First Total Synthesis of (+)-Membrine

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The easily accessible, optically active diselenide **1** is converted into the chiral selenium electrophile **2** and used for oxyselenenylation reactions of alkenes with functionalized nucleophiles. This reaction allows the synthesis of addition products **4**, **6** and **10** with the selenium functionality as precursors for an intramolecular radical cyclization. This strategy is applied to the first total synthesis of optically pure (+)-membrine (**13**) by a short synthetic sequence.

Introduction

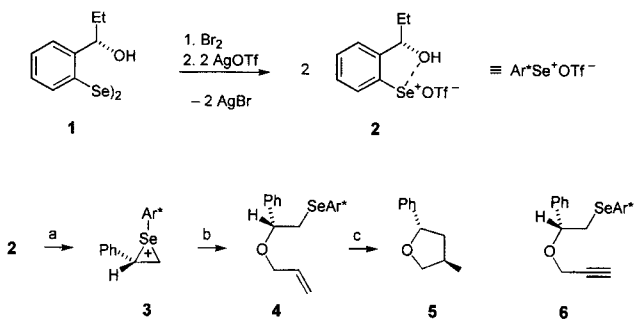
Ligands are interesting and challenging synthetic targets for organic chemists because of the broad range of structures and important biological properties exhibited by some members of this class[1]. The furofuran lignans are one of the largest groups of naturally occurring lignans and the construction of their 3,7-dioxabicyclo[3.3.0]octane (furofuran) skeleton has been accomplished in different ways[2].

Organoselenium compounds are established reagents in organic synthesis and attention has been drawn recently to their application in asymmetric synthesis. Investigations by other research groups[3] and by us[4] showed that optically active diselenides are versatile reagents for the functionalization of non-activated C=C double bonds. The selenenylation reaction is an exquisite method for the generation of heteroatom-substituted asymmetric carbon atoms from alkenes and can be used for intermolecular as well as intramolecular additions with good yields and stereoselectivities. The selenium functionality in these products is an excellent radical precursor. By addition of functionalized nucleophiles in the oxyselenenylation reaction, compounds suitable for an intramolecular radical cyclization can be obtained. Substituted tetrahydrofuran derivatives are the products of the radical cyclization and, with the right choice of substituents, they are good starting materials for the construction of the furofuran skeleton. We previously applied this strategy to the total synthesis of (+)-samin, a component of sesame oil and a known precursor for the synthesis of furofuran lignans[5]. We now report a shorter synthetic route to the 3,7-dioxabicyclo[3.3.0]octane frame and the subsequent reaction to membrine. This is a furofuran lignan that was isolated in 1993 from the grains of *Rollinia membranacea*, a plant growing in the area of Antioquia in Colombia[6].

Results and Discussion

The chiral diselenide **1** was synthesized in one step from optically active 1-phenylpropan-1-ol[5]. The selenium electrophile **2** was generated from **1** by formation of the selenenyl bromide with bromine and exchange of the nucleophilic bromine with the less nucleophilic triflate. Selenonium ions similar to compound **3** can then be generated by addition of **2** to an alkene. We were able to show that even functionalized alcohols can be used as nucleophiles in the addition reaction. However, products **4** and **6**, using respectively allyl and propargyl alcohols as the nucleophile, are obtained only in low yields. This is due to the fact that the selenium electrophile also attacks the double or triple bond of the alcohol. Nevertheless, compounds **4** and **6** are good precursors for intramolecular radical cyclizations leading to functionalized tetrahydrofuran derivatives. The known 2-phenyl-4-methyltetrahydrofuran **5**[7] was obtained from compound **4** in a 1:4 *cis/trans* ratio, as determined by ^{1}H-NMR spectroscopy. The 3-oxa-5-hexenyl system represents the vast majority of synthetic routes to substituted tetrahydrofuran derivatives by radical cyclization reactions[8].

Scheme 1



(a) Styrene. – (b) Allyl alcohol, 29%. – (c) Ph_3SnH, AIBN, 42%.

The synthesis of (+)-membrine (**13**) started with the alkene **7**, which was prepared by TBDMS-protection of the corresponding allyl alcohol[9]. Nucleophiles suitable for subsequent radical cyclizations have to be used in the ad-

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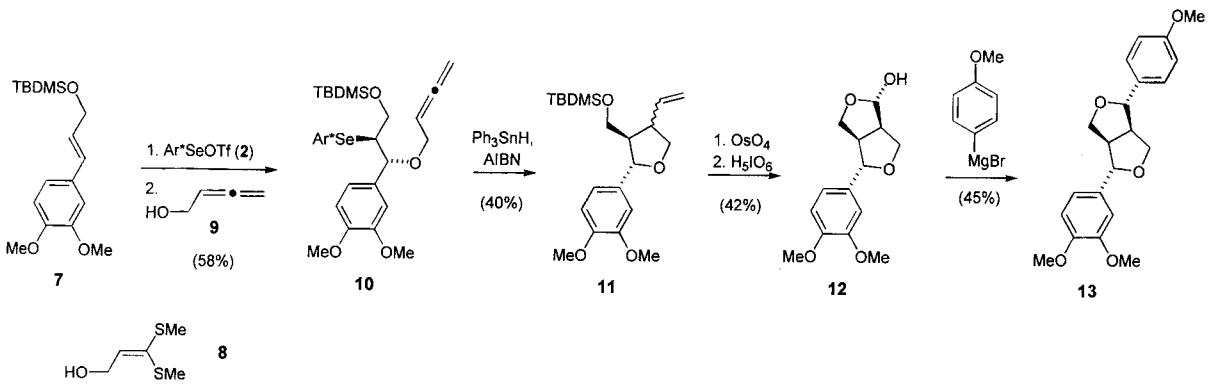
Scheme 2



dition reaction. After cyclization, an aldehyde has to be generated to form the furofuran ring system after cleavage of the TBDMS group. The alcohol **8**[10], with a dithioketeneacetal moiety, did not react as a nucleophile in the addition reaction. Therefore alcohol **9**[11], with an allen moiety, was used as functionalized nucleophile. The addition product **10** was obtained in 58% yield with a diastereomeric excess of about 84%. The two diastereomers were separated by MPLC and the major diastereomer was used for the following steps. The radical cyclization was achieved by treatment of compound **10** with tributyltin hydride and AIBN in refluxing toluene. The tetrahydrofuran derivative **11** was isolated in 40% yield. The steroechemistry of the carbon atom C-2 bearing the aromatic substituent controls the stereochemistry at the neighboring carbon atom C-3. The bulky silyloxymethyl substituent and the large aromatic group occupy pseudo-equatorial positions in the transition state leading to the cyclization product with *anti* stereochemistry at C-2 and C-3. At C-4 a 1:1 mixture of stereoisomers was observed, as in the synthesis of (+)-samin[4].

Oxidation of the vinylic double bond with osmium tetroxide yielded the diol, which was not isolated. The crude diol was treated with periodic acid and cleaved oxidatively to the aldehyde. Under these conditions, the TBDMS protecting group was cleaved. Subsequent epimerization at C-4 and formation of hemiacetal occurred, affording compound **12** with the furofuran moiety in 42% yield. This compound has previously been prepared in racemic form by an alternative route[12]. Compound **12**, as the dimethoxy analogue of (+)-samin, was then treated with an excess of 4-methoxyphenylmagnesium bromide to give the diol. Under the reaction conditions used (refluxing THF), dehydration occurred immediately, yielding (+)-membrine (**13**) in 45% yield. The spectral data obtained for (+)-membrine were found to be identical to those previously published[6]. Comparison of the optical rotation $\{[\alpha]_D^{25} = +67.5$ (c = 0.16, MeOH)$\}$ with the natural product $\{[\alpha]_D = +52.3$ (c = 0.08, MeOH)$\}$ showed that **13** is at least as pure as the natural product.

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Experimental Section

General: All reactions were carried out under a dry argon atmosphere. – NMR: Varian Gemini 300 (300 MHz and 75 MHz, for ^1H and ^{13}C, respectively), $CDCl_3$ as solvent, TMS as internal standard. ^{77}Se NMR spectra: Varian Gemini 400 (76 MHz), $CDCl_3$ as solvent, $(PhSe)_2$ (δ_{Se} = 475) as external standard. – MS: Finnigan-MAT-312 (70 eV). – IR: Perkin Elmer 1600 FT/IR. – Optical rotations: Perkin Elmer 141 polarimeter. – Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone prior to use. – Melting points are uncorrected.

(S)-1-{2-[(R)-2-Allyloxy-2-phenylethylselanyl]phenyl}propan-1-ol (**4**): To a stirred solution of diselenide **1** (214 mg, 0.5 mmol) in dry diethyl ether (10 ml) at −78°C was added a 1 M solution of bromine in CCl_4 (0.53 ml, 0.53 mmol). After 25 minutes, a solution of silver trifluoromethane sulfonate (283 mg, 1.1 mmol) in dry THF (1 ml) was added dropwise. The resulting yellowish heterogeneous solution was stirred for 15 minutes and then cooled to −100°C. Styrene was added (0.58 ml, 5 mmol), followed after 15 minutes by allyl alcohol (0.07 ml, 1 mmol). After stirring for 3 hours at −100°C, the reaction mixture was quenched by the addition of a 7% aqueous solution of citric acid (10 ml). After warming up to room temperature, the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 ml). The combined organic phases were dried with $MgSO_4$ and concentrated. The crude material was then purified by flash chromatography (silica gel, pentane/*tert*-butyl methyl ether 1:5) to afford **4** (110 mg, 29% yield) in a diastereomeric ratio of about 4:1 as a colorless oil; $[\alpha]_D^{25} = -36.3$ (c = 1.2, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3067 cm^{-1}, 3011, 2933, 1600, 1494, 1456, 1261, 1133, 1044, 1017, 811. – ^1H NMR: δ = 0.97 (t, J = 7.4 Hz, 3H), 1.76 (m, 2H), 2.24 (d, J = 4.3 Hz, 1H), 3.10 (m, 1H), 3.32 (m, 1H), 3.70–3.98 (m, 2H), 4.53 (dd, J = 8.3, 5.2 Hz, 1H), 5.03 (m, 1H), 5.10–5.26 (m, 2H), 5.87 (m, 1H), 7.10–7.50 (m, 9H). – ^{13}C NMR: δ = 10.4 (q), 31.2 (t), 36.2 (t), 69.8 (t), 74.6 (d), 80.6 (d), 117.1 (t), 126.3 (d), 126.7 (d), 127.4 (d), 127.9 (d), 128.1 (d), 128.6 (d), 129.7 (s), 133.6 (d), 134.5 (d), 141.0 (s), 146.0 (s). – MS; *m/z* (%): 376 (3) [M^+], 319 (2), 302 (1), 214 (12), 198 (18), 185 (14), 147 (79), 116 (13), 105 (61), 91 (60), 77 (23), 41 (100).

(S)-1-{2-[(R*)-2-Phenyl-2-(prop-2-ynyloxy)-ethylselanyl]-phenyl}propan-1-ol* (**6**): To a stirred solution of diselenide *rac*-**1** (86 mg, 0.2 mmol) in dry diethyl ether (8 ml) at −78°C was added a 1 M solution of bromine in CCl_4 (0.22 ml, 0.22 mmol). After 15

minutes, a solution of silver trifluoromethane sulfonate (144 mg, 0.56 mmol) in dry THF (0.7 ml) was added dropwise. The resulting yellowish heterogenous solution was stirred for 10 minutes, then cooled to −100°C. Styrene was added (0.09 ml, 0.8 mmol), followed after 10 minutes by propargyl alcohol (0.28 ml, 4.8 mmol). After stirring for 2 hours at −100°C, the reaction mixture was quenched by adding 2,4,6-collidine (0.08 ml, 0.6 mmol) followed by a 7% aqueous solution of citric acid (5 ml). After warming up to room temperature, the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 10 ml) and the combined organic phases were dried with $MgSO_4$ and concentrated. The crude material was then purified by flash chromatography (silica gel, pentane/*tert*-butyl methyl ether 1:5) to afford **6** (17 mg, 11% yield) in a diastereomeric ratio of about 11:1 as a colorless oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 3300 cm^{-1}, 3011, 2933, 2356, 1456, 1262, 1133, 1044, 1017, 811. − ^1H NMR: δ = 0.97 (t, *J* = 7.4 Hz, 3H), 1.76 (quint, *J* = 7.4 Hz, 2H), 2.19 (d, *J* = 3.9 Hz, 1H), 2.41 (t, *J* = 2.4 Hz, 1H), 3.13 (1/2 ABX, J_{AB} = 12.1, *J* = 5.4 Hz, 1H), 3.33 (1/2 ABX, J_{AB} = 12.1, *J* = 8.0 Hz, 1H), 3.88 (1/2 ABX, J_{AB} = 15.7, *J* = 2.4 Hz, 1H), 4.12 (1/2 ABX, J_{AB} = 15.7, *J* = 2.4 Hz, 1H), 4.74 (dd, *J* = 8.0, 5.4 Hz, 1H), 5.04 (m, 1H), 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.23−7.39 (m, 6H), 7.45 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.50 (dd, *J* = 7.7, 1.3 Hz, 1H). − ^{13}C NMR: δ = 10.4 (q), 31.3 (t), 35.5 (t), 56.0 (t), 74.6 (d), 74.7 (d), 79.5 (s), 80.0 (d), 126.3 (d), 127.0 (d), 127.6 (d), 128.0 (d), 128.5 (d), 128.7 (d), 129.5 (s), 133.7 (d), 139.8 (s), 146.1 (s). − MS; *m/z* (%): 374 (9) [M^+], 319 (2), 214 (21), 198 (18), 185 (16), 145 (100), 115 (31), 105 (60), 91 (47), 77 (32), 72 (57), 39 (46).

(E)-[3-(3,4-Dimethoxyphenyl)-2-propenyloxy](1,1-dimethylethyl)dimethylsilane (**7**): Imidazole (354 mg, 5.2 mmol) was added to a solution of 3-(3,4-dimethoxyphenyl)-2-propen-1-ol[9] (668 mg, 3.4 mmol) and TBDMSCl (528 mg, 3.5 mmol) in dry DMF (6 ml) at 0°C and the mixture was stirred for 3 hours. The reaction mixture was diluted with water (50 ml) and extracted with *tert*-butyl methyl ether (3 × 30 ml). The combined organic phases were washed with water (3 × 30 ml), dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, pentane/*tert*-butyl methyl ether 10:1), affording **7** (507 mg, 48% yield) as colorless crystals, m.p. 46−48°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 2933 cm^{-1}, 2844, 1600, 1511, 1267, 1133, 1044, 1017, 811. − ^1H NMR: δ = 0.11 (s, 6H), 0.94 (s, 9H), 3.87 (s, 3H), 3.90 (s, 3H), 4.34 (dd, *J* = 5.2, 1.5 Hz, 2H), 6.15 (dt, *J* = 15.6, 5.2 Hz, 1H), 6.52 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.89−6.94 (m, 2H). − ^{13}C NMR: δ = −5.1 (q, 2 C), 18.2 (s), 26.0 (q, 3 C), 55.8 (q), 55.9 (q), 64.0 (t), 108.9 (d), 111.1 (d), 119.5 (d), 127.6 (d), 129.4 (d), 130.2 (s), 148.6 (s), 149.0 (s). − MS; *m/z* (%): 308 (23) [M^+], 251 (14), 177 (100), 146 (11), 131 (4), 73 (7). − $C_{17}H_{28}O_3Si$ (308.50): calcd. C 66.19, H 9.15; found C 65.98, H 9.30.

(2S,3R)-[3-(Buta-2,3-dienyloxy)-3-(3,4-dimethoxyphenyl)-2-[2-[(S)-1-hydroxypropyl]phenylselanyl]propoxy](1,1-dimethylethyl)-dimethylsilane (**10**): To a stirred solution of diselenide **1** (535 mg, 1.25 mmol) in dry diethyl ether (50 ml) at −78°C was added a 1 M solution of bromine in CCl_4 (1.38 ml, 1.38 mmol). After 15 minutes a solution of silver trifluoromethane sulfonate (758 mg, 2.95 mmol) in dry THF (2 ml) was added dropwise. The resulting yellowish heterogenous solution was stirred for 15 minutes and then cooled to −100°C. A solution of alkene **7** in dry diethyl ether (3 ml) was added (507 mg, 1.65 mmol), followed after 10 minutes by 2,3-butadien-1-ol[11] (**9**) (222 mg, 3.17 mmol). After stirring for 3 hours at −100°C, the reaction mixture was quenched by adding 2,4,6-collidine (0.4 ml, 3.6 mmol) and water (15 ml). After warming up to room temperature, the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 ml). The combined organic phases were dried with $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (silica gel, pentane/*tert*-butyl methyl ether 3:1) to afford **10** (570 mg, 58% yield). The two diastereomers were separated by MPLC. Major diastereomer (*2S,3R*): 524 mg; minor diastereomer (*2R,3S*): 46 mg. Major diastereomer: colorless oil; $[\alpha]_D^{25}$ = −25.3 (*c* = 0.95, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2933 cm^{-1}, 2858, 1955, 1513, 1464, 1266, 1191, 1134, 1049. − ^1H NMR: δ = 0.00 (s, 6H), 0.89 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.72 (m, 2H), 2.29 (d, *J* = 4.7 Hz, 1H), 3.53 (dt, *J* = 6.5, 4.6 Hz, 1H), 3.74 (dd, *J* = 10.5, 6.4 Hz, 1H), 3.79 (s, 3H), 3.82−3.87 (m, 1H), 3.88 (s, 3H), 4.00 (m, 2H), 4.71−4.80 (m, 3H), 4.95 (dt, *J* = 7.4, 5.2 Hz, 1H), 5.22 (tt, *J* = 7.4, 6.5 Hz, 1H), 6.79−6.90 (m, 3H), 7.06 (td, *J* = 7.6, 1.6 Hz, 1H), 7.24 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36−7.42 (m, 2H). − ^{13}C NMR: δ = −5.5 (q, 2 C), 10.4 (q), 18.2 (s), 25.8 (q, 3 C), 30.9 (t), 54.9 (d), 55.66 (q), 55.72 (q), 63.2 (t), 66.4 (t), 74.5 (d), 75.4 (t), 79.3 (d), 87.7 (d), 110.2 (d), 110.3 (d), 120.6 (d), 126.1 (d), 127.4 (d), 127.7 (d), 129.4 (s), 131.2 (s), 135.7 (d), 146.7 (s), 148.6 (s), 148.7 (s), 209.2 (s). − ^{77}Se NMR: δ = 267.2. − MS; *m/z* (%): 592 (4) [M^+], 377 (2), 308 (3), 267 (2), 251 (1), 219 (100), 167 (59), 139 (9), 73 (16), 55 (20). − $C_{30}H_{44}O_5SeSi$ (591.67): calcd. C 60.90, H 7.50; found C 60.83, H 7.56.

{(2S,3R,4RS)-[2-(3,4-Dimethoxyphenyl)-4-ethenyltetrahydro-3-furanyl]methoxy}(1,1-dimethylethyl)dimethylsilane (**11**): A solution of triphenyltin hydride (280 mg, 0.80 mmol), AIBN (30 mg, 0.18 mmol) and **10** (320 mg, 0.54 mmol) in toluene (60 ml) was degassed and then heated for 2 hours at 90°C. After cooling, the reaction mixture was concentrated and the residue purified by flash chromatography (silica gel, pentane/*tert*-butyl methyl ether 2:1) affording **11** (80 mg, 40% yield) as a colorless oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 2944 cm^{-1}, 2858, 1595, 1515, 1464, 1266, 1138, 1049. − ^1H NMR: δ = 0.04 (s, 6H), 0.89 (s, 9H), 2.32 (quint, *J* = 6.3 Hz, 1H), 3.07 (m, 1H), 3.65 (m, 2H), 3.70−3.80 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.17 (m, 1H), 4.84 (d, *J* = 6.3 Hz, 1H), 5.00−5.16 (m, 2H), 5.68−5.96 (m, 1H), 6.60−6.90 (m, 3H). − ^{13}C NMR: δ = −5.5 (2 C), 18.1, 25.8 (3 C), 45.9, 53.5, 55.8, 55.9, 61.0, 72.7, 82.4, 109.0, 110.9, 117.0, 118.1, 128.5, 135.4, 137.1, 148.2, 148.9. − MS; *m/z* (%): 378 (65) [M^+], 321 (28), 291 (16), 276 (14), 246 (12), 229 (28), 192 (74), 177 (86), 165 (100), 151 (88), 89 (32), 75 (55), 73 (62), 59 (30).

(1S,3aR,4S,6aR)-4-(3,4-Dimethoxy-phenyl)-tetrahydro-1H,3H-furo[3,4-c]furan-1-ol (**12**): A solution of OsO_4 (0.1 ml, 0.016 mmol, 4% in water) was added to a cold (0°C) solution of **11** (70 mg, 0.18 mmol) and *N*-methylmorpholine-*N*-oxide hydrate (0.30 mmol, 40 mg) in acetone (4 ml), *tert*-butyl alcohol (0.5 ml) and water (0.5 ml). The reaction was complete after stirring for 10 hours (monitored by TLC). The solvent was removed and after dissolving the residue in THF (2 ml) and water (1.5 ml), H_5IO_6 (64 mg, 0.28 mmol) was added. After stirring for 13 hours, the reaction mixture was diluted with water and extracted with *tert*-butyl methyl ether (3 × 20 ml). The combined organic phases were dried and concentrated. Purification of the residue by flash chromatography (silica gel, *tert*-butyl methyl ether) yielded **12** (20 mg, 42% yield) as colorless crystals, m.p. 83−85°C. − $[\alpha]_D^{25}$ = +69.2 (*c* = 1.00, $CHCl_3$). − ^1H NMR: δ = 2.70 (br. s, 1H), 2.91 (m, 1H), 3.10 (q, *J* = 8.4 Hz, 1H), 3.58 (1/2 ABX, J_{AB} = 9.2, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 3.93 (1/2 ABX, J_{AB} = 9.1, *J* = 1.0 Hz, 1H), 4.18 (1/2 ABX, J_{AB} = 9.2, *J* = 5.9 Hz, 1H), 4.36−4.43 (m, 2H), 5.40 (s, 1H), 6.82−6.93 (m, 3H). − ^{13}C NMR: δ = 52.6 (d), 53.6 (d), 55.88 (q), 55.92 (q), 69.3 (t), 71.2 (t), 86.9 (d), 102.2 (d), 109.1 (d), 111.0 (d), 118.5 (d), 133.0 (s), 148.8 (s), 149.2 (s). − MS; *m/z* (%): 266 (100) [M^+], 235 (32), 192 (14), 166 (97), 151 (27), 139 (13), 95 (10), 77 (14), 69 (7), 55 (7), 51 (6).

(1S,3aR,4S,6aR)-1-(3,4-Dimethoxyphenyl)tetrahydro-4-(4-methoxyphenyl)-1H,3H-furo[3,4-c]furan, (+)-Membrine (**13**): To

a solution of **12** (20 mg, 0.075 mmol) in dry THF (3 ml) was added 4-methoxyphenyl magnesium bromide (0.5 mmol, 0.5 ml, 1 M solution in Et_2O) and the mixture was stirred at 70°C for 3 hours. After cooling to 0°C, 2 N HCl (10 ml) was added and extracted with $CHCl_3$ (3 × 10 ml). The combined organic phases were dried and concentrated. Purification of the residue by flash chromatography (silica gel, pentane/*tert*-butyl methyl ether 1:1) yielded **13** (12 mg, 45% yield) as a colorless oil. – $[\alpha]_D^{25}$ = +58.8 (*c* = 0.60, $CHCl_3$). – $[\alpha]_D^{25}$ = +67.5 (*c* = 0.18, MeOH). – IR ($CHCl_3$): $\tilde{\nu}$ = 3010 cm^{-1}, 2937, 2839, 1612, 1515, 1465, 1266, 1235, 1135, 1049, 1016, 812. – ^1H NMR: δ = 3.11 (m, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.84–3.93 (m, 2H), 4.20–4.30 (m, 2H), 4.76 (dd, *J* = 10.2, 7 Hz, 2H), 6.82–6.92 (m, 5H), 7.26–7.30 (m, 2H). – ^{13}C NMR: δ = 54.1 (d), 54.2 (d), 55.3 (q), 55.90 (q), 55.93 (q), 71.5 (t), 71.8 (t), 85.6 (d), 85.8 (d), 109.2 (d), 111.0 (d), 113.9 (d, 2 C), 118.2 (d), 127.3 (d, 2 C), 133.1 (s), 133.6 (s), 148.6 (s), 149.2 (s), 159.2 (s). – MS; *m/z* (%): 356 (100) [M^+], 325 (11), 219 (9), 205 (7), 189 (25), 177 (42), 165 (57), 147 (66), 135 (80), 121 (49), 108 (10), 91 (10), 77 (15), 55 (10).

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