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FULL PAPER

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The Enantiomers of Trinorbornane and Derivatives Thereof

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Herein, we report the synthesis of the enantiomers of trinorbornane, a tetracyclic saturated hydrocarbon with the chemical formula $C_{11}H_{16}$. The preparation of these rigid carbon scaffolds was enabled by the successful chiral separation of its tricyclic precursor, thus allowing the enantiomers to be synthesized through a reductive radical cyclization reaction. Assignment of the absolute conformation of the enantiomers was achieved through VCD experiments. Further, we report an alternative cyclization procedure providing access to hydroxyl and phenyl sulfone functionalized trinorbornanes.

Keywords: chirality, hydrocarbons, vibrational spectroscopy, radical reactions, cyclization.

Introduction

Hydrocarbons are of fundamental interest to chemists and the adjacent fields.[1–4] Carbon-based skeletons are not only key for the diversity of molecular structures on our planet, the structural integrity combined with the chemical inertness of saturated polycyclic hydrocarbons makes them ideal building blocks to control the spatial arrangement of functional subunits with applications ranging from model compounds[5] over catalysts[6] to even pharmaceutically active compounds.[2]

Inspired by the exploration of the chemical space with computational tools by the group of *Jean-Louis Reymond*, we became interested in so far neither isolated nor synthesized intriguing scaffolds.[7,8] Within the subset of C_{11} derivatives, we were fascinated by the particular appealing highly symmetric framework of trinorbornane (tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane, **1**), for which we recently reported the successful synthesis as racemate.[9] Its C_2-symmetric framework consisting of three superposed norbornane units (displayed in red, blue and yellow in *Figure 1* for **1**-S_a) is an example of axial chirality and both enantiomers (1S_a,4*S*,6*R*,7*S*,9*R*)-tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1**-S_a) and (1R_a,4*R*,6*S*,7*R*,9*S*)-tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1**-R_a) are displayed in *Figure 1*.

Fascinated by perspective of obtaining these aesthetically pleasing cage hydrocarbons with the chemical formula $C_{11}H_{16}$ as pure enantiomers, suitable methods for the preparation of these rigid saturated hydrocarbons lacking chromophores were investi-

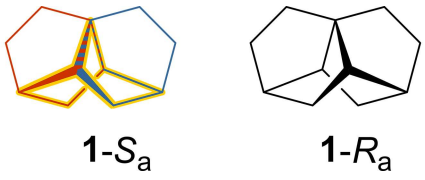

Figure 1. Structure of the enantiomers of trinorbornane **1**-S_a and **1**-R_a.

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gated. Further, alternative cyclization methods were sought, which could thus enable substituted derivatives of this tetracyclic carbon scaffold to be accessed.

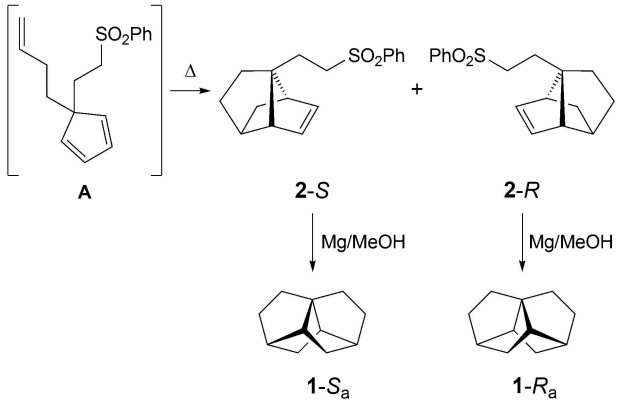
Results and Discussion

The separation of the enantiomers **1**-S_a and **1**-R_a on a preparative scale through chromatographic means was deemed difficult due to the lack of both, polar groups interacting with the solid phase and chromophores needed for the detection of the separated samples. To further increase the challenge, the volatility of these compounds restricts the choice of liquid phase significantly. As more promising strategy, the chiral separation of the racemic brexane[10,11] derivative 1-(2-(phenylsulfonyl)ethyl)tricycle-[4.3.0.0^{4,9}]non-7-ene (**2**), which is formed in an intramolecular *Diels–Alder* reaction, was considered. As the chiral information responsible for the formation of either **1**-S_a or **1**-R_a should already be present in the corresponding brexane precursors **2**-*S* and **2**-*R*, respectively, their separation might enable the subsequent individual synthesis of enantiopure **1**-S_a and **1**-R_a (*Scheme 1*).

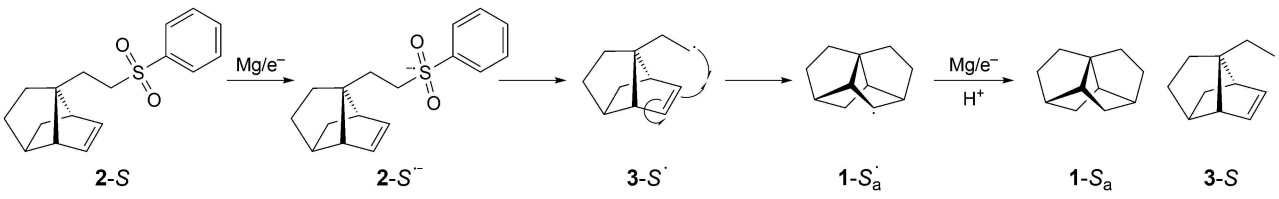
Indeed, we found that using *CHIRALPAK® IG* column with MeCN (further parameters are given in the *Supporting Information* on p. 3) as the mobile phase allowed the preparative separation of the enantiomers (1*S*,4*R*,6*S*,9*R*)-1-[2-(phenylsulfonyl)ethyl]tricyclo [4.3.0.0^{4,9}]non-7-ene (**2**-*S*) and (1*R*,4*S*,6*R*,9*S*)-1-[2-(phenylsulfonyl)ethyl]tricyclo[4.3.0.0^{4,9}]non-7-ene (**2**-*R*). The following reductive radical cyclization of the obtained enantiomers was performed using Mg in methanol as a single electron reduction system.[12–14] This reproducible and preparatively simple method provided **1**-S_a and **1**-R_a in 23% and 20% yield of isolated product, respectively. The lower yield for this transformation can be explained by the unavoidable losses of these volatile compounds during removal of the solvents. From the product distribution observed by GC it is estimated that approximately 50% of the formed tetracyclic target compound could be isolated, even though utmost precautions were undertaken.

As hypothesized, it seems that the preorganization of the carbon scaffold of **2** distorts the quaternary carbon bridgehead such, that the ethyl sulfonyl benzene moiety is placed closer to the distal sp^2 carbons, thus allowing this traceless radical reaction to proceed regiospecifically (*Scheme 2*). Hence, reductive cyclization reaction of **2** yields the distally bridged structure of **1** as the sole cyclization product together with the uncyclized side product **3** in a 5:4 ratio as determined by GC. It is noteworthy that dimeric trinorbornane species, isolated as side product of the radical reaction in the synthesis of racemic trinorbornane,[9] were not observed using the here reported single electron reduction protocol.

To facilitate the isolation of the individual enantiomers **1**-S_a and **1**-R_a by column chromatography (CC), further derivatization of the double bond present in the uncyclized side products **3** was considered. For this mean, the crude mixtures were subjected to oxidizing conditions, thus increasing the polarity of the side product by formation of the epoxide and



Scheme 1. Racemic mixture of sulfone **2** formed through *Diels-Alder* reaction of the *in situ* generated intermediate **A** and the proposed synthesis of the enantiomers of **1** through reductive cyclization of the corresponding enantiomers of **2** after chiral separation.



Scheme 2. Proposed mechanism of the reductive cyclization on the example of **2**-*S* forming **1**-S_a after in total two single electron reduction steps. The observed uncyclized side **3**-*S* is formed by either reduction or hydrogen abstraction of **3**-S$^{\bullet}$.

therefore allowing an efficient isolation of the saturated hydrocarbons **1**-S_a and **1**-R_a by CC followed by sublimation.

The enantiomeric purity of the isolated compounds **1**-S_a and **1**-R_a was evaluated through chiral-GC. The analysis of the chromatograms obtained from the previously prepared racemate and the newly isolated products clearly reveal the successful isolation of the enantiomers of **1** (*Figure 2*).

The small molecular size and the high rigidity of this saturated hydrocarbon scaffold prompted investigation of the enantiomers through vibrational circular dichroism (VCD) spectroscopy.[15] Reliable assignment of the absolute configuration of **1**-S_a and **1**-R_a was achieved by the widely accepted method of comparing the calculated and measured VCD spectra of the chiral structures.[16] Theoretical prediction of the IR and VCD spectrum of **1**-S_a was obtained using the B3PW91[17,18] functional and a 6−311++G(d,p)[19] basis set. The experimental IR and VCD spectra of **1**-S_a and **1**-R_a were measured in CD_2Cl_2 (0.90 and 0.78 M, resp.). The results of the analysis of compounds **1**-S_a and **1**-R_a are shown in *Figure 3*. The calculated and measured spectra of **1**-S_a stand in close agreement to each other, thus allowing unambiguous assignment of the absolute configuration of the isolated enantiomers **1**-S_a and **1**-R_a. Again, due to the strict regioselectivity of the reductive cyclization, the assignment of the absolute configuration to the trinorbornanes, also allowed the retrospective assignment of the enantiomers of the open brexane derivative **2**-*S* and **2**-*R*.

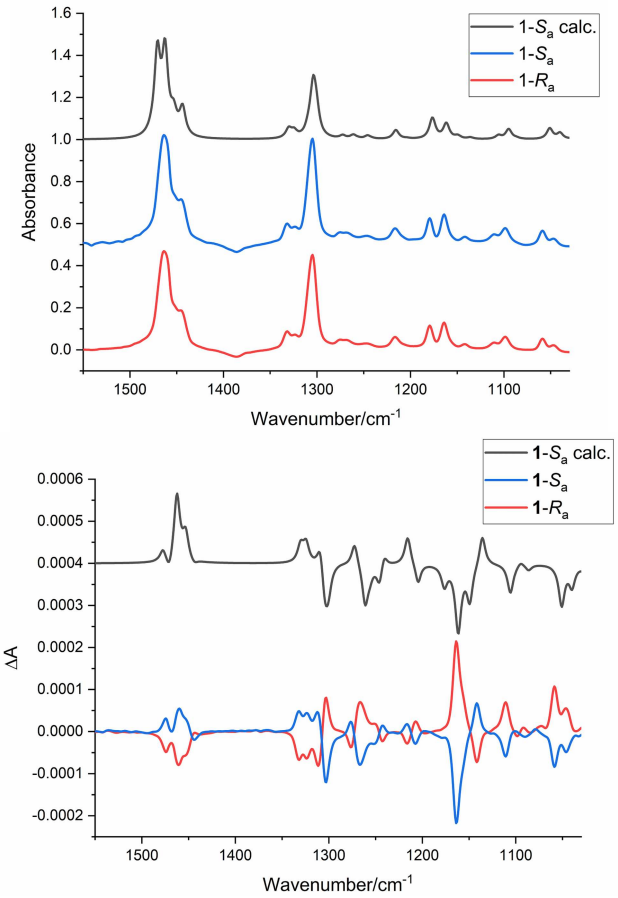


Figure 3. IR (top) and VCD (bottom) spectra of trinorbornane (**1**). Calculated spectra for **1**-S_a enantiomer are shown in black and the measured spectra for the **1**-S_a and **1**-R_a are displayed in blue and red, respectively.

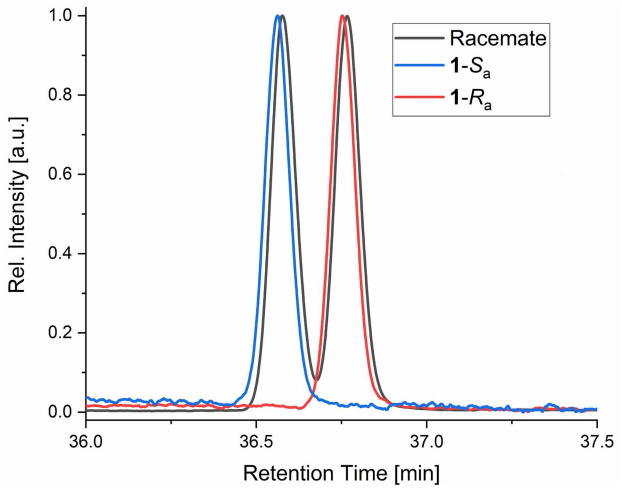
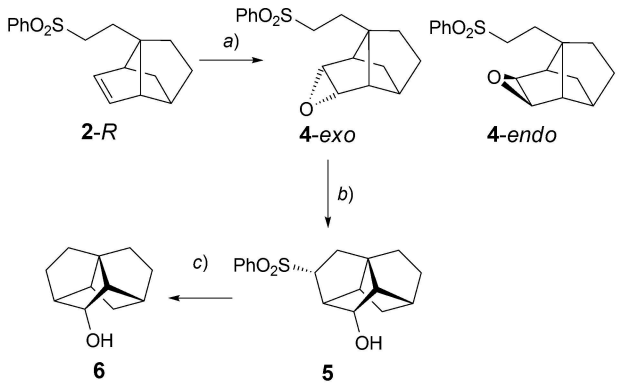


Figure 2. Overlaid chiral-GC chromatograms of the racemic mixture of **1** (black) and the two enantiomers **1**-S_a and **1**-R_a in blue and red, respectively.

Having achieved the separation of the enantiomers **2**-*S* and **2**-*R*, alternative methods for the cyclization step were investigated, to access functionalized trinorbornanes. It was found that subjecting **2**-*R* to epoxidizing conditions using *in situ* generated dioxirane[20] formed the oxiranes **4**-*endo* and **4**-*exo* in 4:6 ratio (*Scheme 3*). Treatment of the mixture containing both isomers with butyl lithium (BuLi) at 0 °C in THF afforded the functionalized trinorbornane derivative **5** after five minutes in 28 % over two steps together with **4**-*endo*, which is sterically not suited for the cyclization step. Further, the addition of a stoichiometric amount of BuLi was crucial to prevent epimerization at the α-sulfonyl carbon of the formed product **5** containing seven stereogenic centers. Desulfonylation of compound **5** using Mg/MeOH allowed the isolation of the enantiomerically pure hydroxy-functionalized trinorbornane **6** in 76 % yield after CC.



Scheme 3. Route for the synthesis of functionalized trinorbornanes *via* epoxide opening reaction. Conditions: *a*) Oxone, $KHCO_3$, acetone, CH_2Cl_2, H_2O, r.t., 24 h; *b*) BuLi, THF, 0 °C, 5 min; *c*) Mg, MeOH, r.t., 2 h.

Conclusions

We report the chiral separation of the brexane derivatives **2**-*S* and **2**-*R* through preparative chiral HPLC, which enabled the preparation of enantiomerically pure trinorbornanes **1**-S_a and **1**-R_a under reductive cyclization conditions using Mg/MeOH as a reproducible and convenient single electron reduction system. The absolute configuration of the obtained enantiomers was unequivocally assigned by comparison of their recorded and simulated VCD spectra. The excellent agreement between the theoretical and experimental results can be attributed to the rigidity of the tetracyclic scaffold of **1**. With the enantiopure precursors **2**-*S* and **2**-*R* in hands, alternative cyclization methods to functionalized trinorbornanes were developed. As first examples the synthesis of the enantiomerically pure and functionalized trinorbornanes as either hydroxyl and phenylsulfone substituted **5** or the hydroxy functionalized derivatives **6** are reported.

Experimental Section

Experimental Method

The racemate **2** was synthesized according to the previously reported procedure.[9] Chiral separation of the **2** was achieved by chiral HPLC (*CHIRALPAK® IG* column) using MeCN as mobile phase. IR and vibrational circular dichroism (VCD) spectra were recorded on a *Bruker PMA 50* accessory coupled to a *Tensor 27 Fourier* transform infrared spectrometer. A photoelastic modulator (*Hinds PEM 90*) set at l/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (*SR830 DSP*). An optical low-pass filter ($<1800\ cm^{-1}$) in front of the photoelastic modulator was used to enhance the signal/noise ratio. Solutions of 23 mg and 26 mg of **1**-R_a and **1**-S_a, respectively, in 200 µl CD_2Cl_2 were prepared and measured in a transmission cell equipped with CaF_2 windows and a 200 µm spacer. The pure solvent served as the reference and was subtracted from the VCD spectra of pure enantiomers to eliminate artifacts. For both enantiomers and the reference, *ca.* 24000 scans at $4\ cm^{-1}$ resolution were averaged.

Computational Method

Density functional theory (DFT) as implemented in Gaussian[21] was used to calculate the structure and the corresponding IR and VCD spectra. The calculations were performed using the B3PW91[17,18] functional and a 6-311++G(d,p)[19] basis set. Prior to the calculation of the spectra all degrees of freedom were completely relaxed. IR and VCD spectra were constructed from calculated dipole and rotational strengths assuming Gaussian band shape with a half-width at half-maximum of $4\ cm^{-1}$. Frequencies were scaled by a factor of 0.977. All calculations were performed for the gas phase species.

Synthetic Procedure

(1S_a,4*S*,6*R*,7*S*,9*R*)-Tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1**-S_a). To a solution of **2**-*S* (230 mg, 0.797 mmol, 1.0 equiv.) in dry MeOH (23 mL) was added activated Mg turnings (968 mg, 39.9 mmol, 50.0 equiv.) under Ar atmosphere. The mixture was sonicated for 5 min and the onset of the exothermic reaction was observed by the evolution of gas. The reaction came to reflux and was stirred at room temperature (in case the reaction became too vigorous the reaction mixture was cooled with a water bath) until all the Mg turnings were consumed (1–2 h). After cooling to room temperature, all the volatiles were transferred by bulb-to-bulb distillation into a flask cooled with N_2 (l). The remaining methanol was removed by distillation through a *Vigreux* column. To the residue was added acetone (6 mL), water (10 mL), *Oxone®* (980 mg, 1.59 mmol, 2.0 equiv.) and $NaHCO_3$ (670 mg, 7.97 mmol, 10.0 equiv.). The reaction was stirred for 16 h at room temperature. The mixture was extracted with pentane (3×10 mL) and the combined organic layers were washed with water (3×10 mL), brine and dried over anhydrous Na_2SO_4. The solvent was

removed by distillation through a *Vigreux* column. The residue was purified by column chromatography (SiO_2, pentane) followed by sublimation yielding the title compound **1**-S_a as white solid (26.6 mg, 0.179 mmol) in 23% yield. $[\alpha]_D^{20} = +136.9$ (MeCN).

(1*R*$_a$,4*R*,6*S*,7*R*,9*S*)-Tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1**-R_a). The title compound was prepared analogously to the **1**-S_a enantiomer described above yielding **1**-R_a as a white solid (23.0 mg, 0.155 mmol) in 20% yield. $[\alpha]_D^{20} = -136.7$ (MeCN).

(1*R*,3*R*,4*R*,5*R*,6*S*,7*R*,9*S*)-3-(Phenylsulfonyl) tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecan-5-ol (**5**) and **4**-*endo*. To a solution of **2**-*R* (49.9 mg, 0.173 mmol, 1.0 equiv.) and $NaHCO_3$ (73.4 mg, 0.865 mg, 5 equiv.) in acetone (2 mL) and water (2 mL) was added *Oxone* (79.8 mg, 0.260 mmol, 1.5 equiv.) and stirred at room temperature for 16 h. The acetone was removed under reduced pressure and the residue diluted with AcOEt (5 mL). The organic phase was washed with water (1× 5 mL), brine (2×5 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained residue containing **4**-*exo* and **4**-*endo* was dissolved in dry THF (2 mL) and BuLi (0.071 mL, 0.68 mL, 1.00 equiv.) was added dropwise at 0 °C. After 5 min, the reaction was quenched by the addition of sat. aq. NH_4Cl and the aqueous layer was extracted with AcOEt (2×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated under reduced pressure and purified by column chromatography (SiO_2; cyclohexane/AcOEt 2:1) yielding **5** as a colorless oil (15.4 mg, 51.1 μmol, 30%) and **4**-*endo* as a colorless oil (26.7 mg, 87.8 μmol, 51%).

Data of Compound **5**: R_f (cyclohexane/AcOEt 2:1; Vis. $KMnO_4$) 0.25. ^{1}H-NMR (500 MHz, (D_6)acetone): 7.95–7.88 (*m*, 2 H, H-14); 7.78–7.71 (*m*, 1 H, H-16); 7.70–7.63 (*m*, 2 H, H-15); 3.92 (*d*, *J* = 3.5, 1 H, OH); 3.85–3.78 (*m*, 1 H, H-5); 3.39 (*dd*, *J* = 8.9, *J* = 4.4, 1 H, H-3); 2.27–2.21 (*m*, 1 H, H-9); 2.23–2.17 (*m*, 1 H, H-7); 2.15 (*d*, *J* = 1.7, 1 H, H-4); 2.06–2.00 (*m*, 1 H, H-2b); 2.03–1.97 (*m*, 1 H, H-8b); 1.96–1.90 (*m*, 1 H, H-6); 1.80 (*ddd*, ^2J = 13.7, ^3J = 8.9, ^4J = 0.8, 1 H, H-2a); 1.68 (*t*, *J* = 1.3, 1 H, H-11b); 1.68–1.62 (*m*, 1 H, H-10a); 1.66–1.57 (*m*, 1 H, H-10b); 1.51–1.45 (*m*, 1 H, H-11a); 1.17–1.09 (*m*, 1 H, H-8a). ^{13}C-NMR (126 MHz, (D_6)acetone): 140.60 (C-13); 134.32 (C-16); 130.15 (C-15); 129.21 (C-14); 75.73 (C-5); 67.30 (C-3); 60.51 (C-1); 57.44 (C-6); 51.67 (C-4); 48.93 (C-9); 38.89 (C-7); 32.46 (C-11); 29.19 (C-8); 27.66 (C-2); 25.67 (C-11). HR-ESI-MS (pos.): 327.1025 ($C_{17}H_{20}NaO_3S^+$, $[M+Na]^+$; calc. 327.1027).

Data of Compound **4**-*endo*: R_f (cyclohexane/AcOEt, 2:1) 0.45. ^{1}H-NMR (500 MHz, (D_6)acetone): 7.93–7.88 (*m*, 2 H, H-13); 7.76–7.69 (*m*, 1 H, H-15); 7.68–7.60 (*m*, 2 H, H-14); 3.29–3.25 (*m*, 1 H, H-2); 3.18–3.12 (*m*, 2 H, H-11); 3.13–3.12 (*m*, 1 H, H-2); 2.19–2.11 (*m*, 1 H, H-1); 2.09–2.02 (*m*, 1 H, H-4); 1.97–1.95 (*m*, 1 H, H-8); 1.94–1.81 (*m*, 2 H, H-10); 1.57–1.46 (*m*, 2 H, H-6a/7a); 1.43–1.27 (*m*, 2 H, H-6b/7b); 1.14 (*ddd*, ^2J = 12.0, ^3J = 6.0, ^{3}J = 2.0, 1 H, H-9b); 1.09–1.04 (*m*, 1 H, H-9a). ^{13}C-NMR (126 MHz, (D_6)acetone): 140.85 (C-12); 134.24 (C-15); 130.05 (C-14); 128.77 (C-13); 54.45 (C-2); 53.74 (C-11); 53.60 (C-3); 49.93 (C-4); 48.18 (C-5); 44.13 (C-1); 40.56 (C- 8); 32.90 (C-7); 30.95 (C-6); 30.51 (C-9); 27.81 (C-10).

(1R,4R,5R,6S,7R,9S)-Tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecan-5-ol (**6**). A mixture of **5** (15.4 mg, 51.1 μmol, 1.0 equiv.) and activated Mg turnings (50 equiv.) in dry MeOH (4 mL) under Ar was sonicated for 5 min. After onset of the exothermic reaction, the mixture was stirred at room temperature until all Mg was consumed. The remaining MeOH was removed under reduced pressure, and the residue was partitioned between sat. aq. NH_4Cl and TBME. The aqueous layer was extracted with TBME (2×5 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, cyclohexane/AcOEt, 1:1) yielding **6** as a colorless solid (6.61 mg, 40.3 μmol, 79%). R_f (cyclohexane/AcOEt, 1:1; Vis. $KMnO_4$) 0.4. ^{1}H-NMR (500 MHz, (D_6)benzene): 3.58 (*dd*, *J* = 5.7, 1.7, 1 H, H-5); 2.24–2.22 (*m*, 1 H, H-7); 2.13–2.08 (*m*, 1 H, H-8b); 1.73–1.70 (*m*, 1 H, H-6); 1.67–1.65 (*m*, 1 H, H-4); 1.64–1.59 (*m*, 1 H, H-11b); 1.54–1.49 (*m*, 2 H, H-3a,H-2a); 1.47–1.44 (*m*, 2 H, H-9, H-2b); 1.44–1.41 (*m*, 1 H, H-11a); 1.40–1.37 (*m*, 1 H, H-10a); 1.34–1.29 (*m*, 1 H, H-10b); 1.26–1.21 (*m*, 1 H, H-3b); 1.15–1.12 (*m*, 1 H, H-8a); 0.42 (*s*, 1 H, OH). ^{13}C-NMR (126 MHz, (D_6)benzene): 76.68 (C-5); 60.83 (C-1); 57.95 (C-6); 50.81 (C-9); 50.04 (C-4); 37.95 (C-7); 32.89 (C-11); 29.93 (C-8); 29.85 (C-3); 25.82 (C-2); 24.73 (C-10). HR-ESI-MS (pos.): 187.1091 ($C_{11}H_{16}Na^+$, $[M+Na]^+$; calc. 187.1093).

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Author Contribution Statement

L. D. B. performed the synthesis, isolation, characterizations of all compounds and wrote the manuscript, *T. B.* performed the VCD analysis (experiments and calculations) and *M. M.* supervised the work and co-wrote the manuscript.

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