Synthetic Analogs of Dioncophylline and Michellamines by Stille Coupling

Abdel-Sattar S. Hamad Elgazwy

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia 11566, Cairo, Egypt. Tel./Fax.; 002024831836 email; hamad@asunet.shams.eun.eg

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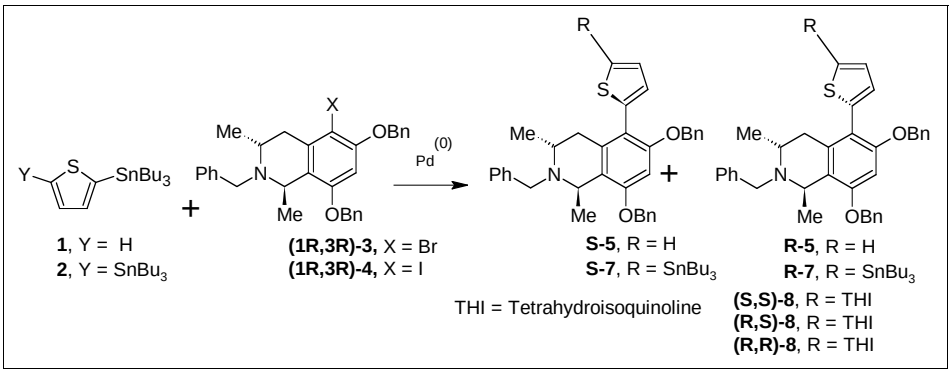

Dioncophielline and Michellamine Analogs **S-5, R-5, S-7, R-7, S,S-8, R,R-8** and **R,S-8** were synthesized by using Stille coupling condition (Pd°-mediated cross coupling) proceeds in low yield when using stannanes **1** or **2** with tetrahydroisoquinolinyl bromide **3**. The addition of tetrahydroisoquinolinyl iodide **4** instead of **3** significantly improves the efficiency of the coupling and providing a variety of Dioncophielline and Michellamine analogs in moderate yields.

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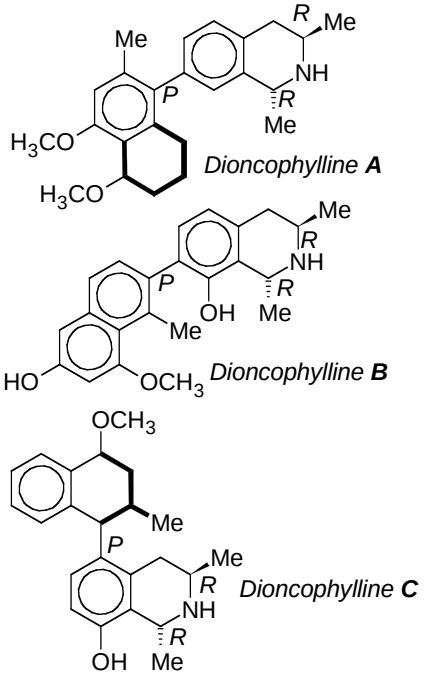
Introduction.

In our continuous studies on the Stille cross coupling reactions, we have recently reported several intriguing reactions of thiophene and bithiophene with isoquinoline [1-2]. In the last decades, the chemistry of naphthylisoquinoline alkaloids had received a great attention with having been fully characterized and found in *Ancistrocladaceae* and *dioncophyllaceae* [3-6]. Dioncophyllum thollonii (Dioncophyllaceae) is known for its activity against leprous skin disease [7-9] (Scheme 1). Naphthylisoquinoline alkaloids and michellamines (A and B) were isolated from *Ancistrocladus korupensis* found in Cameroon by scientists at National Cancer Institute (NCI). This development was part of an effort aimed to identify novel anti-HIV agents from natural sources [10-12]. In a later isolation *korupensamines* A, B, C, and D, (Scheme 2) presumed biogenetic and monomeric precursors of michellamines, were also discovered from A. *Korupensis* [13,14]. In earlier work, many other naphthylisoquinoline alkaloids were isolated from *abbreviatus* and *ancistrobrevine* B in West Africa [15]. The preliminary report disclosed that michellamine A or B each was fully protective against HIV-1 in CEM-SS human lymphoblastoid cells *in vitro* (EC_{50}~20 μM and IC_{50}~200 μM) [10]. 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

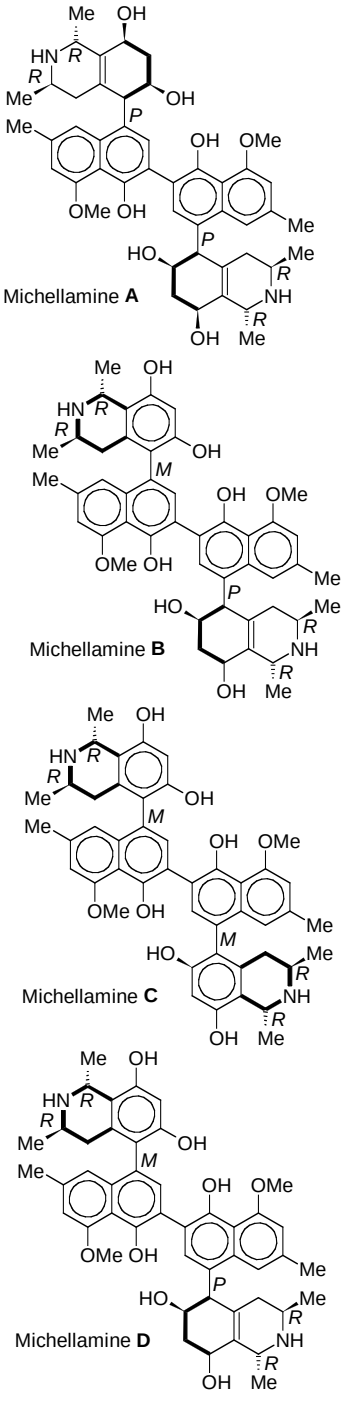
Scheme 1



CEM-SS cells (EC_{50} from 2 to 13 μM) [12]. Michellamine A had an inferior activity of the michellamine B in a test with NIH-DZ strain of HIV-2. The most naturally abundant michellamine B was further tested and found fully protective against eleven 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 recent report showed that michellamine B inhibited enzymatic activities of reverse transcriptases from both HIV-1 and HIV-2 [15]. It also inhibited cellular fusion and syncitium formation. Pharmaco-kinetics studies of michellamine B was also reported recently [17].

Scheme 2

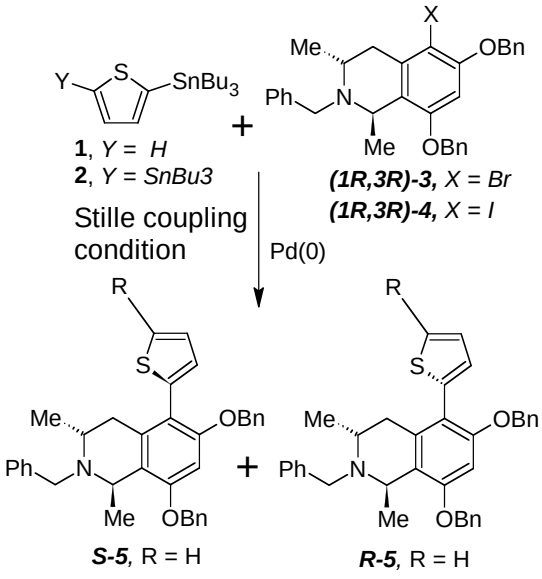


Results and Discussion

The non-racemic tetrahydroisoquinoline (*1R,3R*)-**3** or (*1R,3R*)-**4** was prepared following the procedure described earlier by Hoye *et al*. [18,19] and others [20,21]. Stannanes **1** and **2** were also prepared by us and separated by chromatography using neutral Alumina [22].

We explored here the selected results of this part of our continue interest about Stille [23] cross-coupling reactions of stannanes **1** or **2** with bromide **3** or iodide **4**. Stille coupling reaction has advantage of being slightly more general than the Suzuki reaction, since it does not require base during the reaction condition. However, a major drawback is the toxic tin by-products. The cross- coupling of bromide **3** and/or iodide **4** with stannane **1** provided a ~1:1 ratio of two stereoisomers ***S*-5** and ***R*-5** in 66% yield, as shown in Scheme 3. Those stereoisomers ***S*-5** and ***R*-5** were separated by column chromatography on silica gel (hexanes:EtOAc; 9:2, with 1% Et_3N) or by MPLC. In ^1H NMR spectrum, the position of the benzyl group in stereoisomers ***S*-5** or ***R*-5** was not easy to identify. In stereoisomer ***S*-5**, the spectrum shows two-singlet signal at δ 5.1 and 5.2 for the methylene (CH_2-) protons of benzyl group at positions 6 and 8 respectively. Methylene protons of the benzyl group at position 2, are observed as two doublet signals at δ 3.94 and 3.33 with the same coupling constant (J = 14.1 Hz). In ^1H NMR spectrum for stereoisomer ***R*-5** shows, two doublet signals for methylene (CH_2-) protons at δ 4.84 and 4.79 with the same coupling constant (J = 13.0 Hz)) and other two doublet signals at δ 5.02 and 4.98 with the same coupling constant (J = 12.0 Hz and of benzyl group at positions 6 and 8 respectively are observed. Methylene protons of the

Scheme 3



benzyl group at position 2, shows two doublet signals at δ 3.78 and 3.38 with the same coupling constant (J = 14.0 Hz). These splitting of the methylene protons occur at those positions 2, 6, and 8 due to the strong electrical quadrupole moment effect of those stereoisomers [24-26].

The ^{1}H NMR spectrums of all those stereoisomers clearly showed a correlation between the chemical shift of H(4) and the biaryl (isoquinolinyl- chemical shift of H(4)ax is at down field (high chemical shift) relative to that of H(4)eq the biaryl bonds of those stereoisomer h(4)thiophene) bonds configuration [2]. When ax the biaryl bonds of those stereoisomer has *R*-configuration as *S*-configuration. However, when chemical shift of H(4)eq is at down field (high chemical shift) relative to that of H, as outline in Figure 1.

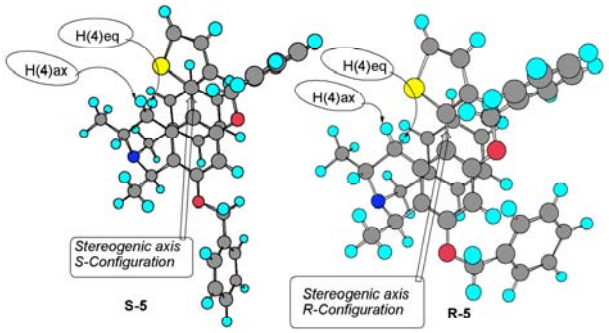


Figure (1); Assignment of configuration of the biaryl bond of atropisomers **S-5** and **R-5**

The biaryl bond of atropisomer *S*-**5** has *S*-configuration, which the resonance of H(4)ax is at downfield (high chemical shift at δ 2.85) relative to H(4)eq (low chemical shift at δ 2.43). The biaryl bond of atropisomer *R*-**5** has *R*-configuration, which the resonance of H(4)eq is at downfield (high chemical shift at δ 2.06) relative to H(4)eq (low chemical shift at d 2.33), which proved that the protons are diastereotopic. Optically purity of the **S-5** and **R-5** was measure by two methods, first method measure by NMR using chiral shift reagent such as tris(heptafluorobutyryl-d-camphorato)europium(III)-[EU(hfbc)$_3$]. In this experiment, we found there is no discernible difference between the two NMR spectra. However, the normal spectrum shows visible difference of the two optical active diastereoisomers of **S-5** and **R-5**. We also measured the optical purity by measuring the observed specific rotation and specific rotation of pure substances, the calculations are shown below.

$$\text{Optical purity} = \frac{\text{Observed specific rotation}}{\text{Specific rotation of pure substance}} \times 100$$

$$\text{Optical purity of S-5} = \frac{+26.3^{o}}{+43.8^{o}} \times 100 = 60.04\%$$

$$\text{Optical purity of R-5} = \frac{+27.6^{o}}{+45.9^{o}} \times 100 = 60.13\%$$

$$\text{Optical purity of S-5} = [\alpha]_D^{20} +89 \text{ (c. 1.25 in CHCl)}$$

$$\text{Optical purity of R-5} = [\alpha]_D^{20} -63 \text{ (c. 1.25 in CHCl)}$$

We examined also the cross coupling of the stannane **2** with the same aryl bromide **3** or iodide **4** in order to synthesize the michellamine analogs **(*S*,*S*)-8, (*R*,*S*)-8, (*R*,*R*)-8**, which was expected to exhibit decreased in the reactivity of cross-coupling reaction compared to the stannane **1** and extremely complicated their purification. Those stereoisomers are sluggish and low yield in case of cross-coupling of one equivalent of **2** with two equivalents of **3** in the presence of 10 mol % Pd(PPh$_3$)$_4$ at 110 °C in toluene, to provide mixture of a hindered stereoisomers **(*S*,*S*)-8, (*R*,*S*)-8, (*R*,*R*)-8** as shown in Scheme 4. The independent Pd° catalyzed biaryl coupling of iodide **4** with stannane **2** followed a similar trend to what was seen with **3** furnished the inseparable mixture of the corresponding stereoisomers **(*S*,*S*)-8, (*R*,*S*)-8, (*R*,*R*)-8** in low yield. The low yield of the cross-coupling product of those stereoisomers was anticipated due to the steric hindrance of the bulky aryl group. This mixture of stereoisomers **(*S*,*S*)-8, (*R*,*S*)-8, (*R*,*R*)-8** in an ~ 2:3:2 ratio were cleanly (as judged from the crude ^{1}H NMR spectrum) produced with nearly quantitative mass recovery (220 mg). An effort was made for separation of all those stereoisomers by using column chromatography on silica gel (hexanes: EtOAc; 100:9: with 4% Et$_3$N) or by HPLC (careful normal-phase or microsorb amino-bond column). Unfortunately a small portion of one stereo-isomer **(*R*,*R*)-8** was separated in 15% yield along with a ~3:2 mixture of stereoisomers **(*R*,*S*)-8** and **(*S*,*S*)-8**, which exhibit a broad peak with a shoulder. These revealed that the stereoisomer **(*R*,*S*)-8** is enriched relative to **(*S*,*S*)-8**. Assignment and identification of the stereoisomer **(*R*,*R*)-8** is based upon a comparative study of its ^{1}H NMR with that of the other separable stereoisomers **(*S*)-5**, **(*R*)-5**.

The reaction mixture was monitored by TLC during the reaction time which, revealed the presence of the intermediate of stereoisomers ***S*-7** and ***R*-7**. Those pairs of intermediate of atropisomers ***S*-7** and ***R*-7** were clearly observed, as judged from the crude ^{1}H NMR (300 MHz, CDCl$_3$) spectrum. Nevertheless, using column chroma-tography on neutral Alumina (hexanes: EtOAc; 15:3: with 2% Et$_3$N) those pairs of atropisomers were separated ***S*-7** and ***R*-7** in 34% yield. But using column chromatography on silica gel (hexanes: EtOAc; 9:2: with 1% Et$_3$N) afforded the corresponding atropisomers ***S*-5** and ***R*-5**. However when using silica gel de-metallation occurs and converted into atropisomers ***S*-5** or ***R*-5** (Scheme 4). This result was consistent with the results described by Miller

et al. [27] for the separation of 2,5-bistannylthiophene **2** using column chromatography on silica gel converted about half of it into mono-5-stannylthiophene and starting materials (thiophene). These results explain why neutral Alumina must be used instead of Silica gel in case of separation of organo-stannanes [22]. It was proved that the stage of aryl bromide was less capable of supporting the oxidative addition step than aryl iodide [28-31]. This report clearly shows 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, the hetero-metal species present to capture the intermediate of aryl palladium iodide. This then explains the consistently lower isolated yield of the coupled product of stereoisomers (***S,S***)-**8**, (***R,S***)-**8,** (***R,R***)-**8**, when the aryl bromide **3** was used instead of the aryl iodide **4**.

Conclusions

Palladium (0) is an effective catalyst for the Stille coupling reaction condition of stannanes **1** and/or **2** with some aryl halides. The optimized conditions (10 mol% $(PdPPh_3)_4$, in toluene at 110 °C) allow for efficient coupling of stannane **1** in yields comparable to or better than that of the corresponding stannane **2**. In addition intermediates have been identified as well as the development of efficient distereoisomers separation methods. Finally we have shown stereoselective coupling protocols for the synthesis of atropisomers. Michellamine analogs have been generated that are highly interesting for us and other scientists.

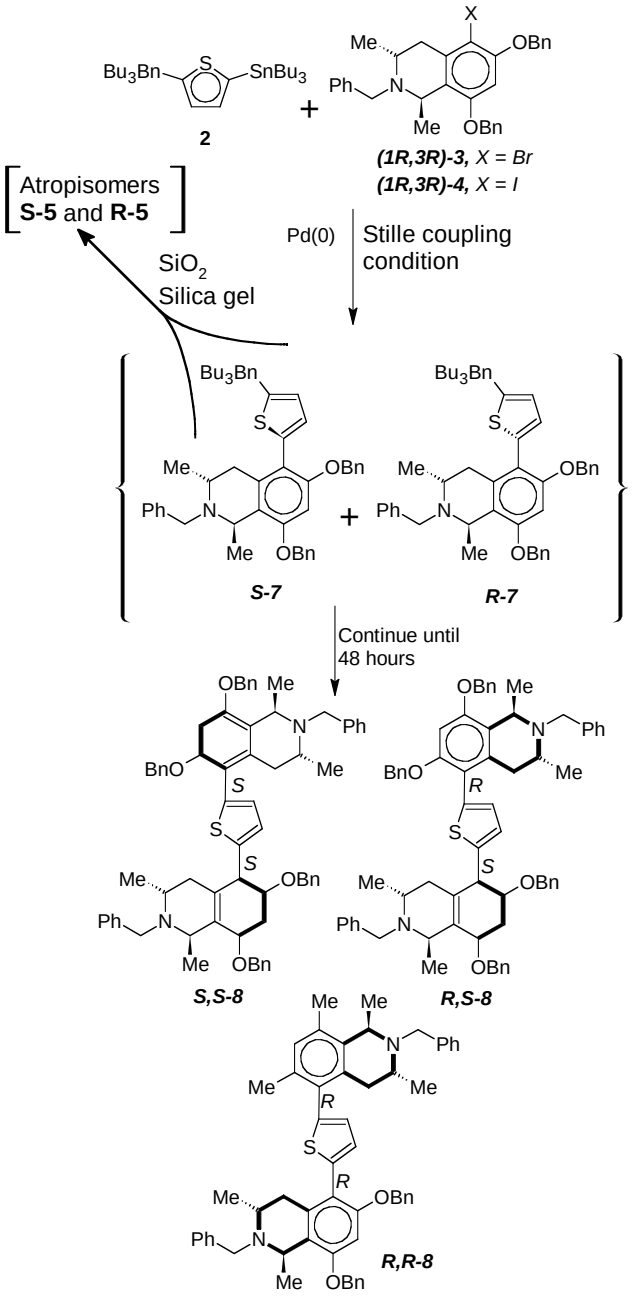
EXPERIMENTAL

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 a Perkin Elmer 781 and Pye Unicam 8725 spectrometers. NMR spectra were record on a Bruker DPX 250 spectrometer and the 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.

General Method**.**

In a screw-capped tube were placed aryl halide (0.01 *M*), one or two equivalents of aryl stannane, and 10 mole % of $Pd(PPh_3)_4$ in toluene. The reaction mixture was sealed under N_2 and heated at 110 ^{0}C for 48 h and then cooled to room temperature. The reaction mixture 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 filtered to remove the unwanted Bu_3SnF solid and the filtrate was evaporated *in vacuo* to give an oily residue, which was

Scheme 4



isolated by extraction with ethyl acetate. The organic layer washed with brine, dried over $MgSO_4$, and evaporated to give oil, which was purified by column chromatography on silica gel.

2'-[-(1*R*),(3*R*)-2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]thiophene (**5**).

The crude product was purified by column chromatography on silica gel (hexanes: EtOAc; 9:2: with 1% Et_3N) afforded the separable stereoisomers ***S*-5** and ***R*-5** (360 mg, 66 % yield) in an ~1:1 ratio, as a reddish-yellow solid, mp. 190-192 °C; IR (KBr) 3100, 3030, 2900, 2800, 1656, 825, 810, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): Stereoisomer ***S*-5**: δ 7.53-7.72 [m, 15H, (3 x

C_6H_5-)], 7.73 [dd, *J* = 1.3 and 4.8 Hz, 1H, Th-H(5')], 7.39 [dd, *J* = 3.6 and 1.3 Hz, 1H, Th-H(3')], 7.16 [dd, *J* = 3.6 and 4.8 Hz, 1H, Th-H(4')], 6.46 [s, 1H, Ar-H(7)], 5.2 [s, 2H, $OCH_2Ph(8)$], 5.1 [s, 2H, $OCH_2Ph(6)$], 4.14 [q, *J* = 6.5 Hz, 1H, CH(1)], 3.94 [d, *J* = 14.1 Hz, 1H, NCHaPh(2)], 3.55 [ddq, *J* = 11.7, 6.6, 4.8 Hz, 1H, CH(3)], 3.33 [d, *J* = 14.1 Hz, 1H, $NCH_bPh(2)$], 2.85 [dd, *J* = 17.7 and 11.7 Hz, 1H, CH(4ax)], 2.43 [dd, *J* = 17.7 and 4.8 Hz, 1H, CH(4eq)], 1.41 [d, *J* = 6.6 Hz, 3H, $CH_3(3)$], 1.27 [d, *J* = 6.6 Hz, 3H, $CH_3(1)$]; Optical Purity of **S-5** = +26.3°/+43.8° x 100 = 60.04%; Optical Activity of **S-5** = $[\alpha]^{20}$ + 89 (c. 1.25 in $CHCl_3$).

The ^{1}H NMR spectrum of stereoisomer ***R*-5** was virtually the same as for stereoisomer ***S*-5** with the following differences: δ 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, 1H, 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, 1H, $NCH_bPh(2)$], 2.33 [dd, *J* = 17.5 and 4.5 Hz, 1H, CH(4eq)], 2.06 [dd, *J* = 17.5 and 12.5 Hz, 1H, CH(4ax)], 1.46 [d, *J* = 6.5 Hz, 3H, $CH_3(1)$]; 1.16 [d, *J* = 6.5 Hz, 3H, $CH_3(3)$] ppm; Optical Purity of **R-5** = + 27.6°/+ 45.9° x 100 = 60.13%; Optical Activity of **R-5** = $[\alpha]^{20}$ - 63 (c. 1.25 in $CHCl_3$).

Anal. Calcd of stereoisomers (***S*-5**) or (***R*-5**): $C_{36}H_{35}SNO_2$ (545.24); C, 79.23; H, 6.46; N, 2.56; S, 5.87. Found: C, 79.24; H, 6.46; N, 2.56; S, 5.76.

2'-[-(1*R*),(3*R*)-2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-5'-tri-(*n*-butylstannyl)thiophene (**7**).

The crude product was purified by column chromatography on neutral Alumina (hexanes:EtOAc; 15:3: with 2% Et_3N) afforded the separable pairs of stereoisomers ***S*-7** and ***R*-7** (285 mg, 34 % yield) as yellow oil. IR (KBr) 2965, 2930, 1660, 1470, 1255, 1100, cm^{-1}.; ^{1}H NMR ($CDCl_3$, 500 MHz): For stereoisomer ***S*-7** δ 7.55-7.77 [m, 15H, (3 x C_6H_5-)], 7.44 [d, *J* = 3.8 Hz, 1H, Th-H(3')], 7.22 [d, 1H, *J* = 3.8 Hz, Th-H(4')], 6.53 [s, 1H, Ar-H(7)], 5.2 [s, 2H, $OCH_2Ph(8)$], 5.11 [s, 2H, $OCH_2Ph(6)$], 4.22 [q, *J* = 6.5 Hz, 1H, CH(1)], 3.82 [d, *J* = 14.2 Hz, 1H, NCHaPh(2)], 3.48 [ddq, *J* = 11.8, 6.5, 4.8 Hz, 1H, CH(3)], 3.40 [d, *J* = 14.2 Hz, 1H, $NCH_bPh(2)$], 2.52 [dd, *J* = 17.8 and 11.8 Hz, 1H, CH(4ax)], 2.15 [dd, *J* = 17.8 and 4.8 Hz, 1H, CH(4eq)], 1.66 (tt, *J* = 8.4 and 7.7 Hz, 6H, thienyl-$SnCH_2CH_2CH_2CH_3$), 1.43 [d, *J* = 6.5 Hz, 3H, $CH_3(3)$], 1.38 (tq, *J* = 7.7 and 7.8 Hz, 6H, thienyl-$Sn(CH_2)_2CH_2CH_3$), 1.18 (t, *J* = 8.4 Hz, 6H, thienyl-$SnCH_2CH_2CH_2CH_3$), 1.11 [d, *J* = 6.5 Hz, 3H, $CH_3(1)$], 0.99 (t, *J* = 7.8 Hz, 9H, thienyl-$Sn(CH_2)_3CH_3$) ppm. The ^{1}H NMR spectrum of stereoisomer ***R*-7** was virtually the same as for stereoisomer ***S*-7** 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, $CH_3(3)$], 1.40 (tq, *J* = 7.7 and 7.8 Hz, 6H, thienyl-$Sn(CH_2)_2CH_2CH_3$), 1.28 (t, *J* = 8.4 Hz, 6H, thienyl-$SnCH_2CH_2CH_2CH_3$), 1.21 [d, *J* = 6.5 Hz, 3H, $CH_3(1)$], 1.11 (t, *J* = 7.8 Hz, 9H, thienyl-$Sn(CH_2)_3CH_3$) ppm.

Anal. Calcd. for stereoisomers (***S*-7**) or (***R*-7**): $C_{48}H_{61}SNO_2Sn$ (835.08): C, 69.04; H, 7.36; N, 1.67; S, 3.84. Found: C, 68.93; H, 7.03; N, 1.60; S, 3.56.

2',5'-Bis[-(*1R*),(3*R*)-2-benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]thiophene (**8**).

The mixture of yellow oil of stereoisomers (***S,S*)-8**, (***R,S*)-8**, (***R,R*)-8** (220 mg, mass recovery) were isolated in an ~2:3:2 ratio; Separation using column chromatography on silica gel (hexanes: EtOAc; 100:9: with 4% Et_3N) or by HPLC (careful normal-phase or microsorb amino-bond column) produced (155 mg, 15% yield) of stereoisomers (***R,R*-8**) along with an 3:2 mixture of stereoisomers (***R,S*)-8**, (***S,S*)-8**: IR (KBr) 3100, 2966, 2930, 1665, 1464, 1255, 1098, 840, 825, 695 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): for stereoisomers (***R,R*-8**): δ 7.51-7.74 [m, 15H, (3 x C_6H_5-)], 7.39 [d, *J* = 3.7 Hz, 1H, Th-H(3')], 7.23 [d, *J* = 3.7 Hz, 1H, Th-H(4')], 6.51[s, 2H, Ar-H(7,7'')], 5.22[s, 4H, $OCH_2(8,8'')$], 5.11[s, 4H, $OCH_2(6,6'')$], 4.15 [q, *J* = 6.7 Hz, 2H, CH(1,1'')], 3.91 [d, *J* = 14.2 Hz, 2H, NCHaPh(2,2'')], 3.56 [ddq, *J* = 11.8, 6.7, 4.9 Hz, 2H, CH(3,3'')], 3.25 [d, *J* = 14.2 Hz, 2H, NCHbPh(2,2'')], 2.71 [dd, *J* = 17.8 and 4.9 Hz, 2H, CH(4eq,4eq'')], 2.45 [dd, *J* = 17.8 and 11.8 Hz, 2H, CH(4ax,4ax'')], 1.40 [d, *J* = 6.7 Hz, 6H, $CH_3(3,3'')$], 1.35 [d, *J* = 6.7 Hz, 6H, $CH_3(1,1'')$] ppm. The ^{1}H NMR spectrum for stereoisomers [(***R,S*)-8** from the mixture of (***R,S*)-8** and (***S,S*)-8**], δ 7.52-7.78 [m, 15H, (3 x C_6H_5-)], 7.38 [d, *J* = 3.6 Hz, 1H, Th-H(3')], 7.22 [d, *J* = 3.6 Hz, 1H, Th-H(4')], 6.49 [s, 2H, Ar-H(7,7'')], 5.25 [s, 4H, OCH2Ph(8,8'')], 5.10 [d, *J* = 12.3 Hz, 2H, OCHaPh(6,6'')], 4.96 [d, *J* = 12.3 Hz, 2H, OCHbPh(6,6'')], 4.08 [q, *J* = 6.6 Hz, 2H, CH(1,1'')], 3.92 [d, *J* = 14.2 Hz, 2H, NCHaPh(2,2'')], 3.58 [ddq, *J* = 11.8, 6.7, 5.1 Hz, 2H, CH(3,3'')], 3.25 [d, *J* = 14.2 Hz, 2H, NCHbPh(2,2'')], 2.77 [dd, *J* = 17.8 and 5.1 Hz, 2H, CH(4eq,4eq'')], 2.26 [dd, *J* = 17.8 and 11.8 Hz, 2H, CH(4ax,4ax'')], 1.44 [d, *J* = 6.6 Hz, 6H, $CH_3(3,3'')$], 1.38 [d, *J* = 6.7 Hz, 6H, $CH_3(1,1'')$] ppm. The ^{1}H NMR spectrum for stereoisomers [(***S,S*)-8** from the mixture of (***R,S*)-8** and (***S,S*)-8**]; δ 7.54-7.77 [m, 15H, (3 x C_6H_5-)], 7.42 [d, *J* = 3.7 Hz, 1H, Th-H(3')], 7.26 [d, *J* = 3.7 Hz, 1H, Th-H(4')], 6.52 [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'')], 4.19 [q, *J* = 6.7 Hz, 2H, CH(1,1'')], 3.99 [d, *J* = 14.2 Hz, 2H, NCHaPh(2,2'')], 3.61 [ddq, *J* = 11.8, 6.7, 5.2 Hz, 2H, CH(3,3'')], 3.33 [d, *J* = 14.2 Hz, 2H, NCHbPh(2,2'')], 2.72 [dd, *J* = 17.8 and 11.8 Hz, 2H, CH(4ax,4ax'')], 2.42 [dd, *J* = 17.8 and 5.2 Hz, 2H, CH(4eq,4eq'')], 1.46 [d, *J* = 6.6 Hz, 6H, $CH_3(3,3'')$], 1.37 [d, *J* = 6.6 Hz, 6H, $CH_3(1,1'')$] ppm. Anal. Calcd of stereoisomers (***R,R*-8**): $C_{68}H_{66}SN_2O_4$ (1007.35); C, 81.07; H, 6.60; N, 2.78; S, 3.18. Found: C, 80.92; H, 6.68; N, 2.74; S, 3.15.

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REFERENCES

[1] A-S. S. Hamad Elgazwy, *J. Heterocyclic. Chem.*, **41**, 755 (2004).

[2] A-S. S. Hamad Elgazwy, *J. Sulfur. Chem.*, **25**, 275, (2004)

[3] G. Bringmann, The Alkaloids; A. Brossi, Ed.; Academic Press: Orlando, FL, Vol. **29**, Chapter 3, 1986.

[4] G. Bringmann, F. Pokorny, The Alkaloids; G. Cordell, Ed.; Academic Press: New York, Vol. **46**, Chapter 4, 1995.
[5] T. R. Govindachari, P. C. Parthasarathy, *Indian J. Chem.*, **8**, 567 (1970).
[6] T. R. Govindachari, P. C. Parthasarathy, *Heterocycles*, **7**, 661 (1977).
[7] M. Lavault, and J. Bruneton, 1980, *Alcaloides du Dioncophyllum thollonii planta Med.* **1980** (suppl.), 17-21.
[8] R. W. Gable, R. L. Martin and M. A. Rizzacasa Australian Journal of Chemistry, *48(12)*, 2013 – 2021 (1995).
[9] G. Francois, G. Timperman, W. Eling, L. A. Assi, J. Holenz, and G. Bringmann *Antimicrob. Agents Chemother*., 41, 2533-2539 (1997).
[10] K. Manfredi, J. W. Blunt, J. H. Cardellina, II, J. B. McMahon, L. L. Pannell, G. M. Cragg, M. R. Boyd, *J. Med. Chem.*, **34**, 3402 (1991).
[11] Y. F. Hallock, J. Dai, H. R. Bokesch, K. B. Dillah, K. P. Manfredi, J. H. Cardellina, II, M. R. Boyd, *J. Chromatogr. A*, **83**, 688 (1994).
[12] M. R. Boyd, Y. H. Hallock, J. H. Cardellina, II, K. P. Manfredi, J. W. Blunt, J. B. McMahon, R. W. Buckheit, Jr., G. Bringmann, M. Schåffer, G. M. Cragg, D. W. Thomas, J. G. Jato, *J. Med. Chem.*, **37**, 1740 (1994).
[13] Y. H. Hallock, K. P. Manfredi, J. W. Blunt, J. H. Cardellina, II, M. Schåffer, K-P. Gulden, G. Bringmann, A. Y. Lee, J. Clardy, G. Francois, M. R. Boyd, *J. Org. Chem.*, **59**, 6349 (1994).
[14] Y. F. Hallock, J. H. Cardellina, T. Kornek, K. P. Gulden, G. Bringmann, M. R. Boyd, *Tetrahedron Lett.*, **36**, 4753 (1995).
[15] G. Bringmann, R. Zagst, H. Reuscher, L. A. Assi, *Phytochemistry*, **31**, 4011 (1992).
[16] J. B. McMahon, M. J. Currens, R. J. Gulakowski, R. W. Buckheit, Jr., C. Lackman-Smith, Y. F. Hallock, M. R. Boyd, *Antimicrob. Agents Chemother.*, **39**, 484 (1995).
[17] J. G. Supko, L. Malspeis, *Antimicrob. Agents Chemother*., **39**, 9 (1994).
[18] T. R. Hoye, M. Chen, L. Mi, O. P. Priest, *Tetrahedron Lett.*, **35**, 8747 (1994).
[19] T. R. Hoye, M. Chen, *J. Org. Chem*., **61**, 7940 (1996).
[20] A. V. Karmer, , J. A. Osborn, *J. Am. Chem. Soc*., **96**, 7832 (1974).
[21] G. Bringmann, S. Harmsen, J. Holenz, T. Geuder, R. Gotz, P. A. Keller, R. Walter, Y. F. Hallock, J. H. Cardellina, II, M. R. Boyd, *Tetrahedron*, **50**, 9643 (1994).
[22] A-S. S. Hamad Elgazwy, *Phosphorus, Sulfur and Silicon*, **175**, 237 (2001).
[23] J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, **25**, 508 (1986); [b] J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.*, **10**, 434 (1977).
[24] A-S. S. Hamad, A. I. Hashem, *Molecules*, **5**, 895 (2000).
[25] K. L. Henold, *Chem. Commun*., 1340 (1970).
[26] A-S. S. Hamad, H. A. Derbala, W. A. Elsayed, A. I. Hashem, *Acta. Chim. Solv.*, **48**, 417 (2001).
[27] L. L. Miller Y. Yu, *J. Org. Chem.*, **60**, 6813 (1995).
[28] J. Vicente, J. A. Abad, R. Bergs, E. Martinez-Viviente, M. C. Ramirez de Arellano, P. G. Jones, *Organometallics*, **19**, 5597 (2000).
[29] A-S. S. Hamad Elgazwy, *Phosphorus, Sulfur and Silicon*, **164**, 131 (2000).
[30] A-S. S. Hamad Elgazwy, *Phosphorus, Sulfur and Silicon*, **170**, 65 (2001).
[31] A. O. Aliprantis, J. W. Canary *J. Am. Chem. Soc*., **116**, 6985 (1994).