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Abdel-Sattar S. Hamad Elgazwy[a]
[a] Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt

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RESEARCH ARTICLE

Synthesis of 2,2′-bithiophene-5,5′-tetrahydroisoquinoline as michellamine analogs

ABDEL-SATTAR S. HAMAD ELGAZWY*

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia 11566, Cairo, Egypt

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Atropisomers of 2,2′-bithiophene-5-tetrahydroisoquinoline, ***S*-8**, ***R*-8**, and 2,2′-bithiophene-5,5′-tetrahydroisoquinoline, (*S*,*S*)**-11**, (*R*,*S*)**-11**, (*R*,*R*)**-11**, analogs of michellamines have been synthesized in low yield under Stille coupling conditions (Pd^0-mediated cross coupling reactions) of stannanes **1** or **2** with non-racemic bromotetrahydroisoquinoline **6**. The use of non-racemic iodotetrahydroisoquinoline **7** instead of **6** significantly improves the efficiency of the coupling, affording the atropisomers in moderate yields.

Keywords: 2,2′-Bithiophene; Tetrahydroisoquinoline; Stannane; Stille coupling

1. Introduction

Over the last several decades, naphthylisoquinoline alkaloids isolated from Ancistrocladaceae and Dioncophyllaceae have received significant attention [1–4]. Naphthylisoquinoline alkaloids and michellamines (A and B) have been isolated from *Ancistrocladus korupensis* found in Cameroon by scientists at the National Cancer Institute (NCI). This development was part of an effort aimed at identifying novel anti-HIV agents from natural sources [5–7]. In a later isolation korupensamines A–D, presumed biogenetic and monomeric precursors of michellamines, were also discovered from *A. korupensis* [8, 9]. In earlier work, other naphthylisoquinoline alkaloids were isolated from *abbreviatus* and *ancistrobrevine* B in West Africa [10]. The preliminary report disclosed that both michellamine A or B were fully protective against HIV-1 in CEM-SS human lymphoblastoid cells *in vitro* ($EC_{50} \sim 20\,\mu M$ and $IC_{50} \sim 200\,\mu M$) [5]. Both alkaloids also inhibited the production of viral reverse transcriptase, P24 antigen, and syncytium-forming units. A later report showed that michellamine A, B, and C were fully protective against both HIV-1 (RF strain) and HIV-2 (CBL-20 strain) in CEM-SS cells (EC_{50} from 2 to $13\,\mu M$) [7]. Michellamine A had an inferior activity to michellamine B in a test

* Corresponding author. E-mail: hamad@asunet.shams.eun.eg

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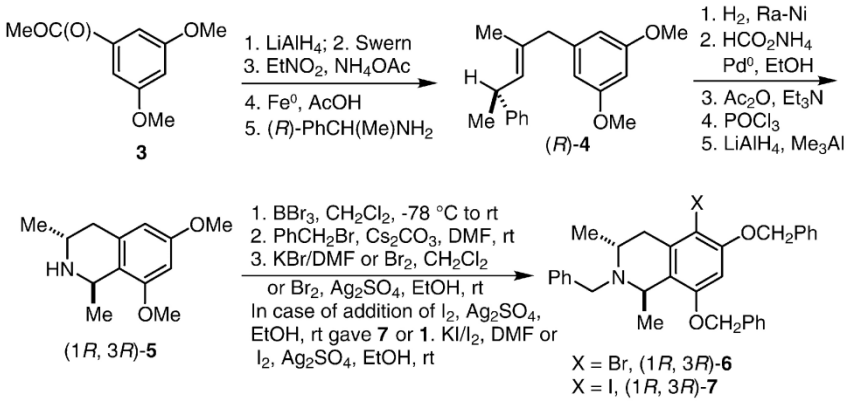
with NIH-DZ strain of HIV-2. The more naturally abundant michellamine B was further tested and found to be fully protective against 11 different HIV-strains in CEM-SS cells and against AZT-resistant G910-6 strain and pyridinone-resistant A17 strain of HIV-1 in MT-2 cells. A more recent report has shown that michellamine B inhibits enzymatic activities of reverse transcriptases from both HIV-1 and HIV-2 [11]. It also inhibits cellular fusion and syncitium formation. Pharmaco-kinetics studies of michellamine B have also been reported [12].

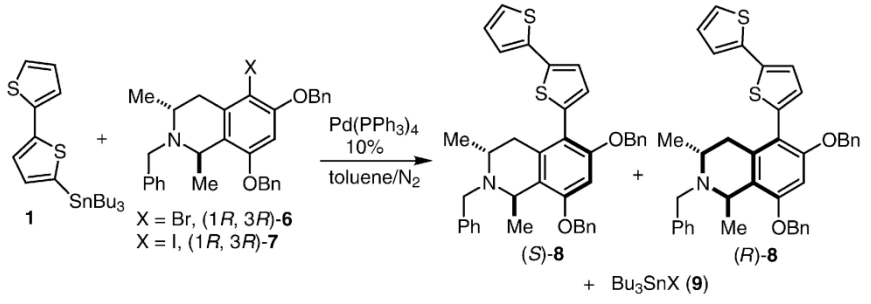
2. Results and discussion

The non-racemic tetrahydroisoquinolines (1*R*,3*R*)**-6** or (1*R*,3*R*)**-7** were prepared following the procedure described earlier by Hoye *et al*. and others [13–16], starting from inexpensive commercial methyl 3,5-dimethoxybenzoate **3** *via* Raney nickel reduction of the non-racemic (α)-methylbenzylimine **4** [17] by a route pioneered by Bringmann [18]. Demethylation of **5** with excess boron tribromide gave a diphenol amine HBr salt, which was tribenzylated with benzyl bromide and cesium carbonate in DMF at room temperature (85%, two steps, scheme 1). Regiospecific iodination with iodine and silver sulfate [19] gave C(5)-activated, benzyl protected (1*R*,3*R*)**-7** or bromination with potassium bromide in DMF gave C(5)-activated, benzyl protected (1*R*,3*R*)**-6**. Stannanes **1** and **2** were also prepared by us [20] and separated by chromatography using neutral alumina. We describe here selected results of this part of our study concerning Stille coupling reactions [21] of stannanes **1** or **2** with bromide **6** or iodide **7**.



SCHEME 1

We were delighted to observe that the palladium(0)-catalyzed cross-coupling of bromide **6** or iodide **7** with stannane **1** provided a ~1:1 ratio of the almost inseparable pairs of atropisomers *S*-**8**/*R*-**8** in 50% yield (scheme 2). Those atropisomers *S*-**8** and *R*-**8** were separated by column chromatography on silica gel (hexanes–EtOAc, 7:2, with 1% Et_3N) or by MPLC. In the ^1H NMR spectrum, the position of the benzyl group in atropisomers *S*-**8** or *R*-**8** was not easy to identify. Atropisomer *S*-**8**, shows a singlet signal at δ 5.1 for the methylene protons of the benzyl group at position 8 and two doublet signals at δ 5.02 and 4.97 with the same coupling constant ($J = 12.3$ Hz), assigned to the methylene protons of the benzyl group at position 6. The methylene protons of the benzyl group at position 2 also appear as two doublets, at δ 3.84 and 3.23 ($J = 14.1$ Hz). In the ^1H NMR spectrum of atropisomer *R*-**8**, two doublets appear at δ 5.02 and 4.98 ($J = 12.3$ Hz) for methylene protons of the benzyl group at position 8. This splitting of the methylene protons occurs due to the strong electrical quadrupole moment effect of the atropisomers [22].



SCHEME 2

The ^{1}H NMR spectrum of all atropisomers clearly showed a correlation between the chemical shift of H(4) and the biaryl (isoquinolinylbithiophene) configuration (stereogenic axis configuration). When the chemical shift of $H(4)_{ax}$ is downfield (high chemical shift) relative to that of $H(4)_{eq}$ the biaryl bonds of the atropisomer has the *S*-configuration. However, when chemical shift of $H(4)_{eq}$ is downfield (high chemical shift) relative to that of $H(4)_{ax}$ the biaryl bonds of those atropisomer has a *R*-configuration (figure 1).

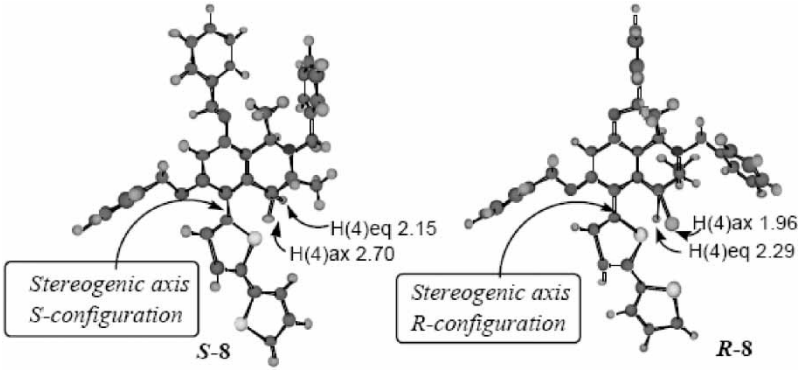
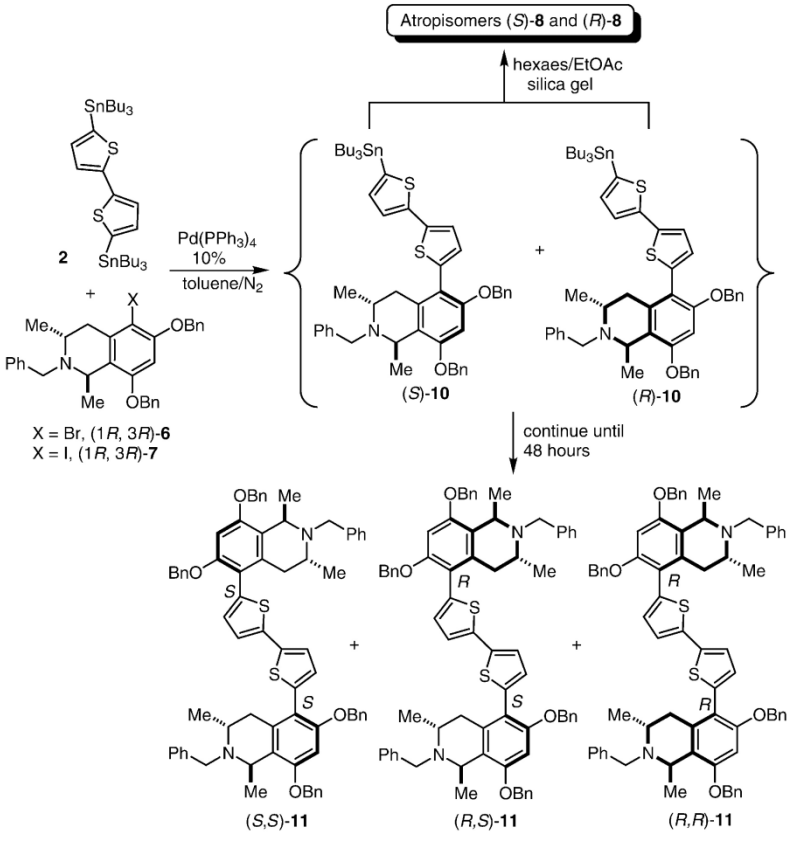


Figure 1. Assignment of configuration of the biaryl bond of atropisomers ***S*-8** and ***R*-8**.

We also examined the reactivity of stannane **2** with the same aryl bromide **6** or iodide **7** for the synthesis of the michellamine analogs (*S*,*S*)**-11**, (*R*,*S*)**-11** and (*R*,*R*)**-11**, a reaction that was expected to exhibit decreased cross-coupling reactivity compared with stannane **1** and, possibly, complications during purification. The desired atropisomer formation was sluggish and low yielding when one equivalent of **2** was coupled with two equivalents of **6** in the presence of 10 mol% $Pd(PPh_3)_4$ at 110 °C in toluene. The reaction produced mixtures of hindered atropisomers (*S*,*S*)**-11**, (*R*,*S*)**-11**, (*R*,*R*)**-11** (scheme 3). The independent Pd^0-catalyzed biaryl coupling of iodide **7** with stannane **2** followed a similar trend to what was seen with **6** and furnished an inseparable mixture of the corresponding atropisomers (*S*,*S*)**-11**, (*R*,*S*)**-11** and (*R*,*R*)**-11** in low yield. The low yield of the cross-coupling product is presumably due to the steric hindrance of the bulky aryl group during the carbon–carbon bond formation. This mixture of atropisomers (*S*,*S*)**-11**, (*R*,*S*)**-11** and (*R*,*R*)**-11**, formed in an ~ 2:3:2 ratio, were cleanly produced with nearly quantitative mass recovery (170 mg) as judged from the ^{1}H NMR spectrum of the crude reaction mixture. An effort was made to separate all the atropisomers by using column chromatography on silica gel (hexanes–EtOAc, 90:7, with 3% Et_3N) or by HPLC with careful normal-phase or microsorb amino-bond column. Unfortunately, only a small portion of one atropisomer (*R*,*R*)**-11** was separated, in 7% yield, along with an ~ 3:2 mixture of atropisomers (*R*,*S*)**-11** and (*S*,*S*)**-11**. Assignment and identification of atropisomer



SCHEME 3

(*R*,*R*)-**11** were based upon a comparative study of the ^{1}H NMR data with the other separable atropisomers (*S*)-**8**, (*R*)-**8**. The reaction mixture was monitored by TLC; during the reaction, evidence for the presence of the intermediates of atropisomers *S*-**10** and *R*-**10** was revealed. Specifically, the intermediate atropisomers *S*-**10** and *R*-**10** were clearly observable in the ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of the crude reaction mixture. Using column chromatography on neutral alumina (hexanes–EtOAc, 7:2, with 1% Et_3N) atropisomers *S*-**10** and *R*-**10** could be separated. However, column chromatography on silica gel (hexanes–EtOAc, 7:2, with 1% Et_3N) afforded the corresponding atropisomers *S*-**8** and *R*-**8**. Clearly, when using silica gel, demetallation occurs and compounds **10** are converted into atropisomers **8** (scheme 3). This is consistent with the results described by Miller *et al*. [23] for the separation of 5,5′-bistannyl-2,2′-bithiophene **2** where column chromatography on silica gel converted about half of the sample into mono-5-stannyl-2,2′-bithiophene and starting materials (2,2′-bithiophene). Neutral alumina is preferred over silica gel for the separation and isolation of these organostannanes [20].

Concerning the rates of the cross-coupling reactions, it is known that aryl bromides are less capable of supporting the oxidative addition step than aryl iodides [24–27]. The present report clearly indicates that the aryl iodide is more reactive than its bromide analogue and that iodide can be efficiently processed through the catalytic cycle, when there is a sufficiently reactive hetero-metal species present to capture the intermediate of aryl palladium iodide.

These results would explain the consistently lower isolated yield of the coupled product of atropisomers (*S*,*S*)**-11**, (*R*,*S*)**-11** and (*R*,*R*)**-11** when the aryl bromide **6** was used instead of the aryl iodide **7**.

3. Conclusions

Palladium(0) is an effective catalyst for the Stille coupling of stannanes **1** or **2** with aryl halides **6** or **7**. The optimized conditions (10 mol% $Pd(PPh_3)_4$, in toluene at 110 °C) allow for efficient coupling of stannane **1** in yields comparable to or better than the corresponding stannane **2**. The overall synthesis involves linear steps from known or commercial materials. Identification of intermediates for more efficient atropisomer separation, study of stereoselective coupling protocols, and michellamine analog preparation are now of high priority for us and other researchers. No special glassware or high-pressure equipment was required since the coupling proceeded readily under inert gases.

4. Experimental

Products were characterized by comparison of their physical data with those of known samples. All yields refer to isolated products. IR spectra were recorded on Perkin Elmer 781 and Pye Unicam 8725 spectrometers. NMR spectra were record on a Bruker DPX 250 spectrometer, and data obtained using an IBM NR-200, IBM NR-300-AF and a Varian VXR-500 (500 MHz) spectrometer. TLC accomplished the purity determination of the substrates and reaction monitoring on silica gel polygram SILG/UV 254 plates. M-H-W Laboratories (Phoenix, AZ) performed elemental analyses.

4.1 *General method*

In a screw-capped tube were placed aryl halide (0.1 M), one or two equivalents of aryl stannane, and 10 mol% of $Pd(PPh_3)_4$ in toluene. The reaction mixture was sealed under N_2 and heated at 110 °C for 48 h and then cooled to room temperature. The so-obtained mixture was quenched with water (25 mL), and KF (250 mg) was added with stirring for 5 h, and then neutralized with 10% aqueous ammonium chloride solution. The resultant mixture was filtrated to remove the unwanted Bu_3SnF solid and the filtrate was evaporated *in vacuo* to give an oily residue, which was isolated by extraction with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by column chromatography on silica gel.

4.2 *5′-[-(1R),(3R)-2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-2′,2″-bithiophene (8)*

The crude product was purified by column chromatography on silica gel (hexanes–EtOAc, 7:2 with 1% Et_3N) to afford the separable atropisomer *S*-**8** and *R*-**8** (227.5 mg, 0.006 mmol, 60% yield) in a ∼1:1 ratio as a reddish-yellow solid, mp 115–117 °C; IR (KBr) ν (cm^{-1}): 3112, 3080, 2954, 2840, 1665, 835, 820, 691. ^1H NMR (300 MHz, $CDCl_3$): atropisomer *S*-**8**: δ (ppm): 7.53–7.72 [m, 15H, (3 × C_6H_5-)], 7.31 [dd, J = 1.2 and 4.8 Hz, 1H, Th-H(5″)], 7.28 [d, J = 3.6 Hz, 1H, Th-H(3′)], 7.22 [dd, J = 1.2 and 3.6 Hz, 1H, Th-H(3″)], 7.16 [d, 1H, J = 3.6 Hz, Th-H(4′)], 7.10 [dd, J = 3.6 and 4.8 Hz, 1H, Th-H(4″)], 6.44 [s, 1H, Ar-H(7)], 5.1 [s, 2H, OCH_2Ph(8)], 5.02 [d, J = 12.3 Hz, 2H, OCHaPh(6)], 4.97 [d, J = 12.3 Hz, 2H, OCHbPh(6)], 4.04 [q, J = 6.6 Hz, 1H, CH(1)], 3.84 [d, J = 14.1 Hz, 1H, NCHaPh(2)], 3.54 [ddq, J = 11.7, 6.6, 4.8 Hz, 1H, CH(3)], 3.23 [d, J = 14.1 Hz, 2H, NCH_bPh(2)], 2.70 [dd, J = 17.7 and 11.7 Hz, 1H, CH(4ax)], 2.15 [dd, J = 17.7 and 4.8 Hz, 1H, CH(4eq)],

1.39 [d, $J = 6.6$ Hz, 3H, $CH_3(3)$], 1.23 [d, $J = 6.6$ Hz, 3H, $CH_3(1)$]. The ^{1}H NMR spectrum of atropisomer ***R*-8** was virtually the same as for atropisomer ***S*-8** with the following differences; δ (ppm): 5.02 [d, 1H, $J = 12.0$ Hz, OCHaPh(8)], 4.98 [d, $J = 12.0$ Hz, 1H, OCHbPh(8)], 4.84 [d, $J = 13.0$ Hz, 2H, OCHaPh(6)], 4.79 [d, 1H, $J = 13.0$ Hz, OCHbPh(6)], 4.13 [q, $J = 6.5$ Hz, 1H, CH(1)], 3.78 [d, $J = 14.0$ Hz, 1H, NCHaPh(2)], 3.39 [ddq, $J =$ 12.5, 6.5, 4.5 Hz, 1H, CH(3)], 3.38 [d, $J = 14.0$ Hz, 2H, $NCH_bPh(2)$], 2.29 [dd, $J = 17.5$ and 4.5 Hz, 1H, CH(4eq)], 1.96 [dd, $J = 17.5$ and 12.5 Hz, 1H, CH(4ax)], 1.40 [d, $J = 6.5$ Hz, 3H, $CH_3(1)$], 1.13 [d, $J = 6.5$ Hz, 3H, $CH_3(3)$].

Anal. (%) for atropisomers (***S*-8**) or (***R*-8**), $C_{40}H_{37}S_2NO_2$, calcd. C, 76.52; H, 5.93; N, 2.23; S, 10.21; found: C, 76.33; H, 5.83; N, 2.36; S, 10.26.

4.3 *5′-[-(1R),(3R)-2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-5″-tri-(n-butylstannyl)-2′,2″-bithiophene (10)*

The crude product was purified by column chromatography on neutral alumina (hexanes–EtOAc, 6:1, with 1% Et_3N) to afford the separable pairs of atropisomer ***S*-10** and ***R*-10** (77 mg, 0.006 mmol, 13% yield) as a yellow oil. IR (KBr) ν (cm^{-1}): 2963, 2927, 1670, 1461, 1252, 1098; ^{1}H NMR ($CDCl_3$, 500 MHz). For atropisomer ***S*-10**; δ (ppm): 7.53–7.72 [m, 15H, ($3 \times C_6H_5$-)], 7.34 [d, $J = 3.6$ Hz, 2H, Th-H(3′,3″)], 7.19 [d, 2H, $J = 3.6$ Hz, Th-H(4′,4″)], 6.51 [s, 1H, Ar-H(7)], 5.12 [s, 2H, $OCH_2Ph(8)$], 5.01 [s, 2H, $OCH_2Ph(6)$], 4.17 [q, $J = 6.6$ Hz, 1H, CH(1)], 3.75 [d, $J = 14.1$ Hz, 1H, NCHaPh(2)], 3.45 [ddq, $J = 11.7$, 6.6, 4.8 Hz, 1H, CH(3)], 3.34 [d, $J = 14.1$ Hz, 1H, $NCH_bPh(2)$], 2.40 [dd, $J = 17.7$ and 11.7 Hz, 1H, CH(4ax)], 2.06 [dd, $J = 17.7$ and 4.8 Hz, 1H, CH(4eq)], 1.63 (tt, $J = 8.4$ and 7.7 Hz, 6H, thienyl-$SnCH_2CH_2CH_2CH_3$), 1.39 [d, $J = 6.6$ Hz, 3H, $CH_3(3)$], 1.36 (tq, $J = 7.7$ and 7.8 Hz, 6H, thienyl-$Sn(CH_2)_2CH_2CH_3$), 1.12 (t, $J = 8.4$ Hz, 6H, thienyl-$SnCH_2CH_2CH_2CH_3$), 1.01 [d, $J = 6.5$ Hz, 3H, $CH_3(1)$], 0.98 (t, $J = 7.8$ Hz, 9H, thienyl-$Sn(CH_2)_3CH_3$) ppm. The ^{1}H NMR spectrum of atropisomer ***R*-10** was virtually the same as for atropisomer ***S*-10** with the following differences: 5.10 [d, 1H, $J = 12.0$ Hz, OCHaPh(8)], 5.06 [d, $J = 12.0$ Hz, 1H, OCHbPh(8)], 4.94 [d, $J = 12.0$ Hz, 2H, OCHaPh(6)], 4.82 [d, 1H, $J = 12.0$ Hz, OCHbPh(6)], 4.15 [q, $J = 6.6$ Hz, 1H, CH(1)], 3.77 [d, $J = 14.0$ Hz, 1H, NCHaPh(2)], 3.42 [m, s, 1H, CH(3)], 3.35 [d, $J = 14.0$ Hz, 2H, $NCH_bPh(2)$], 2.55 [dd, $J = 17.0$ and 4.8 Hz, 1H, CH(4eq)], 2.16 [dd, $J = 17.0$ and 12.0 Hz, 1H, CH(4ax)], 1.40 [d, $J = 6.6$ Hz, 3H, $CH_3(1)$], 1.13 [d, $J = 6.6$ Hz, 3H, $CH_3(3)$], 1.65 (tt, $J = 8.4$ and 7.7 Hz, 6H, thienyl-$SnCH_2CH_2CH_2CH_3$), 1.40 [d, $J = 6.6$ Hz, 3H, $CH_3(3)$], 1.36 (tq, $J = 7.7$ and 7.8 Hz, 6H, thienyl-$Sn(CH_2)_2CH_2CH_3$), 1.15 (t, $J = 8.4$ Hz, 6H, thienyl-$SnCH_2CH_2\ CH_2CH_3$), 1.09 [d, $J = 6.5$ Hz, 3H, $CH_3(1)$], 1.03 (t, $J = 7.8$ Hz, 9H, thienyl-$Sn(CH_2)_3CH_3$) ppm.

Anal. (%) for atropisomers (***S*-10**) or (***R*-10**), $C_{52}H_{63}S_2NO_2Sn$ (917.21), calcd. C, 68.09; H, 6.92; N, 1.52; S, 6.99; found: C, 68.33; H, 7.03; N, 1.60; S, 6.56.

4.4 *5′,5″-Bis[-(1R),(3R)-2-benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-2′,2″-bithiophene (11)*

The mixture (yellow oil) of atropisomers (*S*,*S*)-**11**, (*R*,*S*)-**11**, (*R*,*R*)-**11** (170 mg, mass recovery) were isolated in a ~2:3:2 ratio. Separation using column chromatography on silica gel (hexanes–EtOAc, 90:7, with 3% Et_3N) or by careful normal-phase HPLC produced 47 mg (6 mmol, 7% yield) of atropisomers (*R*,***R*-11**) along with a 3:2 mixture of atropisomers (*R*,*S*)-**11**, (*S*,*S*)-**11**. IR (KBr) ν (cm^{-1}): 3105, 2963, 2927, 1670, 1461, 1252, 1098, 835, 820, 691. ^{1}H NMR (300 MHz, $CDCl_3$): for atropisomers (*R*,***R*-11**); δ (ppm): 7.53–7.72 [m, 15H, ($3 \times C_6H_5$-)], 7.05 [d, $J = 3.6$ Hz, 2H, Th-H(3′,3″)], 7.04 [d, $J = 3.6$ Hz, 2H, Th-H(4′,4″)], 6.44 [s, 2H, Ar-H(7,7‴)], 5.10 [s, 4H, $OCH_2Ph(8,8‴)$], 5.04–5.00 [d, $J =$ 12.3 Hz, 2H, OCHaPh(6,6‴)], 4.97 [d, $J = 12.3$ Hz, 2H, OCHbPh(6,6‴)], 4.04 [q, $J =$ 6.6 Hz, 2H, CH(1,1‴)], 3.85 [d, $J = 14.1$ Hz, 2H, NCHaPh(2,2‴)], 3.54 [ddq, $J = 11.7$,

6.6, 4.8 Hz, 2H, CH(3,3‴)], 3.23 [d, $J = 14.1$ Hz, 2H, NCHbPh(2,2‴)], 2.69 [dd, $J = 17.7$ and 4.8 Hz, 2H, CH(4eq,4eq‴)], 2.45 [dd, $J = 17.7$ and 11.7 Hz, 2H, CH(4ax,4ax‴)], 1.39 [d, $J = 6.6$ Hz, 6H, CH_3(3,3‴)], 1.33 [d, $J = 6.6$ Hz, 6H, CH_3(1,1‴)]. The ^{1}H NMR spectrum for atropisomers [(*R*,*S*)**-11** from the mixture of (*R*,*S*)**-11** and (*S*,*S*)**-11**]; δ (ppm): 7.54–7.77 [m, 15H, (3 × C_6H_5-)], 7.10 [d, $J = 3.6$ Hz, 2H, Th-H(3′,3‴)], 7.08 [d, $J = 3.6$ Hz, 2H, Th-H(4′,4‴)], 6.45 [s, 2H, Ar-H(7,7‴)], 5.15 [s, 4H, OCH_2Ph(8,8‴)], 5.10 [d, $J =$ 12.3 Hz, 2H, OCHaPh(6,6‴)], 4.99 [d, $J = 12.3$ Hz, 2H, OCHbPh(6,6‴)], 4.04 [q, $J =$ 6.6 Hz, 2H, CH(1,1‴)], 3.88 [d, $J = 14.1$ Hz, 2H, NCHaPh(2,2‴)], 3.55 [ddq, $J = 11.7$, 6.6, 4.8 Hz, 2H, CH(3,3‴)], 3.23 [d, $J = 14.1$ Hz, 2H, NCHbPh(2,2‴)], 2.73 [dd, $J = 17.7$ and 4.8 Hz, 2H, CH(4eq,4eq‴)], 2.24 [dd, $J = 17.7$ and 11.7 Hz, 2H, CH(4ax,4ax‴)], 1.41 [d, $J = 6.6$ Hz, 6H, CH_3(3,3‴)], 1.35 [d, $J = 6.6$ Hz, 6H, CH_3(1,1‴)]. The ^{1}H NMR spectrum for atropisomers [(*S*,*S*)**-11** from the mixture of (*R*,*S*)**-11** and (*S*,*S*)**-11**]; δ (ppm): 7.50–7.75 [m, 15H, (3 × C_6H_5-)], 7.09 [d, $J = 3.6$ Hz, 2H, Th-H(3′,3‴)], 7.05 [d, $J = 3.6$ Hz, 2H, Th-H(4′,4‴)], 6.48 [s, 2H, Ar-H(7,7‴)], 5.12 [s, 4H, OCH2Ph(8,8‴)], 5.05 [d, $J =$ 12.3 Hz, 2H, OCHaPh(6,6‴)], 4.98 [d, $J = 12.3$ Hz, 2H, OCHbPh(6,6‴)], 4.15 [q, $J = 6.6$ Hz, 2H, CH(1,1‴)], 3.92 [d, $J = 14.1$ Hz, 2H, NCHaPh(2,2‴)], 3.61 [ddq, $J = 11.7$, 6.6 and 4.8 Hz, 2H, CH(3,3‴)], 3.23 [d, $J = 14.1$ Hz, 2H, NCHbPh(2,2‴)], 2.69 [dd, $J = 17.7$ and 11.7 Hz, 2H, CH(4ax,4ax‴)], 2.35 [dd, $J = 17.7$ and 4.8 Hz, 2H, CH(4eq,4eq‴)], 1.42 [d, $J = 6.6$ Hz, 6H, CH_3(3,3‴)], 1.34 [d, $J = 6.6$ Hz, 6H, CH_3(1,1‴)].

Anal. (%) for atropisomers (*R*,*R*-**11**), $C_{72}H_{68}S_2N_2O_4$, calcd. C, 79.38; H, 6.29; N, 2.57; S, 5.87; found: C, 79.62; H, 5.98; N, 2.74; S, 5.65.

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