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Synthesis and Optical Resolution of Inherently Chiral Difunctionalized Tribenzotriquinacenes

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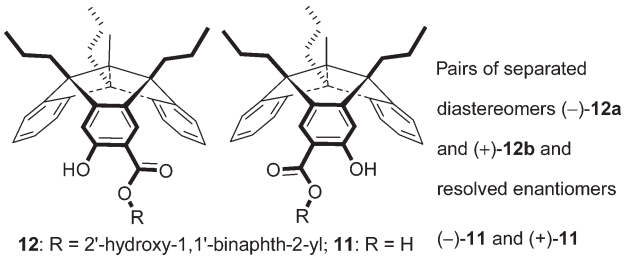

The synthesis of several inherently chiral tribenzotriquinacenes (TBTQs) bearing one single mono- or difunctionalized aromatic nucleus and the optical resolution of one of these derivatives, a TBTQ-based salicylic acid (**11**), are described for the first time. Efficient access to enantiopure, inherently chiral tribenzotriquinacenes may lay a foundation for studies of novel container compounds, supramolecular aggregation, chiral recognition, and asymmetric catalysis.

Tribenzotriquinacenes[1] are conformationally rigid, bowl-shaped molecules that have great potential as host molecules for neutral and charged molecular guests.[2] Owing to their facile accessibility and high versatility for chemical transformations, including bridgehead substitution and extension of the polycyclic framework into different directions of space, tribenzotriquinacenes may become important building blocks for future applied chemical research. A parent congener, 10-methyltribenzotriquinacene (12d-methyl-4b,8b,12b,12d-tetrahydrodibenzo[2,3:4,5]pentaleno[1,6-*ab*]indene, **1**), is available via a four-step sequence on a 50-g scale[3] and can be easily modified in various ways at the bridgehead and/or the peripheral positions.[4] In recent years, further progress has been made in the synthesis of TBTQ derivatives with 6- and 3-fold functionalization at the aromatic periphery, giving rise to C_{3v}-symmetrical (and thus achiral) congeners (e.g., **2a**[4d] and **2b**[5] in Figure 1),[1,6] and, respectively, C_3- and C_1-(and thus chiral) congeners (e.g., **3a** and **4a**[7a] or **3b** and **4b**[7b]). By contrast, monofunctionalized tribenzotriquinacenes or TBTQ derivatives bearing two different functionalities at only one of the three benzene nuclei (cf. **5** in Figure 1), which would represent the simplest inherently chiral members of the growing TBTQ family, have not been reported to date. The investigation of inherently chiral polycyclic systems[8] has been greatly developed in the fields of calixarene,[9] cyclotriveratrylene,[10] helicene,[11] and [2.2]paracyclophane[12] chemistry. Inherently chiral tribenzotriquinacenes with molecular C_3-symmetry promise to be particularly valuable building blocks for covalently bound container molecules and for self-organized supramolecular aggregates, as shown recently in the case of the trinitrotribromo derivative **3b** forming enantiopure solid-state nanocubes.[7b] Therefore, the systematic design and investigation of inherently chiral tribenzotriquinacenes should lead to many interesting new facets of supramolecular chemistry.

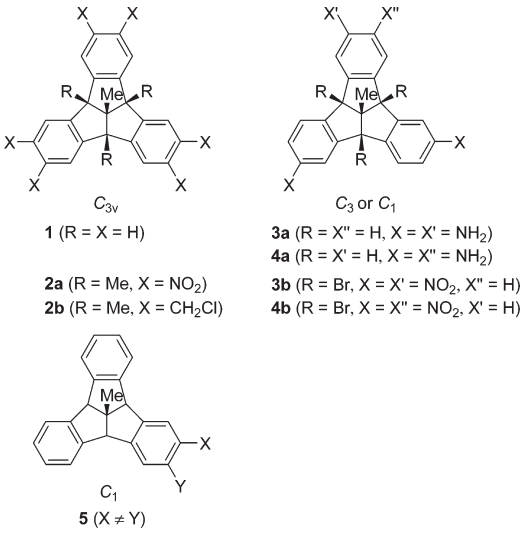

FIGURE 1. C_{3v}-, C_3-, and C_1-symmetrical TBTQs.

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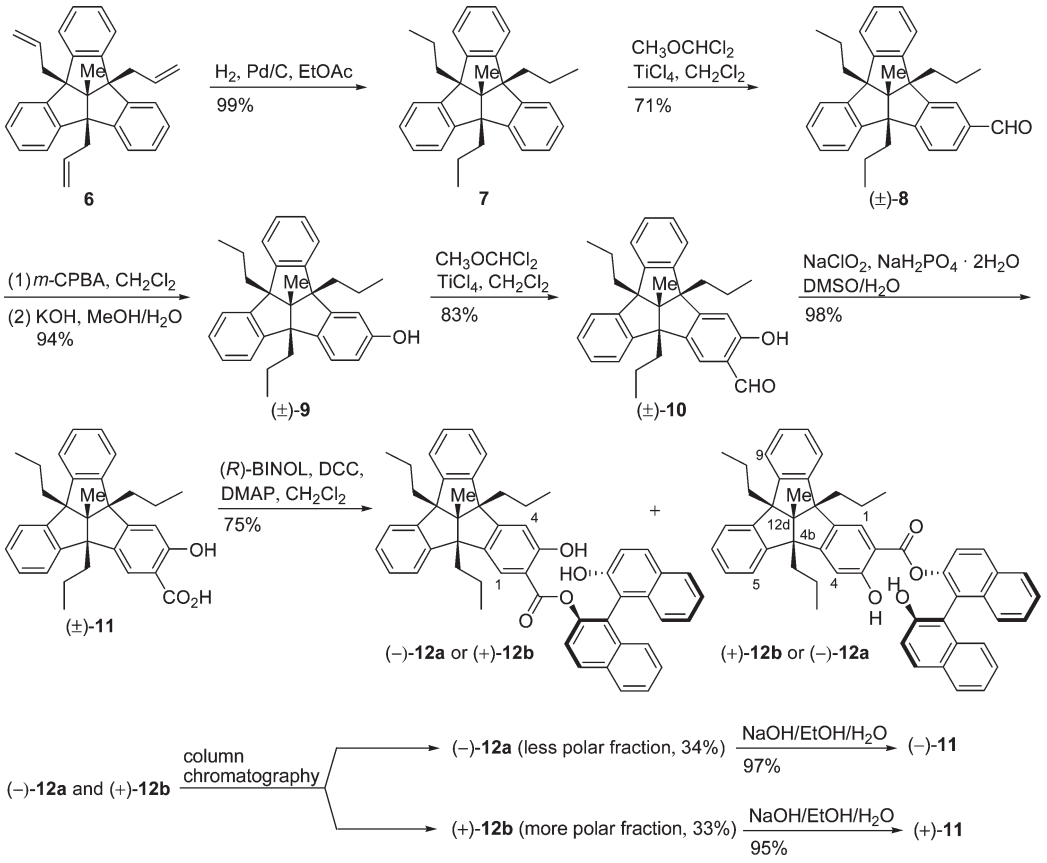
SCHEME 1. Synthesis and Optical Resolution of the TBTQ−Salicylic Acid (±)-11



Inherently chiral tribenzotriquinacenes may be generated in two different ways. The first way is to introduce three different achiral residues at the three bridgehead positions. This approach is difficult because the directed single or double functionalization of the bridgeheads of TBTQ (and of parent triquinacene[13]) is hard to achieve with good efficiency.[4e] Alternatively, inherently chiral TBTQ derivatives can be generated by incomplete substitution reactions at the six outer peripheral positions, thus reducing the original molecular C_{3v}-symmetry to C_3 or C_1. Herein, we demonstrate that this concept can be successfully applied to TBTQ derivatives in which only one of the three indan wings carries the functional groups that induce inherent chirality. As it will be shown, the use of an enantiomerically pure auxiliary, (*R*)-BINOL,[14] has allowed us to prepare the first optically pure tribenzotriquinacene, bearing only one single functionalized aromatic ring, namely, the TBTQ-based salicylic acid **11**.

Starting from the known triallyltribenzotriquinacene **6**,[4e] we prepared the corresponding tri(*n*-propyl) derivative **7** by catalytic hydrogenation in virtually quantitative yield (Scheme 1). Tribenzotriquinacenes bearing solubilizing elongated aliphatic groups at the bridgehead positions promise to be more versatile building blocks for the construction of extended TBTQ-based covalent and supramolecular architectures. Subsequent introduction of a single formyl group into hydrocarbon **7** by use of 1,1-dichloromethyl methyl ether in the presence of stoichiometric amounts of titanium tetrachloride[15] was achieved in good yield giving the racemic monoaldehyde (±)-**8**. Under the conditions used, the formation of doubly formylated products was largely suppressed.[16] Baeyer−Villiger oxidation[17] of the aldehyde **8** using *m*-CPBA followed by saponification of the crude aryl formate with potassium hydroxide in aqueous methanol afforded the corresponding monohydroxytribenzotriquinacene (±)-**9** in an overall 94% yield. In analogy to the first functionalization of **7**, formylation of the TBTQ-phenol **9** was carried out by using $CH_3OCHCl_2/TiCl_4$ under the same

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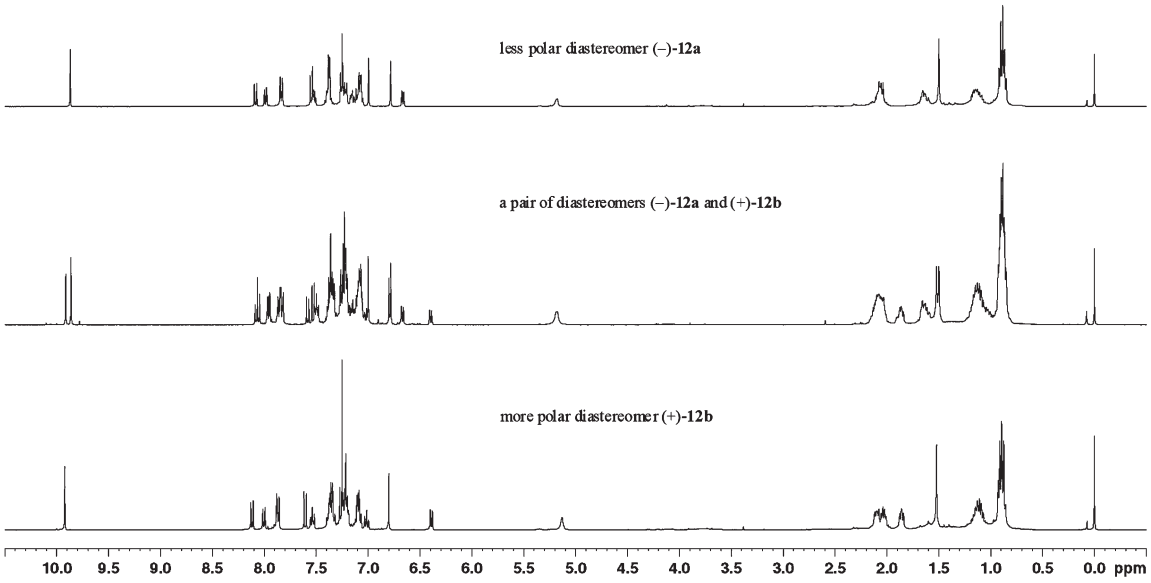

FIGURE 2. ^{1}H NMR spectra of the diastereomers (−)-**12a** and (+)-**12b** (400 MHz, $CDCl_3$).

conditions and without protection of the hydroxy group,[18] giving the TBTQ-salicylic aldehyde (±)-**10** in 83% yield. Subsequent oxidation of compound **10** with sodium chlorite in aqueous, buffered (NaH_2PO_4/Na_2HPO_4) dimethyl sulfoxide[19] afforded the TBTQ-based salicylic acid (±)-**11** in virtually quantitative yield. Compound **11** was found to be quite soluble in dichloromethane and in dimethyl sulfoxide, which enabled the characterization of the compound by both ^{1}H and ^{13}C NMR spectroscopy. Esterification of the racemic acid **11** with (*R*)-BINOL under typical condensation conditions (DCC/DMAP) afforded a pair of diastereomers. Column chromatography or preparative TLC furnished the first-eluting ester, (−)-**12a** [$[\alpha]^{25}_D = -60.0$, $c = 0.27$, CH_2Cl_2] in 34% yield and the second-eluting isomer, (+)-**12b** [$[\alpha]^{25}_D = +52.0$, $c = 0.36$, CH_2Cl_2] in 33% yield, respectively. The diastereomeric esters were characterized by ESI(−) mass spectrometry and by ^{1}H and ^{13}C NMR spectroscopy. Their ^{1}H NMR spectra (Figure 2), in particular, of (−)-**12a** and (+)-**12b** reflect the effectiveness of the separation. Besides several tiny differences of chemical shifts ($\Delta\delta \approx 0.05$ ppm) of some resonances (δ 9.9, 8.1, 7.85, 5.15, and 1.5), a major difference ($\Delta\delta \approx 0.3$ ppm) was found for the arene protons located *ortho* to the free BINOL hydroxyl groups resonating at δ 6.67 and 6.39. Moreover, the chemical shifts and splitting of the methylene resonances of the bridgehead propyl residues differ significantly. Marked differences were also found in the ^{13}C NMR spectra (Supporting Information). Although these observations can hardly be explained at first approximation, it is obvious that, besides strong hydrogen bonds between the BINOL auxiliary and TBTQ backbone, the rigidity of both of these moieties are vital to the successful optical resolution.

Finally, saponification of each of the esters (−)-**12a** and (+)-**12b** furnished the enantiopure TBTQ salicylic acids (−)-**11** [$[\alpha]^{25}_D = -31.0$, $c = 1.01$, CH_2Cl_2] and (+)-**11** [$[\alpha]^{25}_D = +31.0$, $c = 0.73$, CH_2Cl_2] in 97% and 95% yield, respectively. The optical rotations of (−)-**11** and (+)-**11** proved to be of the same magnitude and the CD spectra also showed excellent complementarity (Figure 3), confirming the successful optical resolution of the racemate (±)-**11** into the pure enantiomers. They were fully characterized except for the assignment of their absolute configuration, as our attempts to grow crystals that would be suitable for X-ray structure analysis failed.

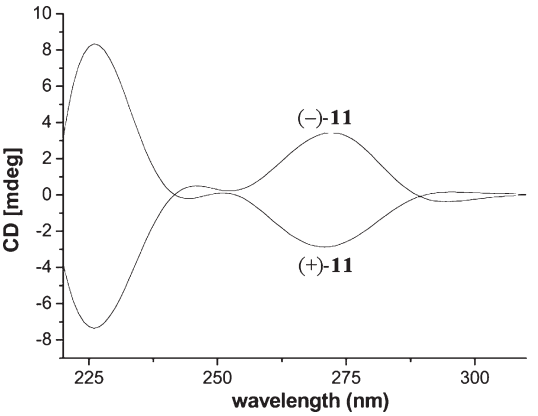

FIGURE 3. CD spectra of the TBTQ-salicyclic acids (−)-**11** and (+)-**11** (CH_2Cl_2).

In summary, we have developed an efficient synthesis of several inherently chiral tribenzotriquinacenes (**8**−**11**) bearing only one single functionalized arene unit. Among these, the TBTQ salicyclic acid **11** represents the first member of this subfamily that has been separated into its two enantiomers, (−)-**11** and (+)-**11**. Efforts to synthesize more elaborate inherently chiral tribenzotriquinacenes, to achieve their optical resolution and to study their use in asymmetric reactions are underway in our laboratories.

Experimental Section

(±)-2-Formyl-12d-methyl-4b,8b,12b-tri(*n*-propyl)-4b,8b,12b,12d-tetrahydrodibenzo[2,3:4,5]pentaleno[1,6-*ab*]indene [(±)-8]. A solution of hydrocarbon **7** (300 mg, 0.71 mmol) in anhydrous dichloromethane (5 mL) was stirred at 0 °C under argon while titanium(IV) chloride (86 μL, 0.78 mmol) was added. The color of the solution

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turned yellow-orange, and 1,1-dichloromethyl methyl ether (68 μL, 0.75 mmol) was injected dropwise. The mixture was stirred for 24 h at ambient temperature, quenched with a small amount of water, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Flash column chromatography of the residue through silica gel (petroleum ether/AcOEt 50:1) afforded formyltribenzotriquinacene (±)-**8** as a colorless solid (227 mg, 71%): mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.82 (s, 1H), 7.63 (dd, J = 8.0, 1.2 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.35 (dd, J = 6.8, 4.0 Hz, 1H), 7.31−7.28 (m, 3H), 7.16−7.12 (m, 4H), 2.22−2.14 (m, 6H), 1.64 (s, 3H), 1.20−1.18 (m, 6H), 0.95−0.90 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0 (C), 155.4 (C), 149.5 (C), 148.1 (C), 147.9 (C), 147.2 (C), 146.9 (C), 136.0 (C), 129.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 124.5 (CH), 124.0 (CH), 123.5 (CH), 123.4 (CH), 123.2 (CH), 72.0 (C), 67.5 (C), 67.4 (C), 66.9 (C), 40.84 (CH_2), 40.76 (CH_2), 40.5 (CH_2), 20.4 (CH_2), 15.1 (CH_3), several Ar-CH, CH_2 and CH_3 resonances were not resolved; IR (KBr) 2958, 1693, 1599, 1479, 1151, 823, 755, 509 cm^{-1}; accurate mass (ESI-MS) m/z [M + H]$^+$ calcd for $C_{33}H_{37}O$ 449.2839, found 449.2843.

Esterification of the Racemic TBTQ-salicylic Acid (±)-11 with (*R*)-BINOL. A solution of salicylic acid (±)-**11** (76 mg, 0.16 mmol) in dichloromethane (2.0 mL) was stirred at room temperature while (*R*)-BINOL (229 mg, 0.80 mmol), dicyclohexylcarbodiimide (DCC, 99 mg, 0.48 mmol), and 4-dimethylaminopyridine (DMAP, 29 mg, 0.24 mmol) were added. The mixture was heated under reflux for 5 h. The insoluble dicyclohexylurea formed was removed by filtration, and the filtrate was concentrated under reduced pressure. Flash column chromatography of the residue through silica gel (petroleum ether/acetone 9:1) afforded the diastereomers (−)-**12a** (41 mg, 34%) as the first-eluting fraction and (+)-**12b** (40 mg, 33%) as the second-eluting fraction.

(−)-2-(2′-Hydroxy-1,1′-binaphthen-2-oxycarbonyl)-3-hydroxy-12d-methyl-4b,8b,12b-tri(*n*-propyl)-4b,8b,12b,12d-tetrahydrodibenzo-[2,3:4,5]pentaleno[1,6-*ab*]indene [(−)-12a]: colorless solid; mp 150−151 °C; $[\alpha]^{25}_D$ −60.0 (CH_2Cl_2, c = 0.27); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.87 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.56−7.51 (m, 2H), 7.40−7.37 (m, 4H), 7.27−7.21 (m, 4H), 7.17−7.07 (m, 5H), 7.00 (s, 1H), 6.78 (s, 1H), 6.67 (d, J = 7.6 Hz, 1H), 5.18 (s, 1H), 2.11−1.60 (m, 6H), 1.50 (s, 3H), 1.19−1.09 (m, 6H), 0.92−0.85 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5 (C), 161.1 (C), 158.2 (C), 151.6 (C), 148.0 (C), 147.7 (C), 147.5 (C), 147.4 (C), 146.8 (C), 139.8 (C), 133.5 (C), 133.3 (C), 132.2 (C), 130.6 (CH), 130.4 (CH), 128.9 (C), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.24 (CH), 127.19 (CH), 126.6 (CH), 126.4 (CH), 125.7 (CH), 124.62 (CH), 124.57 (CH), 123.7 (CH), 123.4 (CH), 123.3 (CH), 123.18 (CH), 123.15 (CH), 122.6 (C), 121.6 (CH), 117.9 (CH), 113.5 (C), 111.2 (CH), 110.8 (C), 71.9 (C), 67.32 (C), 67.30 (C), 66.0 (C), 40.8 (CH_2), 40.4 (CH_2), 40.0 (CH_2), 20.4(CH_2), 20.3 (CH_2), 20.2 (CH_2), 15.1 (CH_3), 15.0 (CH_3), 14.9 (CH_3), two CH_3 resonances were not resolved; IR (KBr) 3326, 2928, 1680, 1276, 817, 780, 696 cm^{-1}; accurate mass [(−)-ESI-MS] m/z [M − H]$^-$ calcd for $C_{53}H_{47}O_4$ 747.3480, found 747.3483.

(+)-2-(2′-Hydroxy-1,1′-binaphthen-2-oxycarbonyl)-3-hydroxyl-12d-methyl-4b,8b,12b-tri(*n*-propyl)-4b,8b,12b,12d-tetrahydrodibenzo-[2,3:4,5]pentaleno[1,6-*ab*]indene [(+)-12b]: colorless solid; mp 150−152 °C; $[\alpha]^{25}_D$ +52.0 (CH_2Cl_2, c = 0.36); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.92 (s, 1H), 8.12 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.56−7.52 (m, 1H), 7.38−7.34 (m, 4H), 7.32 (s, 1H), 7.28−7.20 (m, 5H), 7.11−7.00 (m, 4H), 6.80 (s, 1H), 6.39 (d, 1H, J = 7.6 Hz), 5.13 (s, 1H), 2.12−1.84 (m, 6H), 1.52 (s, 3H), 1.15−1.07 (m, 6H), 0.93−0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (C), 161.2 (C), 157.9 (C), 151.6 (C), 148.3 (C), 147.7 (C), 147.3 (C), 147.2 (C), 146.4 (C), 140.3 (C), 133.4 (C), 132.3 (C), 130.64 (CH), 130.56 (CH), 129.0 (C), 128.4 (CH), 128.2 (CH), 127.59 (CH), 127.56 (CH), 127.33 (CH), 127.29 (CH), 127.1 (CH), 126.7 (CH), 126.5 (CH), 125.7 (CH), 124.5 (CH), 124.4 (CH), 123.6 (CH), 123.4 (CH), 123.3 (CH), 123.1 (CH), 123.0 (CH), 122.6 (C), 121.6 (CH), 118.0 (CH), 113.4 (C), 111.6 (CH), 110.7 (C), 71.9 (C), 67.4 (C), 67.2 (C), 66.1 (C), 40.8 (CH_2), 40.52 (CH_2), 40.50 (CH_2), 20.4 (CH_2), 20.3 (CH_2), 20.2 (CH_2), 15.09 (CH_3), 15.07 (CH_3), 15.04 (CH_3), 15.01 (CH_3), two Ar−C resonances were not resolved; IR (KBr) 3391, 2958, 1714, 1621, 1191, 817, 750, 780 cm^{-1}; accurate mass [(−)-ESI-MS] m/z [M − H]$^-$ calcd for $C_{53}H_{47}O_4$ 747.3480, found 747.3472.

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Supporting Information Available: Experimental procedures, spectral data for other compounds, and ^{1}H, ^{13}C NMR, and DEPT 135 spectra of compounds **7**, (±)-**8**, (±)-**9**, (±)-**10**, (±)-**11**, (−)-**12a**, (+)-**12b**, (−)-**11**, and (+)-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.