# First Synthesis of Enantiomerically Pure Primary Helical Spirocycles Based on the Repetitive Addition of Lithiated Methoxyallene to Chiral 3(2*H*)-Dihydrofuranone Derivatives

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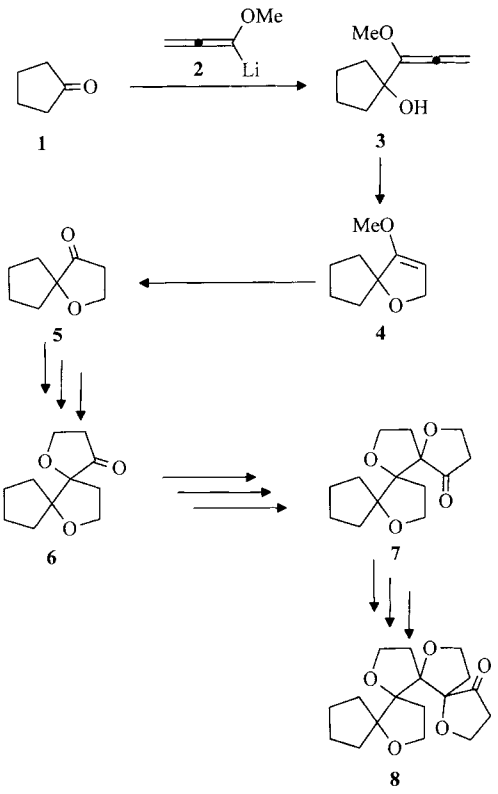
Repetitive additions to chiral 3(2*H*)-dihydrofuranones opened a route to the first enantiomerically pure primary helical spirocyclic compounds. Thus, addition of lithiated methoxyallene **2** to furanone **9** provided adduct **10** with excellent diastereoselectivity. Cyclization with potassium *tert*-butoxide in DMSO followed by acid hydrolysis of the resulting enol ether moiety gave spirocyclic furanone **12** in very good overall yield. Repetition of this three-step sequence converted **12** into **15**. For the next series of reactions cerium compound **16** instead of **2** was employed as nucleophile which resulted in reasonable conversion of **15** into adduct **17**. By application of the usual methods this compound was transformed into the enantiomerically pure tetracyclic spiro compound **19** in moderate overall yield. Functionalized spiro compounds as described in this paper may serve as enantiomerically pure building blocks in supramolecular chemistry.

The pioneering work of Hoff, Brandsma, and Arens with the easily obtainable lithiated methoxyallene[1] **2** motivated us to start our own research, employing chiral amino aldehydes in addition experiments. In previous publications, we demonstrated that the methods developed for transformations of **2** by the Dutch group can be exploited for asymmetric synthesis[2] of a variety of interesting compound classes such as enantiomerically pure 3(2*H*)-dihydrofuranones[3] and (*2S,3S*)-norstatine derivatives[4]. Interestingly, the conversion of **2** to a titanium compound by reaction with $ClTi(OiPr)_3$ completely reversed the regioselectivity of the addition to amino aldehydes, which allowed the stereoselectivity synthesis of (*5R,1'S*)-2(3*H*)-dihydrofuranone derivatives via methoxyalkyne intermediates[5].

In 1980 Magnus and coworkers reported on the synthesis of an interesting new class of compounds, based on a reaction sequence with lithiated methoxyallene **2** (Scheme 1). The crucial steps in this repetitive synthesis were additions of **2** to carbonyl compounds **1**, **5**, **6**, and **7** followed by cyclization and hydrolysis in every circle (as depicted for the sequence **1** → **3** → **4** → **5**)[6]. Magnus suggested "primary helical molecules" as a term for compounds such as **7** or **8**, due to the fact that the helical topology of these compounds is a consequence of their primary structure (bond angles and bond lengths of the tetrahydrofuran ring system) and not, as in the case of DNA[7] and other helical molecules[8], a result of a secondary or tertiary structure. The helical topology of **8** was confirmed by X-ray analysis. However, all of Magnus' compounds are racemic. Therefore, these interesting results inspired us to carry out a similar synthetic sequence starting with our chiral 3(2*H*)-dihydrofuranone derivatives, since the expected enantiomerically pure helical

Scheme 1

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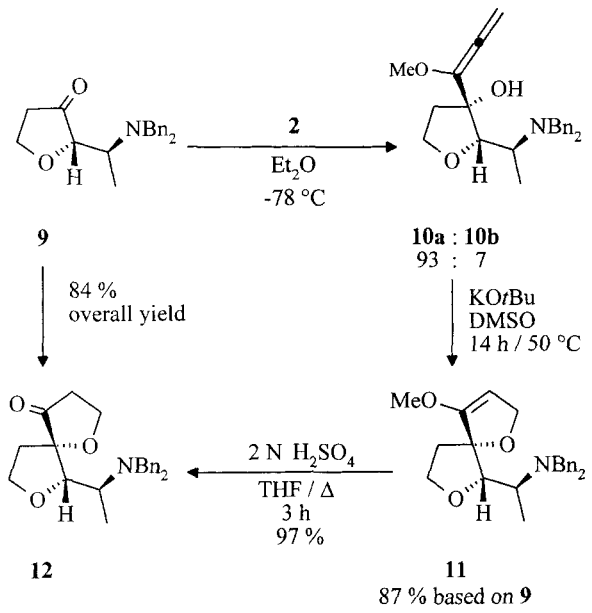
products might serve as interesting building blocks for templates in supramolecular chemistry[9]. We decided to use 3(2*H*)-dihydrofuranone derivative **9**[3b] as the starting material for our studies since it is available on a large scale as a single enantiomer and because its configuration has been established unequivocally by X-ray analysis[10].

## Results

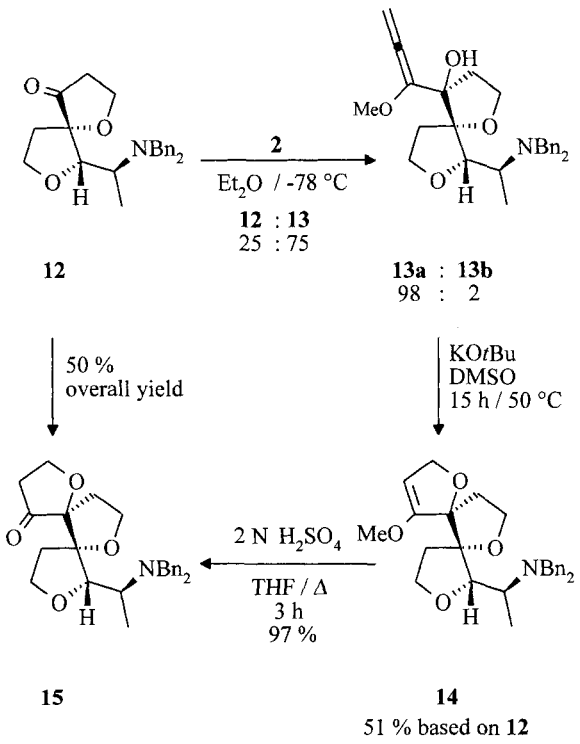
A solution of lithiated methoxyallene **2** in diethyl ether was generated according to the method of Hoff, Brandsma and Arens[1a]. At −78 °C a solution of 3(2*H*)-dihydrofuranone **9** in the same solvent was added and aqueous workup after 2 h provided a 93:7 mixture of diastereomers in excellent crude yield. The nucleophile preferentially approaches *trans* to the bulky 2-substituent[3b] of **9**. As already reported[3], purification of the primary adducts is not possible. Therefore, the crude product **10** was used directly in the subsequent base-induced cyclization with potassium *tert*-butoxide[1b] which produced bicyclic enol ether **11** in good yield. Compound **11** was converted to the spirocyclic ketone **12** in very good yield by treatment with 2 N aqueous sulfuric acid in THF at reflux temperature[1b]. The spirocyclic ketone **12** was obtained diastereomerically pure by a simple recrystallization in 84% yield based on 3(2*H*)-dihydrofuranone **9**.

Scheme 2



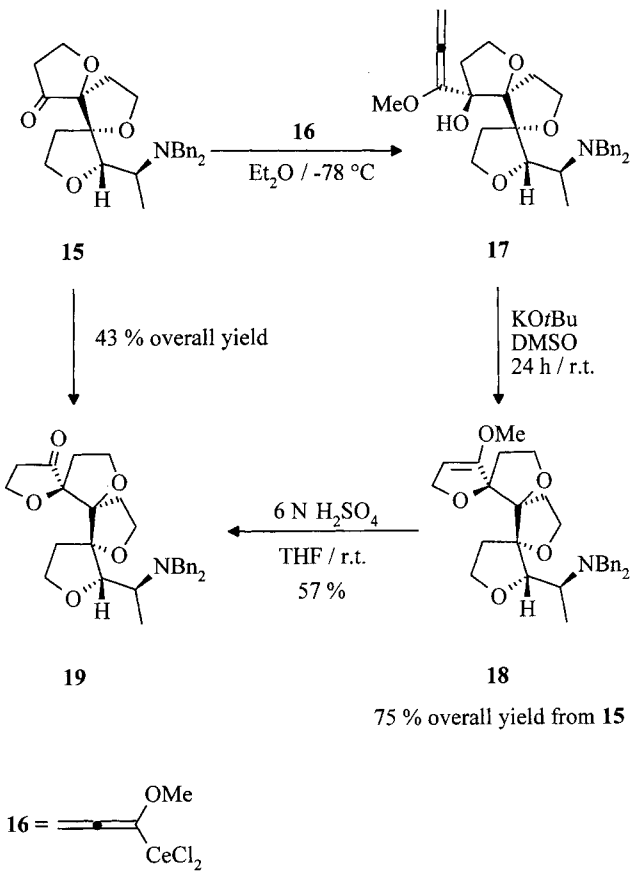

The repeated addition of **2** to the spirocyclic ketone **12** produced again in excellent diastereoselectivity the corresponding primary adduct **13**. However, the conversion of **12** was not complete. The crude product represented a 75:25 mixture of adduct and starting ketone **12** as determined by comparison of the methyl group signals in the $^1$H-NMR spectrum. Magnus and his group faced the same problem during their synthesis of racemic primary helical molecules and were able to gain higher yields by repeating the addition reaction with the obtained crude product[6]. Our efforts to optimize the addition step by using a larger excess of **2** also led to a better adduct to starting material ratio, but resulted in decreased yields in the subsequent cyclization reaction. Since the tricyclic enol ether **14** can easily be obtained as a single diastereomer by a simple recrystallization if the original reaction conditions are used in the addition step, compound **14** is usually prepared according to the original procedure without using a vast excess of **2**. The assumed configuration of **14** was confirmed by two-dimensional NMR experiments. Acid hydrolysis conditions provided the tricyclic ketone **15** as a single diastereomer in 50% yield based on **12**.

Scheme 3




The spiroanellation of a further ring based on the addition of lithiated methoxyallene **2** caused even more problems than the synthesis of the tricyclic system. The addition of **2** to the tricyclic ketone **15** gave only moderate yields of the desired addition product **17**. This problem was solved by a transmetallation reaction of **2** with cerium(III) chloride[11] and addition of the assumed cerium derivative **16** to the carbonyl group of **15**. The reaction provided the desired primary adduct **17** in excellent crude yield and diastereoselectivity. The usual potassium *tert*-butoxide catalysed cyclization reaction afforded tetracyclic system **18**. Acid hydrolysis of the enol ether moiety of **18** produced tetracyclic ketone **19** in 43% overall yield. No traces of the minor diastereomer could be detected by $^1$H-NMR spectroscopy. The shown configuration of compound **19** was unambiguously confirmed by X-ray analysis[12].

Scheme 4




## Conclusion

The first synthesis of enantiomerically pure primary helical compounds such as **15** and **19** could be achieved in good overall efficiency. This route is based on the highly diastereoselective addition of metallated methoxyallene to easily accessible 3(2*H*)-dihydrofuranone **9**. Similarly to additions of other nucleophiles to this carbonyl compound, the alkoxyallene moiety is attached to C-3 with excellent diastereofacial selectivity *anti* to the rather bulky C-2 substituent[3b]. Thus, the sense of the forming helix is already decided in the step **9** → **10** (Scheme 2). The chirality of **9** is transferred to all subsequent products. In contrast, dispiro compound **6** is the first chiral (though racemic) electrophile in the Magnus sequence (Scheme 1). The helicity is therefore decided at a later stage. The repetitive synthesis of this type of spiro compounds may be continued beyond **19** and lead even to extended systems. According to our experience the low conversions employing lithiated methoxyallene **2** can be overcome by transmetallation with $CeCl_3$ to produce a reagent described as **16**.

Enantiomerically pure functionalized spiro compounds such as **12**, **15**, **19**, and **11**, **14**, **18** may serve as interesting building blocks for the construction of templates that contain several chiral polyfuran units, and which may therefore find applications in supramolecular chemistry (e.g. enantioselective molecular recognition). Also, the enantiomerically pure primary helical compounds themselves should be studied in more detail to evaluate their chemical, physical and biological properties.

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## Experimental

All reactions with air- and moisture-sensitive compounds were performed under dry nitrogen or argon (1 atm) in flame-dried reaction flasks by adding the components via syringes. All solvents were dried using standard methods. DMSO was freshly distilled from $CaH_2$ prior to use. Boiling range of petroleum ether: 40–60 °C. – For chromatography, 230–70 mesh silica gel (Merck No. 7734) was employed. – $^1$H NMR: Bruker AC 200 (200 MHz), WM 300 (300 MHz), AM 500 (500 MHz). – $^{13}$C NMR: Bruker AC 200 (50.3 MHz), WM 300 (75.5 MHz). The purity of crude products and the ratios of diastereomers were determined by NMR. Higher order NMR spectra were approximately interpreted as first-order spectra if possible. Missing signals of minor diastereomers were hidden or too weak. – IR spectra were measured with a Beckman IR 5a, a Bruker FT IR IFS spectrometer and a Nicolet 205 spectrometer. – Optical rotations were determined with a Perkin-Elmer P 241 polarimeter ($\alpha \equiv [\alpha]_D$ at 20 °C). – Melting points were determined with a Büchi or a Gallenkamp MPD 350 melting point apparatus and are uncorrected. – 3(2*H*)-Dihydrofuranone **9** was synthesized according to ref.[3]

*(3R,2S,1′S), (3S,2S,1′S)-2-[1-(N,N-Dibenzylamino)ethyl]-3-(1-methoxy-1,2-propadien-1-yl)-3(2H)-tetrahydrofuran-3-ol* (**10**): Lithiated methoxyallene **2** was generated by treating a solution of 1.05 g (15.0 mmol) of methoxyallene in 30 ml of $Et_2O$ at −40 °C with 8.8 ml (14.0 mmol) of *n*-BuLi (2.5 M in hexane). After 5 min, the resulting solution was cooled to −78 °C, and a solution of 3.04 g (9.83 mmol) of **9** in 10 ml of $Et_2O$ was added over a period of 5 min. The mixture was stirred for 1.5 h at −78 °C and the reaction quenched with 20 ml of $H_2O$. Warming to room temperature was followed by extraction with $Et_2O$ (3 × 20 ml) and drying of the combined extracts ($Na_2SO_4$). Removal of the solvent in vacuo yielded 3.70 g of crude **10** as a yellow oil (**10a/10b** = 93:7; purity >90%). IR (film): $\tilde{\nu}$ = 3580–3300 cm$^{-1}$ (OH), 3080–3000 (=C–H), 3000–2760 (C–H), 1950 (C=C=C). – $^1$H NMR (300 MHz, $CDCl_3$) of **10a**: δ = 7.35–7.20 (m, 10H, phenyl), 6.26 (s, 1H, OH), 5.52, 5.49 (AB system, $J_{AB}$ = 7.6 Hz, 1H, each, $=CH_2$), 4.11 (d, *J* = 9.2 Hz, 1H, 2-H), 3.84 (d, *J* = 13.1 Hz, 2H, $NCH_2$), 3.74 (ddd, *J* = 6.0, 7.3, 8.2 Hz, 1H, 5-H), 3.60 (td, *J* = 7.3, 8.2 Hz, 1H, 5-H), 3.37 (s, 3H, OMe), 3.33 (d, *J* = 13.1 Hz, 2H, $NCH_2$), 3.08 (qd, *J* = 6.5, 9.2 Hz, 1H, 1′-H), 2.24 (ddd, *J* = 6.0, 7.3, 12.6 Hz, 1H, 4-H), 1.84 (td, *J* = 7.3, 12.6 Hz, 1H, 4-H), 1.23 (d, *J* = 6.5 Hz, 3H, Me); of **10b**: δ = 1.23 (d, *J* = 6.9 Hz, 3H, Me). – $^{13}$C NMR (75.5 MHz, $CDCl_3$) of **10a**: δ = 197.1 (s, C=C), 138.6 (s, =COMe), 138.2, 129.3, 128.5, 127.3 (s, 3 d, phenyl), 93.0 (t, $=CH_2$), 81.7 (d, C-2), 80.6 (s, C-3), 65.9 (t, C-5), 56.5 (q, OMe), 54.3 (d, C-1′), 53.9 (t, $NCH_2$), 40.3 (t, C-4), 9.1 (q, Me); of **10b**: δ = 140.2 (s, =*C*OMe), 129.7, 128.5, 126.8 (3 d, phenyl), 81.2 (d, C-2), 64.6 (t, C-5), 54.7 (t, $NCH_2$), 36.8 (t, C-4), 10.9 (q, Me).

*(5S,6S,1′S)-6-[1-(N,N-Dibenzylamino)ethyl]-4-methoxy-1,7-dioxaspiro[4,4]non-3-ene* (**11**): A solution of 3.69 g (9.27 mmol) of crude primary adduct **10** in 5 ml of DMSO was added dropwise to a stirred solution of 1.12 g (10.0 mmol) of potassium *tert*-butoxide at 50 °C in 45 ml of DMSO. Stirring was continued for 14 h at this temperature. After cooling to room temperature the reaction was quenched with 20 ml of ice water followed by the addition of 20

ml of $Et_2O$ to the mixture. The layers were separated and the aqueous layer was extracted with a 2:1 mixture of petroleum ether and $Et_2O$ (3 × 30 ml). The combined organic extracts were dried ($Na_2SO_4$) and the solvent was removed in vacuo. The remaining residue was purified by recrystallization from methanol to give 3.25 g of **11** (87% based on **9**) of a colourless solid; m.p. 93–94°C; $\alpha$ = 87.8 (*c* = 1.2, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3080–3000 $cm^{-1}$ (=C–H), 3000–2780 (C–H), 1660 (C=C). – $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.35–7.14 (m, 10H, phenyl), 4.41 (t, *J* = 1.5 Hz, 1H, 3-H), 4.37 (dd, *J* = 1.5, 10.6 Hz, 1H, 2-H), 4.01–3.93 (m, 3H, 2-H, 6-H, 8-H), 3.82 (dt, *J* = 5.1, 8.3 Hz, 1H, 8-H), 3.68 (s, 3H, OMe), 3.61 (s, 4H, $NCH_2$), 2.95 (dq, *J* = 1.5, 6.8 Hz, 1H, 1′-H), 2.21 (td, *J* = 8.3, 12.9 Hz, 1H, 9-H), 1.88 (ddd, *J* = 5.1, 7.4, 12.9 Hz, 1H, 9-H), 1.16 (d, *J* = 6.8 Hz, 3H, Me). – $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ = 155.3 (s, C-4), 140.9, 128.7, 127.9, 126.4 (s, 3 d, phenyl), 93.0 (s, C-5), 91.3 (d, C-3), 84.1 (d, C-6), 71.6, 66.9 (2 t, C-8, C-2), 57.7 (q, OMe), 54.1 (t, $NCH_2$), 51.7 (d, C-1′), 37.2 (t, C-9), 10.0 (q, Me). – $C_{24}H_{29}NO_3$ (379.5): calcd. C 75.96, H 7.70, N 3.69; found C 75.84, H 7.70, N 3.56.

*(5S,6S,1′S)-6-[1-(N,N-Dibenzylamino)ethyl]-1,7-dioxaspiro[4.4]nonan-4-one* (**12**): A solution of 418 mg (1.10 mmol) of **11** in 6 ml of a 1:1 mixture of tetrahydrofuran and 2 N $H_2SO_4$ was heated for 3 h at reflux. After cooling to room temperature, the reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution. Removal of the organic layer was followed by extraction of the remaining aqueous layer with $Et_2O$ (3 × 10 ml). The combined ether extracts were dried with $MgSO_4$. Removal of the solvent under reduced pressure provided 391 mg (97%) of **12** as a pale yellow oil which crystallized upon storage; m.p. 112–113°C; $\alpha$ = 21.0 (*c* = 1.0, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3080–3000 $cm^{-1}$ (=C–H), 3000–2800 (C–H), 1745 (C=O). – $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.29–7.21 (m, 10H, phenyl), 3.98 ($m_c$, 2H, 2-H), 3.88 (dt, *J* = 5.4, 8.4 Hz, 1H, 8-H), 3.74 (dt, *J* = 7.4, 8.4 Hz, 1H, 8-H), 3.58, 3.43 (2 d, *J* = 13.5 Hz, 2H each, $NCH_2$), 3.24 (quint, *J* = 6.8 Hz, 1H, 1′-H), 2.27 ($m_c$, 2H, 3-H), 2.09 (ddd, *J* = 7.4, 8.4, 12.9 Hz, 1H, 9-H), 1.93 (ddd, *J* = 5.4, 7.4, 12.9 Hz, 1H, 9-H), 1.15 (d, *J* = 6.8 Hz, 3H, Me). – $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ = 215.2 (s, C-4), 139.7, 129.3, 128.0, 126.7 (s, 3 d, phenyl), 88.4 (s, C-5), 85.3 (d, C-6), 66.8, 62.5 (2 t, C-8, C-2), 53.8 (t, $NCH_2$), 51.6 (d, C-1′), 37.4, 36.3 (2 t, C-9, C-3), 9.5 (q, Me). – $C_{23}H_{27}NO_3$ (365.5): calcd. C 75.59, H 7.45, N 3.83; found C 75.43, H 7.67, N 3.63.

*(5S,4R,6S,1′S)-, (5S,4S,6S,1′S)-6-[1-(N,N-Dibenzylamino)ethyl]-4-(1-methoxy-1,2-propadien-1-yl)-1,7-dioxaspiro[4.4]nonan-4-ol* (**13**): Lithiated methoxyallene **2** was generated by treating a solution of 280 mg (4.00 mmol) of methoxyallene in 6 ml of $Et_2O$ at –40°C with 2.2 ml (3.50 mmol) of *n*-BuLi (1.6 M in hexane). After 5 min, the resulting solution was cooled to –78°C, and a solution of 1.10 g (3.00 mmol) of **12** in 1 ml of $Et_2O$ was added over a period of 5 min. The mixture was stirred for 2 h at –78°C and the reaction quenched with 2 ml of $H_2O$. Warming of the mixture to room temperature was followed by extraction with $Et_2O$ (3 × 2 ml) and drying ($Na_2SO_4$) of the combined extracts. Removal of the solvent in vacuo yielded 1.27 g of a 25:75 mixture of starting material **12** and product **13** as a yellow oil (**13a/13b** = 98:2). IR (film): $\tilde{\nu}$ = 3600–3300 $cm^{-1}$ (OH), 3100–3000 (=C–H), 3000–2780 (C–H), 1950 (C=C=C), 1750 (C=O, starting material). – $^1H$ NMR (300 MHz, $CDCl_3$) of **13a**: $\delta$ = 8.20 (br. s, 1H, OH), 7.43–7.19 (m, 10H, phenyl), 5.55, 5.50 (AB system, $J_{AB}$ = 7.8 Hz, 1H each, $=CH_2$), 4.26 (d, *J* = 8.9 Hz, 1H, 6-H), 3.84, 3.34 (2 d, *J* = 13.1 Hz, 2H each, $NCH_2$), 3.44 (s, 3H, OMe), 2.14–2.04 (m, 2H, 3-H), 1.84 (part A of ABXY system, $J_{AB}$ = 12.5 Hz, $J_{AX}$ = 6.8 Hz, $J_{AY}$ = 1.8 Hz, 1H, 9-H), 1.72 (part B of ABXY system, $J_{AB}$ = 12.5 Hz, $J_{BX}$ = 7.3 Hz, $J_{BY}$ = 4.8 Hz, 1H, 9-H), 1.19 (d, *J* = 7.0 Hz, 3H, Me), other signals hidden by signals of the starting material; of **13b**: $\delta$ = 5.72, 5.67 (AB system, $J_{AB}$ = 8.0 Hz, 1H each, $=CH_2$). – $^{13}C$ NMR (75.5 MHz, $CDCl_3$) of **13a**: $\delta$ = 198.1 (s, C=C), 137.2 (s, phenyl), 136.3 (s, =*C*OMe), 130.6, 128.7, 127.3 (3 d, phenyl), 94.3 (s, C-4), 91.6 (t, $=CH_2$), 80.7 (d, C-6), 79.1 (d, C-6), 65.2, 64.2 (2 t, C-8, C-2), 56.2 (q, OMe), 53.7 (t, $NCH_2$), 50.4 (d, C-6), 38.8, 37.7 (2 t, C-9, C-3), 8.5 (q, Me); unambiguous assignment of the signals of **13b** was not possible.

*(10S,9S,5R,11′S)-10-[1-(N,N-Dibenzylamino)ethyl]-4-methoxy-1,8,11-trioxadispiro[4.3.4]tridec-3-ene* (**14**): A solution of 1.20 g of the 25:75 mixture of starting material **12** and crude addition product **13** (**13a/13b** = 98:2) in 3 ml of DMSO was added dropwise to a stirred solution of 310 mg (2.76 mmol) of potassium *tert*-butoxide in 15 ml of DMSO at 50°C. Stirring was continued for 15 h at this temperature. After cooling to room temperature the reaction was quenched with 6 ml of ice/water followed by the addition of 6 ml of $Et_2O$ to the resulting mixture. The layers were separated and the aqueous layer was extracted with a 2:1 mixture of petroleum ether and $Et_2O$ (3 × 10 ml), the combined organic extracts were dried ($Na_2SO_4$), and the solvent was removed in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to give 802 mg of a colourless oil which was further purified by crystallization from methanol to give 664 mg (51% based on **12**) of **14** as colourless crystals; m.p. 85–86°C; $\alpha$ = –9.8 (*c* = 1.1, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3100–3000 $cm^{-1}$ (=C–H), 3000–2780 (C–H), 1650 (C=C). – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta$ = 7.33 (d, *J* = 7.2 Hz, 4H, *ortho*-H phenyl), 7.27 (t, *J* = 7.2 Hz, 4H, *meta*-H phenyl), 7.18 (t, *J* = 7.2 Hz, 2H, *para*-H phenyl), 5.08 (s, 1H, 3-H), 4.63 (part A of ABX system, $J_{AB}$ = 11.2 Hz, $J_{AX}$ = 1.1 Hz, 1H, 2-H), 4.44 (part B of ABX system, $J_{AB}$ = 11.2 Hz, $J_{BX}$ = 1.7 H, 1H, 2-H), 3.77 (part A of ABXY system, $J_{AB}$ = 6.6 Hz, $J_{AX}$ = 5.7, $J_{AY}$ = 8.0 Hz, 1H, 12-H), 3.69 (d, *J* = 14.3 Hz, 2H, $NCH_2$), 3.66 (s, 3H, OMe), 3.64 (part A of ABXY system, $J_{AB}$ = 7.7 Hz, $J_{AX}$ = 7.7, $J_{AY}$ = 4.6 Hz, 1H, 7-H), 3.53 (d, *J* = 14.3 Hz, 2H, $NCH_2$), 3.49 (part B of ABXY system, $J_{AB}$ = 7.7 Hz, $J_{BX}$ = 7.7, $J_{BY}$ = 7.7 Hz, 1H, 7-H), 3.39 (part B of ABXY system, $J_{AB}$ = 6.6 Hz, $J_{BX}$ = 8.0, $J_{BY}$ = 8.0 Hz, 1H, 12-H), 3.10 (q, *J* = 6.7 Hz, 1H, 1′-H), 2.16–2.07 (m, 2H, 13-H, 6-H), 1.72 (part Y of ABXY system, $J_{AY}$ = 8.0 Hz, $J_{BY}$ = 8.0, $J_{XY}$ = 12.9 Hz, 1H, 6-H), 1.52 (part Y of ABXY system, $J_{AY}$ = 4.6 Hz, $J_{BY}$ = 7.7, $J_{XY}$ = 12.6 Hz, 1H, 13-H), 1.05 (d, *J* = 6.7 Hz, 3H, Me); assignments were supported by COSY and ROESY spectra. – $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ = 154.7 (s, C-4), 140.7, 128.1, 127.9, 126.4 (s, 3 d, phenyl), 94.1 (d, C-3), 93.2, 92.7 (2 s, C-5, C-9), 82.0 (d, C-10), 70.9 (t, C-2), 66.0, 64.0 (2 t, C-7, C-12), 57.8 (q, OMe), 53.9 (t, $NCH_2$), 53.5 (d, C-1′), 36.0, 35.3 (2 t, C-6, C-13), 9.7 (q, Me). – $C_{27}H_{33}NO_4$ (435.6): calcd. C 74.46, H 7.64, N 3.22; found C 74.90, H 7.83, N 3.50.

*(10S,9S,5R,1′S)-10-[1-(N,N-Dibenzylamino)ethyl]-4-methoxy-1,8,11-trioxadispiro[4.3.4]tridecan-4-one* (**15**): A solution of 302 mg (0.69 mmol) of enol ether derivative **14** in 10 ml of a 1:1 mixture of tetrahydrofuran and 2 N $H_2SO_4$ was heated for 3 h at reflux. After cooling to room temperature, the reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution. Removal of the organic layer was followed by extraction of the remaining aqueous layer with $Et_2O$ (3 × 10 ml). The combined ether extracts were dried with $MgSO_4$. Removal of the solvent under reduced pressure provided 282 mg (97%) of **15** as a colourless oil; $\alpha$ = –61.4 (*c* = 1.1, ethanol). – IR (film): $\tilde{\nu}$ = 3080–3000 $cm^{-1}$ (=C–H), 3000–2890 (C–H), 1745 (C=O). – $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.38 (d, *J* = 7.3 Hz, 4H, *ortho*-H phenyl), 7.27 (t, *J* = 7.3 Hz, 4H, *meta*-H phenyl), 7.18 (t, *J* = 7.3 Hz, 2H, *para*-H phenyl), 4.24 (br. s, 1H, 10-H), 4.19 (part A of ABXY system, $J_{AB}$ = 8.4 Hz,

$J_{AY}$ = 4.4 Hz, 1H, 2-H), 3.92 (part B of ABXY system, $J_{AB}$ = 8.4 Hz, $J_{BX}$ = 8.4 Hz, $J_{BY}$ = 8.4 Hz, 1H, 2-H), 3.87 (part A of ABXY system, $J_{AB}$ = 7.6 Hz, $J_{AX}$ = 7.6 Hz, $J_{AY}$ = 7.6 Hz, 1H, 12-H), 3.87–3.78 (m, 1H, 7-H), 3.78, 3.69 (2 d, $J$ = 15.2 Hz, 2H each, $NCH_2$), 3.65–3.57 (m, 2H, 7-H, 12-H), 3.19 (q, $J$ = 6.5 Hz, 1H, 1'-H), 2.64–2.51 (m, 2H, 3-H), 2.10 (part X of ABXY system, $J_{AX}$ = 7.1 Hz, $J_{BX}$ = 7.1 Hz, $J_{XY}$ = 12.8 Hz, 1H, 13-H), 1.95 (part X of ABXY system, $J_{AX}$ = 7.6 Hz, $J_{BX}$ = 7.6 Hz, $J_{XY}$ = 12.7 Hz, 1H, 6-H), 1.74–1.71 (m, 2H, 6-H, 13-H), 1.17 (d, $J$ = 6.5 Hz, 3H, Me). – $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 214.5 (s, C-4), 141.1, 128.6, 127.9, 126.4 (s, 3 d, phenyl), 92.8 (s, C-5), 88.2 (s, C-9), 83.4 (d, C-10), 66.7, 65.0, 62.4 (3 t, C-2, C-7, C-12), 54.3 (t, $NCH_2$), 53.5 (d, C-1'), 37.8 (t, C-3), 35.3, 35.1 (2 t, C-6, C-13), 9.6 (q, Me). – $C_{26}H_{31}NO_4$ (421.5): calcd. C 74.08, H 7.41, N 3.32; found C 74.00, H 7.40, N 3.20.

*(4S,5S,9S,10S,1'S)-, (4R,5S,9S,10S,1'S)-10-[1-(N,N-Dibenzylamino)ethyl]-4-(1-methoxy-1,2-propadien-1-yl)-1,8,11-trioxadispiro[4.3.4]tridecan-4-ol* (**17**): THF (100 ml) was added to 20.0 g (81.1 mmol) of anhydrous cerium(III) trichloride which was dried in vacuo before use (1 h, 140 °C, 0.01 mbar). The resulting suspension was stirred at room temperature for 12 h and subsequently cooled to −40 °C. At the same temperature, a solution of lithiated methoxyallene (94.6 mmol) **2** in 100 ml of THF was introduced using a syringe, which caused a colour change to brown. After stirring for 2 h at −40 °C, the mixture was cooled to −78 °C and slowly treated with a solution of 990 mg (2.35 mmol) of **15** in 80 ml of THF. After 2 h the cooling bath was removed, 200 ml of ice/water was added, and the reaction mixture was allowed to reach room temperature. After separation of the layers, the aqueous layer was extracted with $Et_2O$ (5 × 100 ml). The combined organic extracts were dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. Volatile impurities were removed by drying the crude product in vacuo ($10^{-3}$ mbar) at room temperature for 3 h. Crude yield: 2.13 g of a brownish oil containing the addition product **17** and unknown polymers. Determination of the ratio of diastereomers was not possible. – $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.10 ($m_c$, 10H, phenyl), 5.71, 5.63 (AB-system, $J_{AB}$ = 8.1 Hz, 1H each, $=CH_2$); other signals were hidden by signals of side products. – $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ = 197.9 (s, C=C), 136.7, 128.5, 127.2, 125.9 (s, 3 d, phenyl), 94.6 (s, C-4), 94.2 (t, $=CH_2$), 10.3 (q, Me); unambiguous assignment of other signals of **17** was not possible.

*(5R,9S,13S,14S,1'S)-14-[1-(N,N-Dibenzylamino)ethyl]-4-methoxy-1,8,12,15-tetraoxatrispiro[4.3.3.4]heptadec-3-ene* (**18**): A solution of 2.13 g of crude **17** in 50 ml of DMSO was added dropwise to a stirred solution of 5.70 g (50.7 mmol) of potassium *tert*-butoxide in 150 ml of DMSO. Stirring was continued for 24 h at room temperature. Subsequently, the reaction was quenched with 100 ml of ice/water followed by addition of 50 ml of $Et_2O$ to the resulting mixture. The layers were separated and the aqueous layer was extracted with a 2:1 mixture of petroleum ether and $Et_2O$ (6 × 100 ml). The combined organic extracts were dried ($Na_2SO_4$). Removal of the solvent in vacuo yielded 863 mg (75% based on **15**) of a brownish oil. A sample of the residue was purified by column chromatography on silica gel [*n*-heptane/methyl acetate (from 98:2 to 2:1)] to give **18** as a colourless oil; α = 17.4 ($c$ = 0.7, $CHCl_3$). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.08 (m, 10H, phenyl), 4.74 (part X of ABX system, $J_{AX}$ = 1.7 Hz, $J_{BX}$ = 1.5 Hz, 1H, 3-H), 4.67 (s, 1H, 14-H), 4.65 (part A of ABX system, $J_{AX}$ = 1.7 Hz, $J_{AB}$ = 11.3 Hz, 1H, 2-H), 4.55 (part B of ABX system, $J_{BX}$ = 1.5 Hz, $J_{AB}$ = 11.3 Hz, 1H, 2-H), 4.06–3.52 (m, 10H, 16-H, 11-H, 7-H, $NCH_2$), 3.68 (s, 3H, OMe), 3.30 (q, $J$ = 6.9 Hz, 1H, 1'-H), 2.39–1.95 (m, 4H, 6-, 10-, or 17-H), 1.68–1.45 (m, 2H, 6-, 10- or 17-H), 1.18 (d, $J$ = 6.9 Hz, 3H, Me). – $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ = 157.4 (s, C-4), 141.9, 128.6, 127.7, 125.9 (s, 3 d, phenyl), 94.0 (s, C-5), 92.9, 92.7 (2 s, C-9, C-13), 92.5 (d, C-3), 83.9 (d, C-14), 70.4 (t, C-2), 67.1, 64.9, 63.7 (3 t, C-7, C-11, C-16), 57.8 (q, OMe), 54.6 (d, C-1'), 54.5 (t, $NCH_2$), 38.3, 36.7, 34.7 (3 t, C-6, C-10, C-17), 11.7 (q, Me).

*(5S,9S,13S,14S,1'S)-14-[1-N,N-Dibenzylamino)ethyl]-1,8,12,15-tetraoxatrispiro[4.3.3.4]heptadecan-4-one* (**19**): A solution of 863 mg (1.74 mmol) of **18** in 100 ml of THF was treated slowly with 100 ml of 25% sulfuric acid. The reaction mixture was stirred at room temperature for 24 h. Subsequently, the mixture was neutralized with a saturated $Na_2CO_3$ solution. After separation of the layers, the aqueous layer was extracted with $Et_2O$. After drying of the combined organic layers ($Na_2SO_4$) and removal of the solvent under reduced pressure, 715 mg of a yellow oil was obtained, which crystallized upon storage. Purification by recrystallization from methanol provided 470 mg (57%) of **19** as colourless crystals; m.p. 122–124 °C; α = −30.8 ($c$ = 0.98, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3055–2930 $cm^{-1}$ (=C–H), 2880–2810 (C–H), 1750 (C=O). – $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, $J$ = 8.0 Hz, 4H, *ortho*-H phenyl), 7.22 (t, $J$ = 8.0 Hz, 4H, *meta*-H phenyl), 7.13 (t, $J$ = 8.0 Hz, 2H, *para*-H phenyl), 4.63 (br. s, 1H, 14-H), 4.43 (part A of ABXY system, $J_{AY}$ = 2.3 Hz, $J_{AX}$ = 9.9 Hz, $J_{AB}$ = 9.9 Hz, 1H, 2-H), 4.04–3.97 (m, 2H, 2-H, 7-, 10- or 16-H), 3.90–3.78 (m, 3H, 7, 10- or 16-H), 3.74 (part A of ABXY system, $J_{AB}$ = 7.7 Hz, $J_{AX}$ = 8.9 Hz, 1H, 7-, 11- or 16-H), 3.73, 3.67 (2 d, $J$ = 14.5 Hz, 4H, $NCH_2$), 3.63 (part B of ABXY system, $J_{BX}$ = 10.5 Hz, 1H, 7-, 11- or 16-H), 3.25 (q, $J$ = 6.8 Hz, 1H, 1'-H), 2.70 (part X of ABXY system, $J_{XB}$ = 10.5 Hz, $J_{XY}$ = 18.6 Hz, 1H, 3-H), 2.53 (part Y of ABXY system, $J_{BY}$ = 6.8 Hz, 1H, 3-H), 2.29 (m, part X of ABXY system, 1H, 6-, 10- or 14-H), 2.20 (part X of ABXY-system, $J_{BX}$ = 2.5 Hz, 1H, 6-, 10- or 14-H), 2.00 (part Y of ABXY system, $J_{AY}$ = 9.5 Hz, $J_{BY}$ = 9.5 Hz, 1H, 6-, 10- or 17-H), 1.61–1.55 (m, 1H, 6-, 10- or 17-H), 1.15 (d, $J$ = 6.8 Hz, 3H, Me). – $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ = 213.9 (s, C-4), 141.8, 128.6, 127.7, 126.0 (s, 3 d, phenyl), 94.7 (s, C-5), 93.1, 88.4 (2 s, C-9, C-13), 83.9 (d, C-14), 66.8 (t, C-2), 64.9, 64.5, 61.2 (3 t, C-7, C-11, C-16), 54.5 (t, $NCH_2$), 54.4 (d, C-1'), 38.4 (d, C-3), 37.1, 35.9, 33.5 (3 t, C-6, C-11, C-18), 11.2 (q, Me). – $C_{29}H_{35}NO_5$ (477.6): calcd. C 74.93, H 7.39, N 2.93; found C 74.34, H 7.42, N 2.90.


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