide (5).** To a stirred solution of LDA (15.8 mmol), prepared from *n*-butyllithium (11.0 mL of a 1.43 M solution in hexane) and *N,N'*-diisopropylamine (2.2 mL), in THF (30 mL) was added a solution of **4**[15] (1.00 g, 3.58 mmol) in THF (15 mL) at -15 °C under argon. After 2h at 0 °C, the resulting light brown suspension was cooled to -65 °C and DMF (2.2 mL, 28.6 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (2:1)) to give the *title compound* **5** as white crystals (0.87 g, 79 %); m.p. 201-203 °C (Found: C, 62.57; H, 7.08; N, 4.41. $C_{16}H_{21}NO_3S$ requires C, 62.52; H, 6.84; N, 4.56 %); IR (KBr) 3400, 2950, 1665, 1645, 1530, 1510, 1445, 1210, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s, 3H), 0.98 (s, 3H), 1.12 (s, 3H), 1.14 (m, 1H), 1.27 (m, 2H), 1.56 (m, 1H), 1.74 (m, 1H), 2.01 (d, *J* 4.0, 1H), 2.07 (d, *J* 4.8, 1H), 3.82 (m, 2H), 6.99 (m, 1H), 7.54 (d, *J* 3.9, 1H), 7.71 (d, *J* 3.9, 1H), 9.93 (s, 1H).

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-[2-(2-thienyl)ethenyl]thiophene-2-carboxamide (6).** To a stirred solution of aldehyde **5** (0.81 g, 2.63 mmol) and phosphonium salt **3**[8b] (1.86 g, 3.95 mmol) in methanol (40 mL) was added a solution of potassium *tert*-butoxide (0.59 g, 5.26 mmol) in methanol (5 mL) at 0 °C. After the resulting yellow suspension was stirred overnight at room temperature, the reaction was quenched by diluted hydrochloric acid and CH_2Cl_2 was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4) and concentrated. The crude product was recrystallized from ethanol–hexane to give the *title compound* **6** (0.77 g, 76 %) as a yellow solid; m.p. 220-222 °C (Found: C, 65.03; H, 6.34; N, 3.31. $C_{21}H_{25}NO_2S_2$ requires C, 65.08; H, 6.50; N, 3.61 %); IR (KBr) 3385, 2955, 1625, 1535, 1520, 1495, 1280, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84(s, 3H), 0.98 (s, 3H), 1.10 (m, 1H), 1.14 (s, 3H), 1.26 (m, 1H), 1.54 (m, 1H), 1.76 (m, 1H), 1.96 (d, *J* 4.4, 1H), 2.23 (br s, 1H), 3.94 (m, 2H), 6.96 (m, 1H), 6.91-7.09 (m, 5H), 7.34 (d, *J* 3.9, 1H).

Benzo[1,2-b:4,3-b']dithiophene-2-carboxylic acid (9). To a stirred solution of **8**[17] (5.00 g, 26.3 mmol) in ether (150 mL) was added *n*-butyllithium (27.6 mmol, 17.2 mL of 1.61 M solution in hexane) at room temperature under argon. After 15min at room temperature, the resulting light brown suspension was poured onto solid CO_2 in ether, and the mixture was stirred until solid CO_2 was disappeared. To the reaction mixture 5 % NaOH solution was added and the aqueous layer was washed with ether. The aqueous layer was acidified by concentrated hydrochloric acid and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4) and concentrated. The resulting residue was recrystallized from xylene to give the *title compound* **9** as a yellow solid (2.69 g, 44 %); m.p. 263-264 °C (Found: C, 56.59; H, 2.62. $C_{11}H_6O_2S_2$ requires C, 56.39; H, 2.58 %); IR (KBr) 2800 (br), 1675, 1515, 1285, 1265, 1180, 1150, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (d, *J* 5.2, 1H), 7.77 (d, *J* 5.2, 1H), 7.82 (d, *J* 9.1, 1H), 7.97 (d, *J* 9.1, 1H), 8.53 (s, 1H).

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (7).** **(i) *Photocyclization*:** A solution of **6** (150 mg, 0.37

mmol) and iodine (9.5 mg, 0.037 mmol) in benzene (100 mL) was irradiated under air atmosphere for 7h at room temperature. The reaction mixture was washed with aqueous $Na_2S_2O_3$ and extracted with benzene. The combined organic extracts were washed with aqueous $NaHCO_3$, brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (3:1)) to give the *title compound* **7** as white crystals (78 mg, 54 %). **(ii) *via Acid chloride*:** *exo*-Amino alcohol **1** was prepared according to literature procedures.[15] The optical rotation of (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2,3-iminomethanoepoxybicyclo[2.2.1]heptane-9-one, the precursor of **1**, is $[\alpha]^{22}_D$ -43.4 (c 2.02, $CHCl_3$) (lit.,[27] $[\alpha]^{22}_D$ -33 (c 0.625, CH_2Cl_2)). To a stirred suspension of **9** (0.67 g, 2.86 mmol) in dry benzene (15 mL) was added thionyl chloride (0.42 mL, 5.27 mmol) and the mixture was heated under reflux for 2h. The solvent was distilled away from the resulting yellow solution under reduced pressure. The crude benzodithiophene carbonyl chloride (**10**) was dried *in vacuo* for 2h and used without further purification. To a stirred solution of a mixture of *exo*-amino alcohol **1** (0.49 g, 2.86 mmol), pyridine (0.19 mL, 2.29 mmol) and DMAP (0.14 g, 1.14 mmol) in dry CH_2Cl_2 (15 mL) was added a solution of **10** in dry CH_2Cl_2 (10 mL) at 0 °C and the mixture was stirred at room temperature overnight. To the reaction mixture was added a cold dilute hydrochloric acid and the aqueous layer was extracted with CH_2Cl_2 and washed with brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (3:1))to give the *title compound* **7** as white crystals (0.80 g, 75 %); m.p. 252-254 °C (Found: C, 65.18; H, 6.15; N, 3.57. $C_{21}H_{23}O_2NS_2$ requires C, 65.42; H, 6.01; N, 3.63 %); IR (KBr) 3300, 2950, 1620, 1540, 1520, 1495, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.02 (s, 3H), 1.12 (m, 1H), 1.18 (s, 3H), 1.27 (m, 1H), 1.58 (m, 1H), 1.80 (m, 1H), 2.00 (d, *J* 4.4, 1H), 2.96 (m, 1H), 3.99 (m, 2H), 7.07 (m, 1H), 7.52 (d, *J* 5.5, 1H), 7.56 (d, *J* 5.5, 1H), 7.57 (d, *J* 8.8, 1H), 7.72 (d, *J* 8.8, 1H), 7.92 (s, 1H).

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-formylbenzo[1,2-b:4,3-b']dithiophene-2-carboxamide (11).** To a stirred solution of LDA (45.7 mmol), prepared from *n*-butyllithium (29.1 mL of a 1.57 M solution in hexane) and *N,N'*-diisopropylamine (6.4 mL), in THF (60 mL) was added a solution of **7** (4.00 g, 10.4 mmol) in THF (90 mL) at -20 °C under argon. After 2h at 0 °C, the resulting dark green suspension was cooled to -65 °C and then DMF (6.5 mL, 83 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 and washed with brine and dried (Na_2SO_4) and concentrated. The crude product was recrystallized from ethanol to give the *title compound* **11** as white crystals (3.37 g, 79 %); m.p. 249-251 °C (Found: C, 63.91; H, 5.72; N, 3.45. $C_{22}H_{23}O_3NS_2$ requires C, 63.89; H, 5.61; N, 3.39 %); IR (KBr) 3400, 2950, 1670, 1635, 1540, 1520, 1485, 1250, 1130 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 0.80 (s, 3H), 0.92 (s, 3H), 1.09 (m, 1H), 1.13 (s, 3H), 1.20 (m, 1H), 1.49 (m, 1H), 1.69 (m, 1H), 1.91 (d, *J* 3.7, 1H), 3.79 (m, 2H), 5.80 (d, *J* 5.2, 1H), 7.63 (d, *J* 4.7, 1H), 8.15 (d, *J* 8.8, 1H), 8.21 (d, *J* 8.8, 1H), 8.67 (s, 1H), 9.06 (s, 1H), 10.17 (s, 1H).

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-[2-(2-naphto[2,1-b]thienyl)ethenyl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (13).** To a stirred solution of a mixture of aldehyde **11** (1.16 g, 2.80 mmol) and phosphonium chloride **12**[8b] (1.66 g, 3.36 mmol) in a mixture of methanol (50 mL) and THF (30 mL) was added a solution of potassium *tert*-butoxide (0.63 g, 5.60 mmol) in methanol (8 mL) at 0 °C, and the reaction mixture was stirred overnight. The precipitated product was filtered off with suction and washed with CH_2Cl_2 and dried *in vacuo* to give the *title*

compound **13** as orange powder (1.38 g, 83 %). An analytically pure sample of **13** was obtained by recrystallization from $CHCl_3$; m.p. 289-290 °C (dec.) (Found: C, 70.29; H, 5.29; N, 2.27. $C_{35}H_{31}O_2NS_3$ requires C, 70.79; H, 5.26; N, 2.36 %); IR (KBr) 3330, 2950, 1620, 1520, 1485, 1040, 805, 770 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 0.81 (s, 3H), 0.89-1.25 (m, 2H), 0.94 (s, 3H), 1.15 (s, 3H), 1.44-1.74 (m, 2H), 1.95 (d, *J* 2.5, 1H), 3.79 (m, 2H), 5.71 (d, *J* 3.3, 1H), 7.42 (d, *J* 4.3, 2H), 7.56 (m, 1H), 7.81-7.99 (m, 6H), 8.02 (s, 1H), 8.18 (d, *J* 4.3, 2H), 8.38 (s, 1H).

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-(Triisopropylsilyl)oxy-1,7,7-trimethylbicyclo-[2.2.1]heptan-3-yl]-5-[2-(2-naphto[2,1-b]thienyl)ethenyl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (14).** The triisopropylsilylation was carried out according to a literature method.[20] To a stirred suspension of **13** (0.41 g, 0.68 mmol) in CH_2Cl_2 were added triisopropylsilyl triflate (0.24 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.36 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and the suspension was stirred overnight. The reaction was quenched by dropwise addition of dilute HCl. Brine was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous $NaHCO_3$, and brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (5:1)) to give the *title compound* **14** as a yellow solid (0.51 g, 100 %); m.p. 127-130 °C (Found: C, 70.04; H, 6.95; N, 2.05. $C_{44}H_{51}O_2NS_3Si$ requires C, 70.45; H, 6.85; N, 1.87 %); IR (KBr) 2945, 2865, 1655, 1515, 1465, 885, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (s, 3H), 0.85-1.32 (m, 5H), 1.04 (s, 3H), 1.17 (d, *J* 5.2, 18H), 1.21 (s, 3H), 1.41-1.82 (m, 2H), 2.08 (d, *J* 2.6, 1H), 4.13 (m, 2H), 6.99 (d, *J* 3.2, 1H), 7.34 (d, *J* 3.8, 2H), 7.44-7.86 (m, 7H), 7.93 (d, *J* 8.7, 1H), 7.97 (s, 1H), 8.06 (s, 1H), 8.29 (d, *J* 8.7, 1H).

N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo-[2.2.1]heptan-3-yl][1]benzothieno[5,4-b]naphto[1',2':4,5]thieno[3,2-e][1]benzothiophene-2-carboxamide (15).** (i) ***From compound 13. Olefin **13** (0.30 g, 0.50 mmol) and iodine (0.13 g, 0.50 mmol) were dissolved in benzene (1.6 L) and argon was bubbled through the stirred solution for 2h before photo-irradiation. Propylene oxide (12.0 mL, 250 mmol) was added to the mixture and the resulting solution was irradiated for 5h at room temperature with argon flow. The reaction mixture was washed with 15 % $Na_2S_2O_3$ solution and extracted with benzene. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4). Evaporation of solvents followed by chromatography (silica, hexane–ethyl acetate (3:1)) gave the diastereomeric mixture (45:55) of the *title compound* **13** as a yellow solid (0.27 g, 91 %). Flash chromatography on silica (hexane–ethyl acetate (10:1–5:1)) gave 0.12 g of (+)-(*P*)-**18** and 0.13 g of (-)-(*M*)-**18** and the unresolved mixtures.

(-)-(*M*)-**18**: m.p. 286-288 °C (Found: C, 70.88; H, 4.98; N, 2.26. $C_{35}H_{29}O_2NS_3$ requires C, 71.04; H, 4.94; N, 2.37 %); $[\alpha]_D$ -2380 (c 0.052, $CHCl_3$); IR (KBr) 3375, 2950, 1645, 1620, 1520, 1480, 1150, 800, 785, 745, 525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3H), 0.88 (s, 6H), 0.85-1.58 (m, 5H), 1.76 (d, *J* 3.7, 1H), 3.64 (m, 2H), 5.49 (m, 1H), 6.70 (s, 1H), 6.77 (m, 1H), 7.36 (m, 1H), 7.53 (d, *J* 8.3, 1H), 7.89-8.16 (m, 7H).

(+)-(*P*)-**18**: m.p. 189-192 °C (Found: C, 70.76; H, 5.18; N, 2.50. $C_{35}H_{29}O_2NS_3$ requires C, 71.04; H, 4.94; N, 2.37 %); $[\alpha]_D$ +2070 (c 0.058, $CHCl_3$); IR (KBr) 3385, 2950, 1635, 1520, 1480, 1150, 800, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (s, 6H), 0.98 (s, 3H), 0.83-1.32 (m, 4H), 1.39-1.72 (m, 2H), 3.72 (m, 2H), 5.70 (m, 1H), 6.68 (s, 1H), 6.72 (m, 1H), 7.28 (m, 1H), 7.46 (d, *J* 8.4, 1H), 7.88-8.14 (m, 7H).

(ii) ***From compound 14.*** Olefin **14** (0.51 g, 0.68 mmol) and iodine (0.09 g, 0.68 mmol) were dissolved in benzene (1.1 L) and argon was bubbled through the stirred solution for 2h before photo-irradiation. Propylene oxide (12.0 mL, 250 mmol) was added to the mixture and the resulting solution was irradiated for 7h at room temperature with argon flow. The reaction mixture was washed with 15 % $Na_2S_2O_3$ solution and extracted with benzene. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4) and concentrated. This material **16** was dissolved in dry THF (10 mL) and tetrabutylammonium fluoride (0.68 mL, 0.68 mmol) of 1M solution in THF was added. The mixture was stirred for 2h at room temperature and quenched with brine. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (10:1)) to give the diastereomeric mixture (32:68) of the *title compound* **15** as a yellow solid (0.31 g, 61 %).

(-)-(*M*)-Methyl [1]benzothieno[5,4-b]naphto[1',2':4,5]thieno[3,2-e][1]benzothiophene-2-carboxylate (19). The conversion of (-)-(*M*)-**18** into the corresponding methyl ester was carried out according to a literature procedure.[22] To a stirred solution of **15** (88 mg, 0.15 mmol) in dry CH_2Cl_2 (3 mL) was added DMAP (27 mg, 0.23 mmol) and triethylamine (0.03 ml, 0.23mmol) under argon atmosphere. A solution of di-*tert*-butyl dicarbonate (0.10 g, 0.45 mmol) in dry CH_2Cl_2 (1 mL) was added and the resulting solution was stirred for 1h. The solvent was evaporated and the crude product was purified by column chromatography (silica, hexane–ethyl acetate (5:1)) to give the *N*-Boc derivative **17** (78 mg, 76 %) as a yellow solid. This material was dissolved in dry THF (1 mL) and methanol (1 mL), and sodium methoxide (0.18 mL, 2M in methanol) was added. After the mixture was stirred overnight at room temperature, brine was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (10:1)) to give (-)-(*M*)-**15** (29.4 mg, 68 %) and the *title compound* (-)-(*M*)-**19** as a yellow solid (5.3 mg, 16 %); m.p. 229-231 °C (Found: C, 68.67; H, 3.37. $C_{26}H_{14}O_2S_3$ requires C, 68.70; H, 3.10 %); $[\alpha]_D$ -2770 (c 0.053, $CHCl_3$); IR (KBr) 1710, 1510, 1290, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 6.70 (m, 1H), 6.98 (d, *J* 2.0, 1H), 7.27 (m, 1H), 7.38 (d, *J* 8.8, 1H), 7.96 (m, 3H), 8.06 (d, *J* 3.0, 2H), 8.12 (d, *J* 3.0, 2H).

***N*-[(1*R*,2*R*,3*S*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (20).** *endo*-Amino alcohol **2** ($[\alpha]^{25}_D$ +36.0 (c 1.04, MeOH) (lit.,[28] $[\alpha]^{20}_D$ +34.9 (c 1, MeOH))) was prepared according to literature procedures.[15] To a stirred suspension of **9** (1.00 g, 4.27 mmol) in dry benzene (40 mL) was added thionyl chloride (0.63 mL, 8.54 mmol) and the mixture was heated under reflux for 4h. The solvent was distilled away from the resulting yellow solution under reduced pressure. The crude benzodithiophene carbonyl chloride **10** was dried *in vacuo* for 2h and was used without further purification. To a stirred solution of a mixture of *endo*-amino alcohol **2** (0.73 g, 4.27 mmol), pyridine (0.26 mL, 3.42 mmol) and DMAP (0.21 g, 1.71 mmol) in dry CH_2Cl_2 (30 mL) was added a solution of benzodithiophene carbonyl chloride **10** in dry CH_2Cl_2 (10 mL) at 0 °C and the mixture was stirred at room temperature overnight. To the reaction mixture was added cold dilute hydrochloric acid, and the aqueous layer was extracted with CH_2Cl_2 and washed with brine and dried (Na_2SO_4) and concentrated. The crude product was recrystallized from ethanol to give the *title compound* **20** as white crystals (1.20 g, 73 %); m.p. 274-276 °C (Found: C, 65.38; H, 6.12; N, 3.54. $C_{21}H_{23}O_2NS_2$ requires C, 65.42; H, 6.01; N, 3.63 %); IR (KBr) 3350, 1620, 1525, 1345, 1105, 1030, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 6H), 1.02 (s,

3H), 1.17 (m, 1H), 1.52 (m, 2H), 1.92 (m, 1H), 2.13 (t, *J* 4.2, 1H), 4.18 (d, *J* 8.8, 1H), 4.41 (m, 1H), 7.02 (d, *J* 6.5, 1H), 7.51 (d, *J* 8.8, 1H), 7.65 (d, *J* 8.8, 1H), 7.90 (s, 1H).

***N*-[(1*R*,2*R*,3*S*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-formyl-benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (21).** To a stirred solution of LDA (11.4 mmol), prepared from *n*-butyllithium (7.1 mL of a 1.61 M solution in hexane) and *N,N'*-diisopropylamine (1.6 mL), in THF (30 mL) was added a solution of **20** (1.00 g, 2.59 mmol) in THF (50 mL) at -20 °C under argon atmosphere. After 2h at 0 °C, the resulting dark green suspension was cooled to -65 °C and then DMF (1.6 mL, 20.7 mmol) in THF (8 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 and washed with brine and dried (Na_2SO_4) and concentrated. The crude product was recrystallized from ethanol to give the *title compound* **21** as white crystals (0.88 g, 82 %); m.p. 265-267 °C (Found: C, 63.75; H, 5.63; N, 3.27. $C_{22}H_{23}O_3NS_2$ requires C, 63.89; H, 5.61; N, 3.39 %); IR (KBr) 3350, 2955, 1670, 1640, 1540, 1520, 1250, 1130 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 0.86 (s, 3H), 0.92 (s, 3H), 0.98 (s, 3H), 1.13 (m, 1H), 1.48 (m, 2H), 1.97 (m, 2H), 3.92 (m, 1H), 4.31 (m, 1H), 5.49 (d, *J* 5.5, 1H), 7.56 (d, *J* 6.1, 1H), 8.11 (d, *J* 8.9, 1H), 8.20 (d, *J* 8.9, 1H), 8.80 (s, 1H), 8.98 (s, 1H), 10.19 (s, 1H).

***N*-[(1*R*,2*R*,3*S*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-[2-(2-naphto[2,1-b]thienyl)ethenyl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (22).** To a stirred solution of aldehyde **21** (0.67 g, 1.62 mmol) and phosphonium chloride **12** (0.86 g, 1.73 mmol) in a mixture of methanol (30 mL) and THF (25 mL) was added a solution of potassium *tert*-butoxide (0.37 g, 3.24 mmol) in methanol (4 mL) at 0 °C, and the reaction mixture was stirred overnight. The precipitated product was filtered off with suction, washed with CH_2Cl_2 and dried *in vacuo* to give the *title compound* **22** as orange powder (0.78 g, 81 %). An analytically pure sample of **22** was obtained by recrystallization from $CHCl_3$; m.p. 308-310 °C (dec.) (Found: C, 70.61; H, 5.28; N, 2.44. $C_{35}H_{31}O_2NS_3$ requires C, 70.79; H, 5.26; N, 2.36 %); IR (KBr) 3380, 2950, 1630, 1520, 1490, 925, 830, 800 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 0.87 (s, 3H), 0.93 (s, 3H), 0.99 (s, 3H), 1.14 (m, 1H), 1.51 (m, 2H), 1.99 (m, 2H), 3.93 (m, 1H), 4.31 (m, 1H), 5.48 (m, 1H), 7.43-7.72 (m, 4H), 7.82-8.05 (m, 5H), 8.18 (s, 1H), 8.40 (m, 3H), 8.60 (s, 1H).

***N*-[(1*R*,2*R*,3*S*,4*S*)-2-(Triisopropylsilyl)oxy-1,7,7-trimethylbicyclo-[2.2.1]heptan-3-yl]-5-[2-(2-naphto[2,1-b]thienyl)ethenyl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (23).** Triisopropylsilylation was carried out according to a literature method.[22] To a stirred suspension of **22** (0.31 g, 0.52 mmol) in dry CH_2Cl_2. (40 mL) were added triisopropylsilyl triflate (0.18 mL, 0.67 mmol) and 2,6-lutidine (0.12 mL, 1.04 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and the suspension was stirred overnight. The reaction was quenched by the dropwise addition of 5% HCl aqueous solution. Brine was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous $NaHCO_3$, and brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (5:1)) to give the *title compound* **23** as yellow solid (0.40 g, 100 %); m.p. 126-130 °C (Found: C, 69.94; H, 6.90; N, 1.86. $C_{44}H_{51}O_2NS_3Si$ requires C, 70.45; H, 6.85; N, 1.87 %); IR (KBr) 2945, 2865, 1655, 1515, 1490, 1110, 1060, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 1.04-1.33 (m, 3H), 1.15 (d, *J* 7.3, 18H), 1.53 (m, 2H), 1.98 (m, 3H), 2.26 (m, 1H), 4.30-4.53 (m, 2H), 6.91 (d, *J* 5.7, 1H), 7.34 (d, *J* 5.2, 1H), 7.43-7.86 (m, 2H), 7.62 (s, 1H), 7.70-7.85 (m, 4H), 7.93 (d, *J* 7.8, 1H), 7.97 (s, 1H), 8.11 (s, 1H), 8.29 (d, *J* 7.8, 1H).

N*-[(1*R*,2*R*,3*S*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo-[2.2.1]heptan-3-yl][1]benzothieno[5,4-b]naphto[1',2':4,5]thieno[3,2-e][1]benzothiophene-2-carboxamide (24).** (i) ***From compound 22. Olefin **22** (0.15 g, 0.26 mmol) and iodine (0.068 g, 0.26 mmol) were dissolved in benzene (1.1 L) and argon was bubbled through the stirred solution for 2h before photo-irradiation. Propylene oxide (6.0 mL, 125 mmol) was added to the mixture and the resulting solution was irradiated for 5h at room temperature with argon flow. The reaction mixture was washed with 15 % $Na_2S_2O_3$ solution and extracted with benzene. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4). Evaporation of solvents followed by chromatography (silica, hexane–ethyl acetate (3:1)) gave the diastereomeric mixture (50:50) of the *title compound* **24** as a yellow solid (0.14 g, 91 %).

(ii) ***From compound 23.*** Olefin **23** (0.25 g, 0.33 mmol) and iodine (0.085 g, 0.33 mmol) were dissolved in benzene (1.1 L) and argon was bubbled through the stirred solution for 2h before photo-irradiation. Propylene oxide (8.0 mL, 170 mmol) was added to the mixture and the resulting solution was irradiated for 5h at room temperature with argon flow. The reaction mixture was washed with 15 % $Na_2S_2O_3$ solution and extracted with benzene. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4) and concentrated. This material **25** was dissolved in dry THF (10 mL) and tetrabutylammonium fluoride (0.66 mL, 0.66 mmol) of 1M solution in THF was added. The mixture was stirred for 2h at room temperature and quenched with brine. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica (hexane–ethyl acetate (10:1)) to give the diastereomeric mixture (75:25) of the *title compound* **24** (0.17 g, 85 %). Further purification of **24** by silica gel chromatography (hexane–ethyl acetate (10:1)) gave optically pure (+)-(*P*)-**26:** m.p. 280-283 °C (Found: C, 71.26; H, 4.96; N, 2.45. $C_{35}H_{29}O_2NS_3$ requires C, 71.04; H, 4.94; N, 2.37 %); $[\alpha]_D$ +2320 (c 0.050, $CHCl_3$); IR (KBr) 3370, 2950, 1640, 1525, 1155, 800, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 3H), 0.90 (s, 3H), 0.97 (s, 3H), 1.02-1.40 (m, 2H), 1.40 (d, *J* 8.0, 1H), 1.46-1.93 (m, 2H), 2.05 (t, *J* 4.3, 1H), 3.33 (m, 1H), 4.02 (m, 1H), 5.64 (d, *J* 5.4, 1H), 6.73 (s, 1H), 6.76 (m, 1H), 7.30 (m, 1H), 7.55 (d, *J* 8.3, 1H), 7.94 (d, *J* 8.3, 1H), 7.99-8.15 (m, 7H).

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