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Stille coupling of thiophene with a tetrahydroisoquinoline alkaloid

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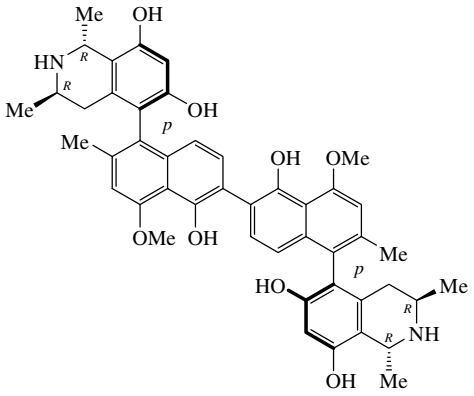
The Stille coupling of tributylstannylthiophenes with halogenated tetrahydroisoquinolines produces analogues of michellamine alkaloids.

The naphthylisoquinoline alkaloids are of interest because of a potent anti-HIV activity.[1–3] Atropisomeric alkaloids (michellamines A, B and C) were isolated from *Ancistrocladus korupensis* found in Cameroon.[4]

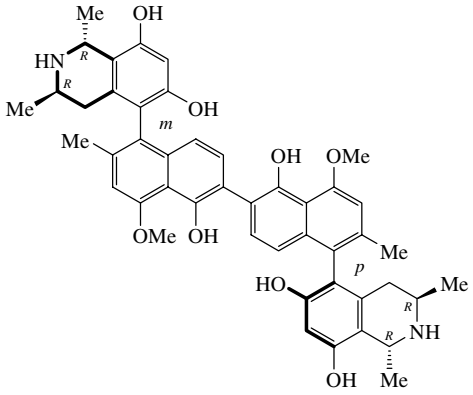
The most naturally abundant michellamines A, B and C were tested and found fully protective against different HIV strains. Michellamine B inhibited enzymatic activities of reverse transcriptases from both HIV-1 and HIV-2.[5]

The aim of this work was to synthesise michellamine analogues containing a thiophene ring as a subunit instead of a binaphthalene ring. This was performed by reaction of thiophene stannane **1** with aryl halides **3** or **4** and all have used palladium coupling steps to construct the key thiophenetetrahydroisoquinoline biaryl bond (*cf.*, **1** + **3** or **1** + **4**) to protected (*R*)-**5** and (*S*)-**5**. We describe here a comparative study of the Pd^0-catalysed construction of hindered biaryl bonds such as that found in **5**, **7** and **8**.

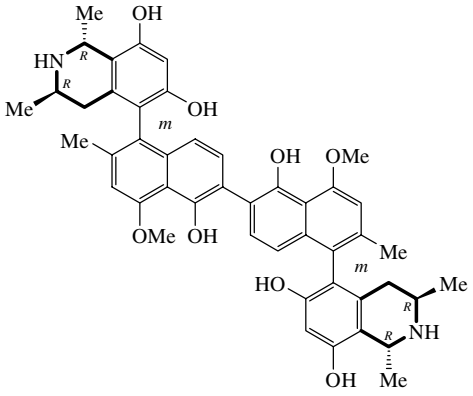
For this purpose, we planned to join together non-racemic tetrahydroisoquinoline bromide (1*R*,3*R*)-**3**† or iodide (1*R*,3*R*)-**4**



Michellamine A

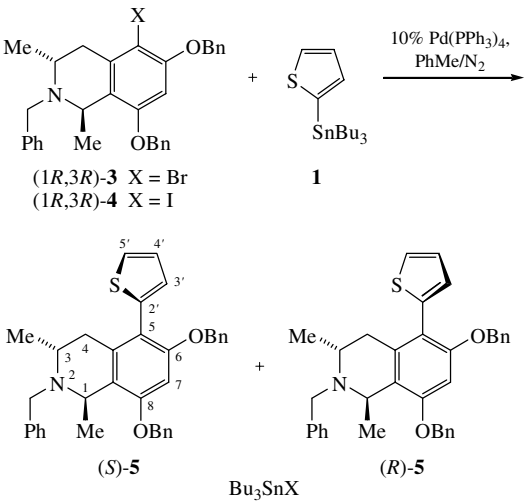


Michellamine B



Michellamine C

† Tetrahydroisoquinoline derivatives **3** and **4** were prepared following a published procedure.[6–9]



Scheme 1

with thiophene stannanes **1** and **2**,‡ using the Stille cross-coupling reaction.[11] The Stille coupling reaction has an advantage of being slightly more general than the Suzuki reaction, since it does not require a base.

The cross-coupling of bromide **3** or iodide **4** with stannane **1** provided a ~1:1 ratio of two stereoisomers (*R*)-**5** and (*S*)-**5** in 66% yield (Scheme 1). These stereoisomers (*R*)-**5** and (*S*)-**5** were separated by column chromatography on silica gel.§

The ^{1}H NMR spectra of stereoisomers **5** are similar but clearly show the difference of the biaryl (isoquinolinyl–thiophene) bond configurations. In the spectrum of isomer (*S*)-**5**, the chemical shift of H(4)$_{ax}$ (2.85 ppm) is at lower field relative to that of H(4)$_{eq}$ (2.43 ppm), in the spectrum of (*R*)-**5** the ratio is reversed (2.06 and 2.33 ppm, respectively). This known correlation between the chemical shift of H(4) and biaryl configuration[12] has been used to assign the configurations of isomers **5**. We examined the cross coupling of stannane **2** with aryl halogenides **3** and **4** in order to synthesise michellamine analogues (*R*,*R*)-**8**, (*R*,*S*)-**8**, (*S*,*S*)-**8**. The cross-coupling of 1 equiv. of **2** (662 mg, 1 mmol) with 2 equiv. of **3** (940 mg, 2 mmol) in the presence of 10 mol% Pd(PPh$_3$)$_4$ in toluene at 110 °C, leads to a mixture of hindered stereoisomers **8**, as shown in Scheme 2.¶ The independent Pd^0 catalysed biaryl coupling of iodide **4** with stannane **2** followed a similar trend to what was seen with **3** furnished the inseparable mixture of corresponding stereoisomers **8** in a low yield (530 mg, 17.5%). The low yield of the cross-coupling product of stereoisomers **8** was anticipated to the sterical hindrance of the bulky aryl group. This mixture contained stereoisomers (*S*,*S*)-**8**, (*R*,*S*)-**8**, (*R*,*R*)-**8** in a ~2:3:2 ratio (as judged from the crude ^{1}H NMR spectrum).

By chromatography, only a small portion of stereoisomer (*R*,*R*)-**8** was separated in 15% yield along with a ~3:2 inseparable mixture of stereoisomers (*R*,*S*)-**8** and (*S*,*S*)-**8**. The assignment and identification of the stereoisomers **8** was based upon the comparizon of their ^{1}H NMR spectra with those of (*R*)-**5** and (*S*)-**5**. When reaction mixture was monitored by TLC during the reaction time, the formation of intermediates (*R*)-**7** and (*S*)-**7** was detected.†† These intermediates could be separated and isolated in 34% total yield using column chromatography on neutral alumina. However, chromatography on silica gel afforded only (*R*)-**5** and (*S*)-**5** due to protodestannylation, in accord with the results described by Miller *et al.*[13] for silica gel chromatography of bis(stannylthiophene) **2**.

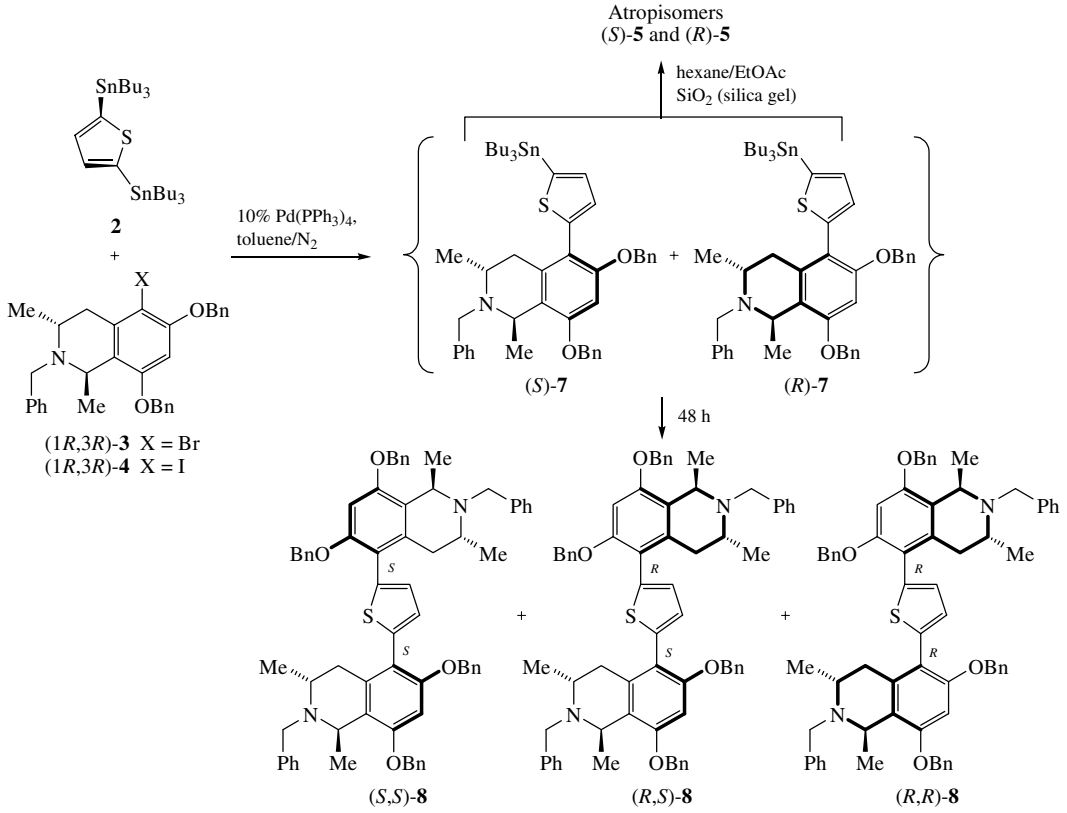
‡ Stannanes **1** and **2** were pepared as described in ref. 10 and separated by chromatography using neutral alumina.

§ All yields refer to isolated products. IR spectra were recorded on Perkin Elmer 781 and Pye Unicam 8725 spectrometers. NMR spectra were recorded on a Bruker DPX 250 spectrometer and the data were obtained using IBM NR-200, IBM NR-300-AF and a Varian VXR-500 (500 MHz) spectrometer.

General method. Aryl halide (1*R*,3*R*)-**3** or -**4** (1 mmol), 1 or 2 equiv. of aryl stannane **1** or **2** (2 mmol) and 10 mol% Pd(PPh$_3$)$_4$ in toluene were placed in a screw-capped tube. The reaction mixture was sealed under N_2 and heated at 110 °C for 48 h and then cooled to room temperature. The reaction mixture was quenched with water (25 ml) and KF (250 mg), stirred for 5 h and then neutralised with a 10% aqueous ammonium chloride solution. The resultant mixture was filtered off to remove the solid Bu_3SnF 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 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]thiophenes* **5**. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 9:2 with 1% Et$_3$N) affording individual stereoisomers (*R*)-**5** and (*S*)-**5** (360 mg, 66% total yield) in a ~1:1 ratio, reddish yellow solids, mp 190–192 °C for (*S*)-**5** and mp 220–222 °C for (*R*)-**5**. IR (KBr, ν/cm^{-1}) 3100, 3030, 2900, 2800, 1656, 825, 810, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ: (*S*)-**5**: 7.53–7.72 (m, 15H, 3Ph), 7.73 [dd, 1H, Th-H(5′), *J* 1.3 and 4.8 Hz], 7.39 [dd, 1H, Th-H(3′), *J* 3.6 and 1.3 Hz], 7.16 [dd, 1H, Th-H(4′), *J* 3.6 and 4.8 Hz], 6.46 [s, 1H, Ar-H(7)], 5.2 [s, 2H, OCH$_2$Ph(8)], 5.1 [s, 2H, OCH_2Ph(6)], 4.14 [q, 1H, H(1), *J* 6.5 Hz], 3.94 [d, 1H, NCH_aPh(2), *J* 14.1 Hz], 3.55 [ddq, 1H, H(3), *J* 11.7, 6.6 and 4.8 Hz], 3.33 [d, 1H, NCH_bPh(2), *J* 14.1 Hz], 2.85 [dd, 1H, H(4ax), *J* 17.7 and 11.7 Hz], 2.43 [dd, 1H, H(4eq), *J* 17.7 and 4.8 Hz], 1.41 [d, 3H, Me(3), *J* 6.6 Hz], 1.27 [d, 3H, Me(1), *J* 6.6 Hz]. The ^{1}H NMR spectrum of stereoisomer (*R*)-**5** was virtually the same as for stereoisomer (*S*)-**5** with the following differences: 5.02 [d, 1H, OCH_aPh(8), *J* 12.0 Hz], 4.98 [d, 1H, OCH_bPh(8), *J* 12.0 Hz], 4.84 [d, 1H, OCH_aPh(6), *J* 13.0 Hz], 4.79 [d, 1H, OCH_bPh(6), *J* 13.0 Hz], 4.13 [q, 1H, H(1), *J* 6.5 Hz], 3.78 [d, 1H, NCH_aPh(2), *J* 14.0 Hz], 3.39 [ddq, 1H, H(3), *J* 12.5, 6.5 and 4.5 Hz], 3.38 [d, 1H, NCH_bPh(2), *J* 14.0 Hz], 2.33 [dd, 1H, H(4eq), *J* 17.5 and 4.5 Hz], 2.06 [dd, 1H, H(4ax), *J* 17.5 and 12.5 Hz], 1.46 [d, 3H, Me(1), *J* 6.5 Hz], 1.16 [d, 3H, Me(3), *J* 6.5 Hz]. Found (%): C, 79.24; H, 6.46; N, 2.56; S, 5.76. Calc. for stereoisomers (*S*)-**5** or (*R*)-**5**, $C_{36}H_{35}NO_2S$ (545.24) (%): C, 79.23; H, 6.46; N, 2.56; S, 5.87.

¶ *2′,5′-Bis[(1*R*,3*R*)-2-benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]thiophenes* **8**. The cross-coupling of **2** (66.2 mg, 0.1 mmol) with 2 equiv. of **3** (94.0 mg, 0.2 mmol) or **4** (117.8 mg, 0.2 mmol) in the presence of 10 mol% Pd(PPh$_3$)$_4$ was carried out in toluene at 110 °C. The reaction mixture was refluxed for 48 h and then worked up according to the general method described above to provide a mixture of hindered stereoisomers **8**. The independent Pd^0 catalysed biaryl coupling of iodide with stannane **2** (662 mg, 1 mmol) followed a similar trend to what was seen with **3** furnished the inseparable mixture of corresponding stereoisomers **8** in a low yield (530 mg, 17.5%). Separation using column chromatography on silica gel (hexane–EtOAc, 100:9 with 4% Et$_3$N) or by HPLC (normal-phase or microsorb amino-bond column) produced stereoisomer (*R*,*R*)-**8** (15.5 mg, 5% yield) from the mixture, along with a 3:2 mixture of stereoisomers (*R*,*S*)-**8**, (*S*,*S*)-**8** in 12.4% total yield (37.5 mg). IR (KBr, ν/cm^{-1}): 3100, 2966, 2930, 1665, 1464, 1255, 1098, 840, 825, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ: (*R*,*R*)-**8**: 7.51–7.74 (m, 15H, 3Ph), 7.39 [d, 1H, Th-H(3′), *J* 3.7 Hz], 7.23 [d, 1H, Th-H(4′), *J* 3.7 Hz], 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, 2H, H(1,1″), *J* 6.7 Hz], 3.91 [d, 2H, NCH_aPh(2,2″), *J* 14.2 Hz], 3.56 [ddq, 2H, H(3,3″), *J* 11.8, 6.7 and 4.9 Hz], 3.25 [d, 2H, NCH_bPh(2,2″), *J* 14.2 Hz], 2.71 [dd, 2H, H(4eq,4″eq), *J* 17.8 and 4.9 Hz], 2.45 [dd, 2H, CH(4ax,4″ax), *J* 17.8 and 11.8 Hz], 1.40 [d, 6H, Me(3,3″), *J* 6.7 Hz], 1.35 [d, 6H, Me(1,1″), *J* 6.7 Hz]. The ^{1}H NMR spectrum for stereoisomer (*R*,*S*)-**8** [from the mixture of (*R*,*S*)-**8** and (*S*,*S*)-**8**]: 7.52–7.78 (m, 15H, 3Ph), 7.38 [d, 1H, Th-H(3′), *J* 3.6 Hz], 7.22 [d, 1H, Th-H(4′), *J* 3.6 Hz], 6.49 [s, 2H, Ar-H(7,7″)], 5.25 [s, 4H, OCH_2Ph(8,8″)], 5.10 [d, 2H, OCH_aPh(6,6″), *J* 12.3 Hz], 4.96 [d, 2H, OCH_bPh(6,6″), *J* 12.3 Hz], 4.08 [q, 2H, H(1,1″), *J* 6.6 Hz], 3.92 [d, 2H, NCH_aPh(2,2″), *J* 14.2 Hz], 3.58 [ddq, 2H, H(3,3″), *J* 11.8, 6.7 and 5.1 Hz], 3.25 [d, 2H, NCH_bPh(2,2″), *J* 14.2 Hz], 2.77 [dd, 2H, CH(4eq,4″eq), *J* 17.8 and 5.1 Hz], 2.26 [dd, 2H, CH(4ax,4″ax), *J* 17.8 and 11.8 Hz], 1.44 [d, 6H, Me(3,3″), *J* 6.6 Hz], 1.38 [d, 6H, Me(1,1″), *J* 6.7 Hz]. The ^{1}H NMR spectrum for stereoisomer (*S*,*S*)-**8** [from the mixture of (*R*,*S*)-**8** and (*S*,*S*)-**8**] δ: 7.54–7.77 (m, 15H, 3Ph), 7.42 [d, 1H, Th-H(3′), *J* 3.7 Hz], 7.26 [d, 1H, Th-H(4′), *J* 3.7 Hz], 6.52 [s, 2H, Ar-H(7,7″)], 5.15 [s, 4H, OCH_2Ph(8,8″)], 5.10 [d, 2H, OCH_aPh(6,6″), *J* 12.3 Hz], 4.99 [d, 2H, OCH_bPh(6,6″), *J* 12.3 Hz], 4.19 [q, 2H, H(1,1″), *J* 6.7 Hz], 3.99 [d, 2H, NCH_aPh(2,2″), *J* 14.2 Hz], 3.61 [ddq, 2H, H(3,3″), *J* 11.8, 6.7 and 5.2 Hz], 3.33 [d, 2H, NCH_bPh(2,2″), *J* 14.2 Hz], 2.72 [dd, 2H, CH(4ax,4″ax), *J* 17.8 and 11.8 Hz], 2.42 [dd, 2H, CH(4eq,4″eq), *J* 17.8 and 5.2 Hz], 1.46 [d, 6H, Me(3,3″), *J* 6.6 Hz], 1.37 [d, 6H, Me(1,1″), *J* 6.6 Hz]. Found (%): C, 80.92; H, 6.68; N, 2.74; S, 3.15. Calc. for (*R*,*R*)-**8**, $C_{68}H_{66}N_2O_4S$ (1007.35): C, 81.07; H, 6.60; N, 2.78; S, 3.18.



Scheme 2

In summary, the palladium(0)-catalysed Stille coupling reaction was shown to be an effective method for the simple synthesis of michellamine analogues, which are of interest for biological testings.

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†† *2'-[(1*R*,3*R*)-2-Benzyl-6,8-dibenzyloxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-5'-(tri*-n-*butylstannyl)thiophenes* **7**. The cross-coupling of **2** (66.2 mg, 0.1 mmol) with **3** (94.0 mg, 0.2 mmol) or **4** (117.8 mg, 0.2 mmol) proceeded in the presence of 10 mol% $Pd(PPh_3)_4$. The reaction mixture was sealed under N_2 and heated at 110 °C in toluene for 6 h, then cooled to room temperature and processed according to the general method to provide a mixture of isomers **7**. The product was purified by column chromatography on neutral alumina (hexane–EtOAc, 15:3 with 2% Et_3N) giving stereoisomers (*S*)-**7** and (*R*)-**7** (28.5 mg, 11.37% yield) as yellow oil. IR (KBr, ν/cm^{-1}): 2965, 2930, 1660, 1470, 1255, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ: for *S*-**7**: 7.55–7.77 (m, 15H, 3Ph), 7.44 [d, 1H, Th-H(3′), *J* 3.8 Hz], 7.22 [d, 1H, Th-H(4′), *J* 3.8 Hz], 6.53 [s, 1H, Ar-H(7)], 5.2 [s, 2H, OCH_2Ph(8)], 5.11 [s, 2H, OCH_2Ph(6)], 4.22 [q, 1H, H(1), *J* 6.5 Hz], 3.82 [d, 1H, NCH_aPh(2), *J* 14.2 Hz], 3.48 [ddq, 1H, H(3), *J* 11.8, 6.5 and 4.8 Hz], 3.40 [d, 1H, NCH_bPh(2), *J* 14.2 Hz], 2.52 [dd, 1H, H(4ax), *J* 17.8 and 11.8 Hz], 2.15 [dd, 1H, H(4eq), *J* 17.8 and 4.8 Hz], 1.66 (tt, 6H, $SnCH_2CH_2CH_2Me$, *J* 8.4 and 7.7 Hz), 1.43 [d, 3H, Me(3), *J* 6.5 Hz], 1.38 (tq, 6H, $Sn(CH_2)_2CH_2Me$, *J* 7.7 and 7.8 Hz), 1.18 (t, 6H, $SnCH_2CH_2CH_2Me$, *J* 8.4 Hz), 1.11 [d, 3H, Me(1), *J* 6.5 Hz], 0.99 (t, 9H, $Sn(CH_2)_3Me$, *J* 7.8 Hz). The ^{1}H NMR spectrum of (*R*)-**7** was virtually the same as for stereoisomer (*S*)-**7** with the following differences: 5.10 [d, 1H, OCH_aPh(8), *J* 12.0 Hz], 5.06 [d, 1H, OCH_bPh(8), *J* 12.0 Hz], 4.94 [d, 2H, OCH_aPh(6), *J* 12.0 Hz], 4.82 [d, 1H, OCH_bPh(6), *J* 12.0 Hz], 4.15 [q, 1H, H(1), *J* 6.6 Hz], 3.77 [d, 1H, NCH_aPh(2), *J* 14.0 Hz], 3.42 [ms, 1H, H(3)], 3.35 [d, 2H, NCH_bPh(2), *J* 14.0 Hz], 2.55 [dd, 1H, H(4eq), *J* 17.0 and 4.8 Hz], 2.16 [dd, 1H, H(4ax), *J* 17.0 and 12.0 Hz], 1.40 [d, 3H, Me(1), *J* 6.6 Hz], 1.13 [d, 3H, Me(3), *J* 6.6 Hz], 1.65 (tt, 6H, $SnCH_2CH_2CH_2Me$, *J* 8.4 and 7.7 Hz), 1.40 [d, 3H, Me(3), *J* 6.6 Hz], 1.40 [tq, 6H, $Sn(CH_2)_2CH_2Me$, *J* 7.7 and 7.8 Hz], 1.28 (t, 6H, $SnCH_2CH_2CH_2Me$, *J* 8.4 Hz), 1.21 [d, 3H, Me(1), *J* 6.5 Hz], 1.11 [t, 9H, $Sn(CH_2)_3Me$, *J* 7.8 Hz]. Found (%): C, 68.93; H, 7.03; N, 1.60; S, 3.56. Calc. for (*S*)-**7** or (*R*)-**7**, $C_{48}H_{61}NO_2SSn$ (835.08) (%): C, 69.04; H, 7.36; N, 1.67; S, 3.84.

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