EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201500365

A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring

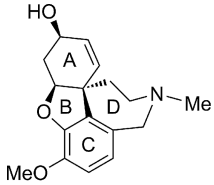
Jeremy Nugent,[a] Eliška Matoušová,[a] and Martin G. Banwell*[a]

Keywords: Natural products / Total synthesis / Alkaloids / Alder-ene reactions / Diels–Alder reactions / Cycloaddition

The tetracyclic alkaloid galanthamine is used clinically in a number of countries for the symptomatic treatment of mild to moderate forms of Alzheimer's disease, and this feature coupled with its novel molecular architecture has prompted an extensive focus on its synthesis. The present study reports a new and distinct synthesis of galanthamine wherein the AB-ring substructure and associated quaternary carbon centre are constructed by using a palladium-catalyzed intramolecular Alder-ene reaction. The product of this process is engaged in a Tsuji–Trost-type reaction to generate a semicyclic diene that participates in a normal-electron-demand Diels–Alder reaction to generate, after oxidation of the initially formed adduct, the aromatic C-ring of the target alkaloid. Modified Bischler–Napieralski chemistry is then deployed to construct the seven-membered D-ring and thereby furnishing narwedine, an established precursor to both (+)- and (–)-galanthamine.

Introduction

The tetracyclic Amaryllidaceae alkaloid (–)-galanthamine (**1**) (Figure 1) has been isolated from a range of plant sources including the Caucasian snowdrop (*Galanthus woronowii*) and the Red Spider Lily (*Lycoris radia*).[1] Since the early 1950s it has been used in various clinical settings and is currently marketed in many countries for the symptomatic treatment of the early stages of Alzheimer's disease.[1,2] Galanthamine's effectiveness in this regard derives, at least in part, from its capacity to cross the blood-brain barrier and inhibit acetylcholine esterase in a selective, competitive and reversible manner.[1] The compound has also been shown to act at the nicotinic acetylcholine receptor.[3]



1

Figure 1. Structure of (–)-galanthamine (**1**).

The significant and increasing clinical demand for galanthamine together with the erosion of the habitat of certain of the producing plants is creating supply issues. Various attempts are being made to address these[4] but, thus far, no commercially viable synthesis of the alkaloid has been established.[5] Nevertheless, a range of ingenious approaches to galanthamine has been described with the first of these, reported by Barton and Kirby in 1962,[6] involving a biomimetic but low yielding intramolecular oxidative phenolic coupling reaction that established the entire ABCD-ring framework from an AC-ring precursor. Certain refinements of this basic process have been described,[7] including asymmetric variants,[8] and one has served as the basis for a pilot plant-scale production process.[9] Intramolecular Heck reactions that result in the formation of the ABC-ring substructure, including the pivotal quaternary carbon center of galanthamine, from an AC-ring precursor represents another effective approach.[10] Various others have been described[11] including ones that exploit D-glucose[12] or an enantiopure and enzymatically derived *cis*-1,2-dihydrocatechol[13] as precursors to the A-ring. Syntheses of a range of biologically active analogues of galanthamine have also been reported.[14]

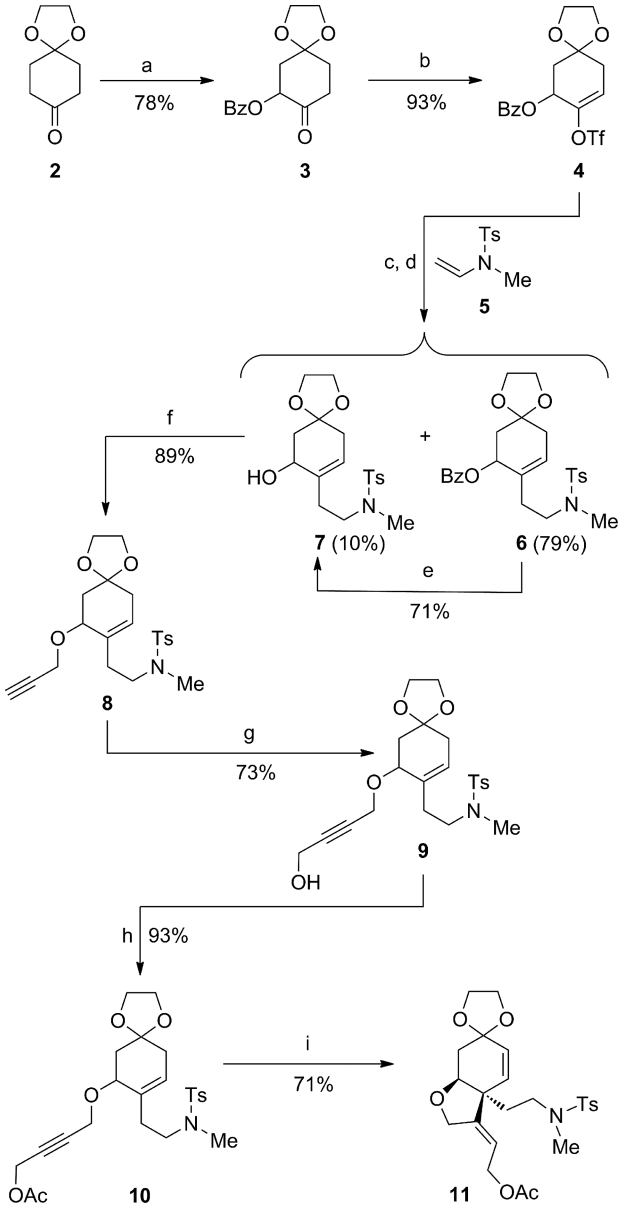
Herein we report a synthesis of galanthamine that is distinct from all previous ones in that a de novo construction of the aromatic C-ring is involved and by which means a range of hitherto inaccessible analogues of this natural product should become available. The pivotal features of our approach are, (i) the use of a Pd-catalyzed intramolecular Alder-ene (IMAE) reaction to construct the AB-ring substructure bearing an angular β-aminoethyl group, (ii) a Tsuji–Trost-type reaction leading to a diene that participates in a completely regioselective Diels–Alder reaction with propynal and (iii) the ready elaboration of the Diels–Alder adduct to the aromatic and methoxylated C-ring of galanthamine.

[a] Research School of Chemistry, Institute of Advanced Studies, The Australian National University,
Canberra, ACT 2601, Australia
E-mail: Martin.Banwell@anu.edu.au
http://rsc.anu.edu.au/~mgb/

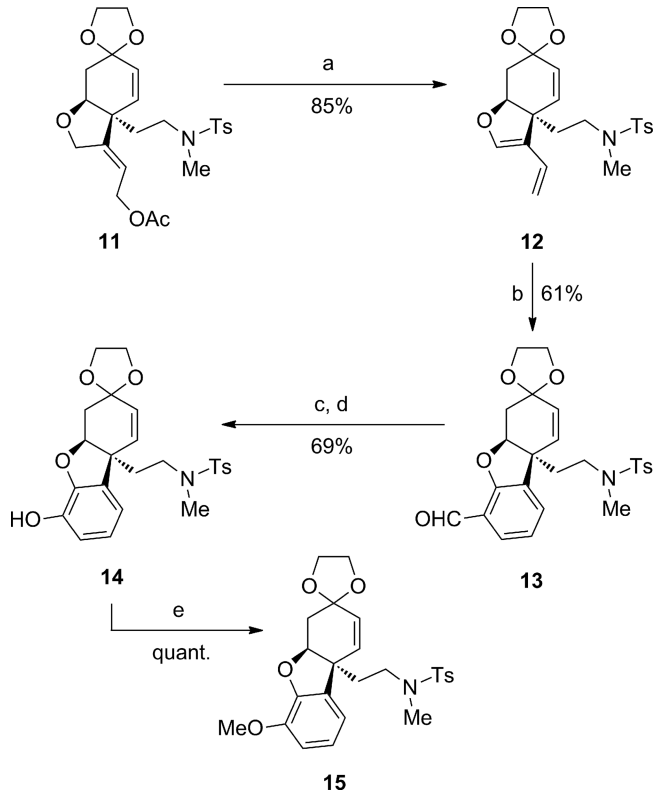
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500365.

Results and Discussion

The opening stages of the synthesis, including the IMAE reaction, are shown in Scheme 1 and involve, as the first step, reaction of the commercially available monoethylene ketal **2** of cyclohexane-1,4-dione with *N*-methyl-*O*-benzoylhydroxylamine (MeNHOBz)[15] and thus affording the α-benzoyloxy derivative **3**[15] in 78% yield. This last compound was then converted, under standard conditions and in 93% yield, into the corresponding enol triflate **4** that was itself subjected to a Pd^0-catalyzed cross-coupling reaction with the in situ generated organoborane derived from 9-BBN and enamine derivative **5**[16] and thus delivering a mixture of amine derivative **6** (79%) and the corresponding alcohol **7** (10%).[17] Saponification of the benzoate residue within the former product with aqueous sodium hydroxide afforded additional quantities of alcohol **7** (71%) that was readily converted into the corresponding propargyl ether **8** (89%) upon treatment with propargyl bromide in the presence of sodium hydride. In anticipation of the above-mentioned diene-forming event and also in order to prevent dimerization of terminal alkyne **8**[18] this was "capped" with a hydroxymethyl group through its deprotonation with *n*BuLi, followed by reaction of the ensuing anion with paraformaldehyde. The resulting alcohol **9** (73%) was acetylated under standard conditions, and the ensuing ester **10** (93%) then engaged in a $Pd(OAc)_2$-mediated IMAE reaction under conditions originally defined by Trost and Pedregal in 1992[19] and exploited by us on various occasions more recently.[18,20] As a result, the hexahydrobenzofuran **11** embodying the AB-ring substructure of galanthamine was obtained in 71% yield. The use of the strong σ-donating ligand *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) in this reaction was essential to its success.



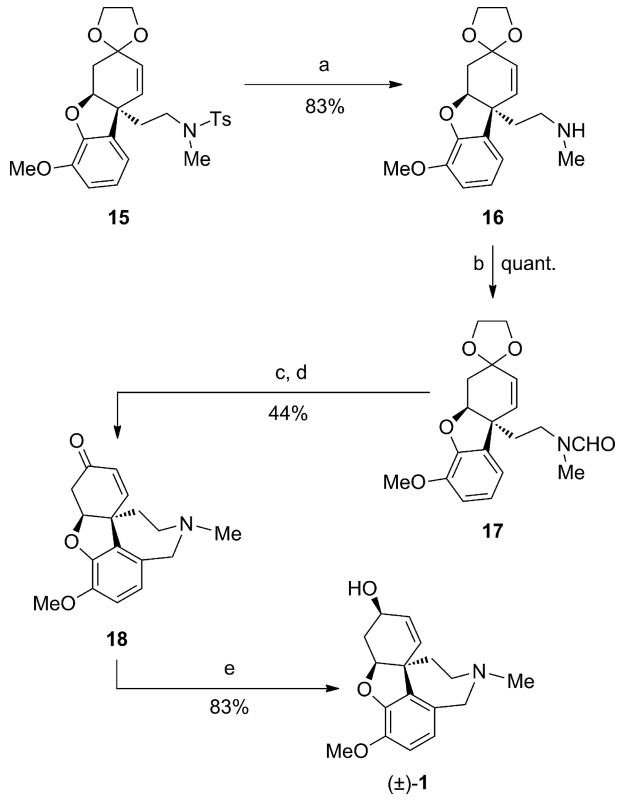
Scheme 1. Reaction sequence leading to the IMAE product **11**. Reagents and conditions: (a) MeNHOBz, DMSO, room temp., 2 h; (b) LiHMDS, then $PhNTf_2$, THF, –78 °C to room temp., ca. 4 h; (c) compound **5**, 9-BBN, THF, then NaOH (aq.), 0 °C to room temp., ca. 16 h; (d) compound **4**, $PdCl_2dppf{\cdot}CH_2Cl_2$, THF, room temp., 2 h, then H_2O_2; (e) NaOH, MeOH, 65 °C, 3 h; (f) $HCCCH_2Br$, nBu_4NI, NaH, THF, 0 °C to room temp., 48 h; (g) *n*BuLi then $(H_2CH)_n$, THF, –78 °C to room temp., 48 h; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 6 h; (i) $Pd(OAc)_2$, BBEDA, C_6H_6, 80 °C, 5 h.



Scheme 2. Construction of the aromatic C-ring: formation of compound **15**. Reagents and conditions: (a) $Pd(Ph_3P)_4$, DBU, $C_6H_5CH_3$, room temp. to 112 °C, ca. 2 h; (b) HCCCHO, DTBMP, then MnO_2, C_6H_6, room temp., 96 h; (c) *m*-CPBA, CH_2Cl_2, room temp., 46 h; (d) K_2CO_3, MeOH, room temp., 16 h; (e) MeI, NaH, THF, 0 °C to room temp., 25 h.

The next phase of the synthesis was the benzannulation of compound **11** in order to establish the aromatic C-ring of galanthamine. The means for doing so was achieved as shown in Scheme 2 and involved first treatment of this substrate with $Pd(Ph_3P)_4$ in the presence of the nitrogenous base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), thus effecting the elimination of the elements of acetic acid and so generating the diene **12** (85%). This last compound participated in a Diels–Alder cycloaddition reaction with propynal[21] at room temperature, and the so-formed adduct was immediately oxidized with manganese dioxide to afford benzaldehyde **13** (61%). The hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was added to prevent acid-catalyzed fragmentation of the initially formed adduct. On reaction with *m*-chloroperbenzoic acid, compound **13** engaged in a Dakin oxidation reaction, and the product aryl formate was cleaved with potassium carbonate in methanol. The resulting phenol **14** (69%) was then *O*-methylated with methyl iodide in the presence of sodium hydride, thus producing the methoxyarene **15** (quant.) that embodies the aromatic C-ring of galanthamine.

The completion of the synthesis of target **1** from arene **15** clearly requires introduction of the heterocyclic D-ring. The procedure for doing so is shown in Scheme 3 and involved, as the first step, treatment of compound **15** with



Scheme 3. Installation of the D-ring and completion of the synthesis. Reagents and conditions: (a) Mg, MeOH, ultrasonication, 16 h; (b) EtOCHO, 54 °C, 6 h; (c) Tf_2O, 2-chloropyridine, CH_2Cl_2, –78 °C to room temp., 20 h; (d) $NaB(OAc)_3H$, CH_2Cl_2, room temp., 2 h, then satd. aq. $NaHCO_3$; (e) L-selectride, THF, –78 °C, 3 h.

magnesium in methanol[22] that resulted in cleavage of the associated tosyl residue and formation of the secondary amine **16** (83%). Simple heating of this last compound with neat ethyl formate provided the formamide **17** in quantitative yield, and this was subjected to a Bischler–Napieralski-type cyclodehydration reaction under conditions defined by Movassaghi and Hill.[23] Subsequent and successive treatment of the crude reaction mixture with sodium triacetoxy(hydrido)borate followed by saturated aqueous sodium hydrogen carbonate afforded (±)-narwedine (**18**) in 44% yield. The spectroscopic data acquired on this tetracyclic compound are in complete accord with those reported by Magnus and co-workers.[11c]

Since racemic narwedine is readily converted into either (+)- or (–)-galanthamine, the present work constitutes a formal total synthesis of both enantiomeric forms of the title alkaloid.[24] In order to further corroborate the structural assignments presented above, (±)-narwedine (**18**) was subjected to diastereoselective reduction with L-selectride,[24,25] thereby affording (±)-galanthamine [(±)-**1**] in 83% yield. The ^1H and ^{13}C NMR spectroscopic data obtained on this material also proved a good match for those recorded on the natural product.[13]

Conclusions

The work detailed here highlights the effectiveness of the palladium-catalyzed IMAE reaction for constructing hexahydrobenzofurans bearing angular substituents and, thereby, quaternary carbon centers such as those associated with galanthamine (**1**). Furthermore, the use of a Diels–Alder reaction to construct the aromatic C-ring of this alkaloid should provide the means for assembling analogues that incorporate unusual functionalities in this part of the molecular framework. Work directed towards such ends are now underway in these laboratories.

Experimental Section

General Experimental Procedures: Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ with a Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^1H NMR spectra, signals arising from the residual protio forms of the solvent were used as the internal standards. ^1H NMR spectroscopic data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of thereof. The signal due to residual $CHCl_3$ appearing at δ_H = 7.26 ppm and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C = 77.0 ppm were used to reference ^1H and ^{13}C NMR spectra, respectively. The signal due to residual CH_2Cl_2 appearing at δ_H = 5.30 ppm and the central resonance of the CD_2Cl_2 "multiplet" appearing at δ_C = 53.5 ppm were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (IR: $\tilde{\nu}_{max}$) were recorded with a Perkin–Elmer 1800 series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer, while high-

resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded with a magnetic-sector machine. Melting points were measured with an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized with a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (concd.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out according to protocols defined by Still et al.[26] with silica gel 60 (40–63 μm) as the stationary phase and with the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab chemical companies. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried by using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[27] Where necessary, reactions were performed under nitrogen.

8-{[(Trifluoromethyl)sulfonyl]oxy}-1,4-dioxaspiro[4.5]dec-8-en-7-yl Benzoate (4): A magnetically stirred solution of ketone **3**[15] (9.73 g, 35.2 mmol) in dry THF (190 mL) maintained under nitrogen was cooled to –78 °C and then treated with LiHMDS (46 mL of a 1 M solution in THF, 46 mmol). The resulting mixture was stirred at –78 °C for 0.5 h, then warmed to –40 °C and treated with *N*-phenylbis(trifluoromethanesulfonimide) (16.4 g, 46 mmol). The resulting mixture was warmed to room temperature over a period of 3 h before being quenched with NH_4Cl (150 mL of a saturated aqueous solution) and extracted with diethyl ether (3× 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 4:1 v/v petroleum ether/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.5 in 3:1 v/v petroleum ether/ethyl acetate) afforded enol triflate **4** (13.37 g, 93%) as a tan solid, m.p. 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (m, 2 H), 7.59 (m, 1 H), 7.46 (m, 2 H), 6.02 (t, *J* = 4.0 Hz, 1 H), 5.88 (m, 1 H), 4.05–3.95 (complex m, 4 H), 2.66 (dt, *J* = 18.4 and 3.1 Hz, 1 H), 2.57–2.42 (complex m, 2 H), 2.14 (dd, *J* = 13.2 and 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 144.9, 133.5, 130.1, 128.6, 120.7, 118.8 (q, *J* = 320.0 Hz), 106.1, 67.8, 65.0, 64.9, 37.6, 34.8 (one signal obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 2965, 2893, 1726, 1601, 1421, 1267, 1248, 1211, 1142, 1064, 877, 712 cm^{-1}. MS (EI): *m*/*z* (%) = 408 (2) [M$^{+\cdot}$], 303 (5), 287 (10), 275 (15), 153 (100), 105 (56). HRMS (EI): calcd. for $C_{16}H_{15}F_3O_7S$ [M$^{+\cdot}$] 408.0491; found 408.0485.

8-[2-(*N*,4-Dimethylphenylsulfonamido)ethyl]-1,4-dioxaspiro[4.5]dec-8-en-7-yl Benzoate (6) and *N*-[2-(9-Hydroxy-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl]-*N*,4-dimethylbenzenesulfonamide (7): A magnetically stirred solution of sulfonamide **5**[16] (15.84 g, 75 mmol) in dry THF (75 mL) maintained under nitrogen was cooled to 0 °C and then treated dropwise with 9-BBN (150 mL of a 0.5 M solution in THF, 75 mmol). After 0.17 h at 0 °C, the reaction mixture was warmed to room temperature and then stirred for 16 h before being treated dropwise with NaOH (75 mL of a 3 M aqueous solution). The resulting mixture was stirred at room temperature for 0.33 h and then treated with a solution of enol triflate **4** (21.76 g, 40 mmol) and $PdCl_2$dppf·CH_2Cl_2 (6.80 g, 6 mmol, 0.20 mol equiv.) in dry THF (120 mL). The resulting mixture was stirred at room temperature for 2 h, then cooled to 0 °C, quenched with H_2O_2 (100 mL of a 30% aqueous solution) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 7:3 v/v petroleum ether/ethyl acetate elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 7:3 v/v petroleum ether/ethyl acetate) gave benzoate **6** (14.80 g, 79%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.3 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.3 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 5.77 (t, *J* = 6.7 Hz, 1 H), 5.72 (t, *J* = 3.1 Hz, 1 H), 4.01–3.95 (complex m, 4 H), 3.14 (ddd, *J* = 13.5, 8.6 and 7.2 Hz, 1 H), 3.06 (ddd, *J* = 13.5, 8.7 and 5.8 Hz, 1 H), 2.66 (s, 3 H), 2.53–2.42 (complex m, 1 H), 2.40 (s, 3 H), 2.38–2.26 (complex m, 4 H), 1.99 (dd, *J* = 13.2 and 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 143.3, 135.0, 133.3, 132.9, 130.3, 129.7 (6), 129.8 (1), 128.6, 127.5, 126.0, 107.4, 71.2, 64.7, 64.6, 49.2, 37.2, 36.1, 35.2, 31.6, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 2969, 2926, 2887, 1713, 1599, 1451, 1339, 1268, 1160, 1108, 949, 715 cm^{-1}. MS (EI): *m*/*z* (%) = 471 (3) [M$^{+\cdot}$], 349 (10), 273 (9), 198 (100), 155 (52), 91 (47). HRMS (EI): calcd. for $C_{25}H_{29}NO_6S$ [M$^{+\cdot}$] 471.1716; found 471.1712.

Concentration of fraction B (R_f = 0.2 in 1:1 v/v petroleum ether/ethyl acetate) gave allylic alcohol **7** (1.40 g, 10%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.50 (m, 1 H), 4.13 (dt, *J* = 10.9 and 4.0 Hz, 1 H), 4.04–3.89 (complex m, 4 H), 3.27 (ddd, *J* = 13.5, 8.4 and 7.1 Hz, 1 H), 3.06 (ddd, *J* = 13.5, 8.5 and 5.4 Hz, 1 H), 3.00 (d, *J* = 10.9 Hz, 1 H), 2.72 (s, 3 H), 2.49–2.42 (complex m, 1 H), 2.41 (s, 3 H), 2.38–2.25 (complex m, 3 H), 2.07–1.96 (complex m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 136.7, 134.9, 129.7, 127.5, 123.1, 108.2, 68.5, 64.5 (3), 64.5 (0), 49.2, 39.0, 36.1, 34.8, 32.4, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 3523, 2956, 2921, 2887, 1336, 1159, 1048, 948, 721 cm^{-1}. MS (EI): *m*/*z* (%) = 367 (3) [M$^{+\cdot}$], 349 (2), 281 (18), 198 (100), 155 (70), 91 (53). HRMS (EI): calcd. for $C_{18}H_{25}NO_5S$ [M$^{+\cdot}$] 367.1453; found 367.1457.

***N*-[2-(9-Hydroxy-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl]-*N*,4-dimethylbenzenesulfonamide (7):** A magnetically stirred solution of benzoate **6** (14.8 g, 31.4 mmol) in methanol (500 mL) was treated with NaOH (100 mL of a 3 M aqueous solution) and the resulting solution heated at reflux for 3 h. The cooled reaction mixture was quenched with NH_4Cl (40 mL of a saturated aqueous solution) and then concentrated under reduced pressure. The ensuing residue was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography (silica gel; 4:1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v petroleum ether/ethyl acetate), allylic alcohol **7** (8.18 g, 71%) as a clear, yellow oil. This material was identical, in all respects, with that obtained in the preceding step.

***N*,4-Dimethyl-*N*-{2-[9-(prop-2-yn-1-yloxy)-1,4-dioxaspiro[4.5]dec-7-en-8-yl]ethyl}benzenesulfonamide (8):** A magnetically stirred solution of allylic alcohol **7** (9.50 g, 25.9 mmol) in anhydrous THF (68 mL) was treated with tetra-*n*-butylammonium iodide (2.01 g, 4.53 mmol) and propargyl bromide (5.8 mL of a 80% solution in toluene, 51.8 mmol) before being cooled to 0 °C and treated portionwise with NaH (2.34 g of a 60% dispersion in mineral oil, 51.8 mmol). After having been stirred at 0 °C for 0.17 h, the reaction mixture was warmed to room temperature and then stirred for 48 h before being quenched with NH_4Cl (50 mL of a saturated

aqueous solution) and extracted with diethyl ether (3× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 7:3 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.4), propargyl ether **8** (9.30 g, 89%) as a clear, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 5.52 (m, 1 H), 4.31–4.25 (complex m, 1 H), 4.24 (dd, J = 16.0 and 2.4 Hz, 1 H), 4.15 (dd, J = 16.0 and 2.4 Hz, 1 H), 4.02–3.90 (complex m, 4 H), 3.20–3.05 (complex m, 2 H), 2.75 (s, 3 H), 2.50–2.43 (complex m, 1 H), 2.42 (s, 3 H), 2.38 (t, J = 2.4 Hz, 1 H), 2.35–2.14 (complex m, 4 H), 1.82 (dd, J = 12.8 and 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 135.1, 135.0, 129.7, 127.6, 124.0, 107.9, 80.3, 75.0, 74.6, 64.6, 64.5, 56.1, 49.5, 36.6, 35.9, 35.1, 31.6, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 3271, 2956, 2928, 2884, 2115, 1598, 1456, 1337, 1160, 1074, 1019, 948, 817, 731 cm^{-1}. MS (ESI): m/z (%) = 428 (100) [M + Na]$^+$, 406 (5) [M + H]$^+$, 351 (10). HRMS (ESI): calcd. for $C_{21}H_{27}NNaO_5S$ [M + Na]$^+$ 428.1508; found 428.1506.

***N*-(2-{9-[(4-Hydroxybut-2-yn-1-yl)oxy]-1,4-dioxaspiro[4.5]dec-7-en-8-yl}ethyl)-*N*,4-dimethylbenzenesulfonamide (9):** A magnetically stirred solution of propargyl ether **8** (9.30 g, 22.9 mmol) in anhydrous THF (100 mL) was cooled to –78 °C and then treated with *n*BuLi (16.7 mL of a 1.5 M solution in hexanes, 25.2 mmol). The ensuing solution was stirred at this temperature for 1 h before being treated with paraformaldehyde (2.06 g, 68.7 mmol). The resulting suspension was warmed to room temperature and, after 48 h, quenched with NH_4Cl (50 mL of a saturated aqueous solution), then extracted with diethyl ether (3× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 1:2 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.3), propargyl alcohol **9** (7.28 g, 73%) as a clear, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.50 (t, J = 3.8 Hz, 1 H), 4.39–4.28 (complex m, 4 H), 4.18 (dt, J = 15.9 and 1.7 Hz, 1 H), 3.95 (m, 4 H), 3.25 (m, 1 H), 3.12 (m, 1 H), 2.73 (s, 3 H), 2.51 (m, 2 H), 2.42 (s, 3 H), 2.36–2.12 (complex m, 4 H), 1.82 (dd, J = 12.8 and 7.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 135.1, 134.8, 129.8, 127.6, 124.3, 107.8, 85.5, 81.5, 73.6, 64.6, 64.5, 55.9, 51.1, 49.4, 36.1, 35.9, 34.8, 31.8, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 3468, 2926, 2883, 2250, 1956, 1597, 1335, 1160, 1069, 947, 817, 730 cm^{-1}. MS (ESI): m/z (%) = 458 (100) [M + Na]$^+$, 350 (85). HRMS (ESI): calcd. for $C_{22}H_{29}NNaO_6S$ [M + Na]$^+$ 458.1613; found 458.1614.

4-({8-[2-(*N*,4-Dimethylphenylsulfonamido)ethyl]-1,4-dioxaspiro[4.5]dec-8-en-7-yl}oxy)but-2-yn-1-yl Acetate (10): A magnetically stirred solution of propargyl alcohol **9** (7.82 g, 18.0 mmol) in anhydrous dichloromethane (100 mL) was cooled to 0 °C and then treated with triethylamine (3.00 mL, 21.6 mmol), DMAP (220 mg, 1.8 mmol) and acetic anhydride (2.1 mL, 21.6 mmol). The resulting solution was stirred at 0 °C for 6 h before being quenched with NH_4Cl (50 mL of a saturated aqueous solution) and extracted with dichloromethane (3× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 1:1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.7 in 1:2 v/v petroleum ether/ethyl acetate), propargyl acetate **10** (7.99 g, 93%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.01 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 5.51 (m, 1 H), 4.68 (t, J = 1.9 Hz, 2 H), 4.27 (dt, J = 16.1 and 1.9 Hz, 1 H), 4.23 (m, 1 H), 4.19 (dt, J = 16.1 and 1.9 Hz, 1 H), 4.10–3.90 (complex m, 4 H), 3.19 (ddd, J = 13.2, 9.3 and 6.6 Hz, 1 H), 3.10 (ddd, J = 13.2, 9.3 and 5.3 Hz, 1 H), 2.74 (s, 3 H), 2.42 (s, 3 H), 2.37–2.13 (complex m, 5 H), 2.07 (s, 3 H), 1.82 (dd, J = 12.8 and 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 143.2, 135.1, 135.0, 129.7, 127.5, 124.0, 107.9, 83.3, 80.4, 75.1, 64.6, 64.5, 56.3, 52.4, 49.4, 36.5, 35.9, 35.0, 31.6, 21.6, 20.8 ppm. IR: $\tilde{\nu}_{max}$ = 2958, 2928, 2879, 1956, 1747, 1594, 1338, 1224, 1160, 1071, 1071, 1027, 947, 730 cm^{-1}. MS (ESI): m/z (%) = 500 (100) [M + Na]$^+$, 350 (90). HRMS (ESI): calcd. for $C_{24}H_{31}NNaO_7S$ [M + Na]$^+$ 500.1719; found 500.1714.

(*Z*)-2-{(3a*S*,7a*S*)-*rel*-3a-[2-(*N*,4-Dimethylphenylsulfonamido)ethyl]-7,7a-dihydro-2*H*-spiro(benzofuran-6,2′-[1,3]dioxolan)-3(3a*H*)-ylidene}ethyl Acetate (11): A magnetically stirred solution of propargyl acetate **10** (1.06 g, 2.1 mmol) in anhydrous benzene (30 mL) was treated with $Pd(OAc)_2$ (71 mg, 0.32 mmol) and *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) (75 mg, 0.32 mmol). The resulting solution was heated at reflux for 5 h and then concentrated under reduced pressure to give a brown oil that was subjected to flash chromatography (silica gel; 1:1 v/v petroleum ether/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.5 in 1:2 v/v petroleum ether/ethyl acetate) then gave allylic acetate **11** (754 mg, 71%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.9 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 5.65 (d, J = 10.4 Hz, 1 H), 5.64 (d, J = 10.4 Hz, 1 H), 5.39 (m, 1 H), 4.58 (d, J = 14.2 Hz, 1 H), 4.53–4.41 (complex m, 3 H), 4.15 (dd, J = 8.2 and 4.5 Hz, 1 H), 4.01–3.90 (complex m, 4 H), 3.01 (t, J = 8.2 Hz, 2 H), 2.69 (s, 3 H), 2.43 (s, 3 H), 2.06 (s, 3 H), 2.03–1.73 (complex m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 149.1, 143.5, 134.7, 133.2, 129.8, 127.7, 127.6, 115.9, 104.5, 79.8, 68.1, 65.1, 64.6, 61.7, 48.4, 46.7, 36.4, 35.3, 35.2, 21.7, 21.0 ppm. IR: $\tilde{\nu}_{max}$ = 2953, 2926, 2874, 1737, 1339, 1230, 1160, 1064, 1027, 738 cm^{-1}. MS (ESI): m/z (%) = 500 (100) [M + Na]$^+$, 478 (30) [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{31}NNaO_7S$ [M + Na]$^+$ 500.1719; found 500.1719.

***N*,4-Dimethyl-*N*-{2-[(3a*S*,7a*S*)-*rel*-3-vinyl-7,7a-dihydro-3a*H*-spiro(benzofuran-6,2′-[1,3]dioxolan)-3a-yl]ethyl}benzenesulfonamide (12):** A magnetically stirred solution of allylic acetate **11** (1.40 g, 2.93 mmol) in anhydrous toluene was treated with $Pd(PPh_3)_4$ (339 mg, 0.29 mmol) and the resulting solution stirred at room temperature for 0.17 h before being treated with DBU (1.32 mL, 8.79 mmol) and then heated at reflux for 2 h. The cooled reaction mixture was subjected without concentration to flash chromatography (neutral alumina; 3:1 → 1:1 petroleum ether/ethyl acetate gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.8 in 1:2 v/v petroleum ether/ethyl acetate), diene **12** (1.03 g, 85%) as a viscous, clear and colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 6.42 (s, 1 H), 6.17 (dd, J = 17.9 and 11.5 Hz, 1 H), 5.98 (d, J = 10.3 Hz, 1 H), 5.72 (d, J = 10.3 Hz, 1 H), 5.11 (d, J = 17.9 Hz, 1 H), 4.87 (d, J = 11.5 Hz, 1 H), 4.64 (dd, J = 6.6 and 5.1 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.14 (ddd, J = 13.7, 11.6 and 5.0 Hz, 1 H), 2.96 (ddd, J = 13.7, 11.6 and 5.0 Hz, 1 H), 2.72 (s, 3 H), 2.43 (s, 3 H), 2.21 (dd, J = 14.0 and 6.6 Hz, 1 H), 2.12–1.96 (complex m, 2 H), 1.82 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 143.4, 134.9, 132.4, 129.8, 127.7, 127.5 (4), 127.5 (1), 119.7, 110.0, 103.5, 83.8, 65.1, 64.6, 48.6, 46.6, 35.4, 35.3, 35.0, 21.7 ppm. IR: ṽmax = 2958, 2921, 2883, 2848, 1732, 1633, 1437, 1339, 1160, 1119, 721, 696, 542 cm^{-1}. MS (EI): m/z (%) = 417 (5) [M$^{+\cdot}$], 278 (53), 277 (100), 262 (90), 205 (70), 155 (22), 91 (47). HRMS (EI): calcd. for $C_{22}H_{27}NO_5S$ [M$^{+\cdot}$] 417.1610; found 417.1611.

***N*-{2-[(4a*S*,9b*S*)-*rel*-6-Formyl-4,4a-dihydro-9b*H*-spiro(dibenzo[*b*,*d*]-furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*,4-dimethylbenzenesulfon-**

amide (13): A magnetically stirred solution of diene **12** (530 mg, 1.27 mmol) in anhydrous benzene (30 mL) was treated with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (261 mg, 1.27 mmol) and propynal (140 μL, 2.54 mmol), the ensuing mixture maintained at room temperature for 48 h and then treated with MnO_2 (1.10 g, 12.7 mmol). The resulting mixture was stirred at room temperature for a further 48 h, then filtered through a pad of Celite and the filtrate concentrated under reduced pressure. The ensuing orange oil was subjected to flash chromatography (silica gel; 1:1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1:2 v/v petroleum ether/ethyl acetate), benzaldehyde **13** (363 mg, 61%) as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (s, 1 H), 7.64 (dd, J = 7.6 and 1.4 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 2 H), 7.36 (dd, J = 7.6 and 1.4 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.00 (t, J = 7.6 Hz, 1 H), 5.95 (d, J = 10.1 Hz, 1 H), 5.81 (d, J = 10.1 Hz, 1 H), 4.98 (dd, J = 8.8 and 5.5 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.04 (ddd, J = 13.7, 10.1 and 5.8 Hz, 1 H), 2.93 (ddd, J = 13.7, 10.1 and 5.8 Hz, 1 H), 2.68 (s, 3 H), 2.41 (s, 3 H), 2.26 (dd, J = 13.4 and 5.3 Hz, 1 H), 2.07 (dd, J = 13.4 and 8.8 Hz, 1 H), 1.97 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 160.3, 143.6, 134.4, 134.0, 131.6, 129.8, 129.5, 129.2, 128.1, 127.5, 121.5, 120.6, 103.9, 86.0, 65.1, 64.8, 47.2, 46.4, 38.2, 36.3, 35.4, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 2958, 2925, 2887, 1685, 1610, 1450, 1338, 1160, 1016, 945, 732 cm^{-1}. MS (ESI): m/z (%) = 492 (100) [M + Na]$^+$, 470 (4) [M + H]$^+$. HRMS (ESI): calcd. for $C_{25}H_{27}NNaO_6S$ [M + Na]$^+$ 492.1457; found 492.1457.

***N*-{2-[(4a*S*,9b*S*)-6-Hydroxy-4,4a-dihydro-9b*H*-spiro(dibenzo[*b*,*d*]-furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*,4-dimethylbenzenesulfonamide (14):** A magnetically stirred solution of benzaldehyde **13** (300 mg, 0.64 mmol) in anhydrous dichloromethane (42 mL) was treated with *m*-CPBA (237 mg of 70% purity, 0.96 mmol). The resulting mixture was maintained at room temperature for 46 h, then quenched with NaS_2O_3 (10 mL of a 50% aqueous solution) and extracted with dichloromethane (3× 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, the ensuing brown oil dissolved in MeOH (56 mL) and the solution thus obtained treated with K_2CO_3 (884 mg, 6.4 mmol). The ensuing reaction mixture was kept at room temperature for 16 h, then concentrated under reduced pressure and the residue thus obtained treated with distilled water (30 mL) and extracted with dichloromethane (3× 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica gel; 1:4 v/v diethyl ether/dichloromethane elution). Concentration of the relevant fractions (R_f = 0.5) then gave phenol **14** (200 mg, 69%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.3 Hz, 2 H), 6.85–6.73 (complex m, 2 H), 6.68 (dd, J = 7.0 and 1.7 Hz, 1 H), 5.86 (d, J = 10.1 Hz, 1 H), 5.75 (d, J = 10.1 Hz, 1 H), 4.85 (dd, J = 7.7 and 5.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.06 (m, 1 H), 2.94 (m, 1 H), 2.68 (s, 3 H), 2.42 (s, 3 H), 2.17 (m, 2 H), 1.96 (m, 2 H) (signal due to phenolic group hydrogen obscured or overlapping) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 143.5, 141.4, 134.6, 132.4, 132.3, 129.8, 127.8, 127.5, 122.2, 116.0, 114.7, 103.9, 84.7, 65.0, 64.6, 48.6, 46.5, 37.3, 36.0, 35.3, 21.7 ppm. IR: $\tilde{\nu}_{max}$ = 3400, 2962, 2926, 2883, 1681, 1618, 1597, 1470, 1337, 1159, 1089, 1017, 946, 731, 549 cm^{-1}. MS (EI): m/z (%) = 457 (70) [M$^{+\cdot}$], 302 (62), 259 (51), 245 (80), 198 (100), 155 (87), 91 (97). HRMS (EI): calcd. for $C_{24}H_{27}NO_6S$ [M$^{+\cdot}$] 457.1559; found 457.1560.

***N*-{2-[(4a*S*,9b*S*)-*rel*-6-Methoxy-4,4a-dihydro-9b*H*-spiro(dibenzo-[*b*,*d*]furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*,4-dimethylbenzene-sulfonamide (15):** A magnetically stirred solution of phenol **14** (220 mg, 0.48 mmol) in anhydrous THF (12 mL) was cooled to 0 °C, treated with NaH (38 mg of a 60% dispersion in mineral oil, 0.96 mmol), kept at this temperature for 1 h and then treated with MeI (0.18 mL, 2.88 mmol) before being warmed to room temperature and stirred for 24 h. The ensuing mixture was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3× 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown oil was subjected to flash chromatography (silica gel; 1:2 v/v petroleum ether/ethyl acetate) to give, after concentration of the appropriate fractions (R_f = 0.6), methyl ether **15** (226 mg, quant.) as a colorless, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 6.87 (m, 1 H), 6.75 (m, 2 H), 5.91 (d, J = 10.1 Hz, 1 H), 5.76 (d, J = 10.1 Hz, 1 H), 4.83 (dd, J = 8.5 and 5.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.86 (s, 3 H), 3.08 (ddd, J = 13.7, 10.8 and 5.6 Hz, 1 H), 2.90 (ddd, J = 13.7, 10.8 and 5.6 Hz, 1 H), 2.67 (s, 3 H), 2.42 (s, 3 H), 2.20 (dd, J = 13.5 and 5.3 Hz, 1 H), 2.13 (dd, J = 13.5 and 8.5 Hz, 1 H), 1.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 145.3, 143.4, 134.7, 132.4 (4), 132.3 (6), 129.8, 128.4, 127.6, 121.9, 115.3, 111.9, 104.2, 84.6, 65.0, 64.7, 56.0, 48.4, 46.5, 38.0, 36.3, 35.3, 21.7 ppm. IR: $\tilde{\nu}_{max}$ = 2953, 2926, 1618, 1593, 1491, 1458, 1339, 1279, 1160, 1015, 951, 732 cm^{-1}. MS (EI): m/z (%) = 471 (80) [M$^{+\cdot}$], 316 (60), 259 (100), 216 (35), 198 (40), 155 (40), 91 (63). HRMS (EI): calcd. for $C_{25}H_{29}NO_6S$ [M$^{+\cdot}$] 471.1716; found 471.1717.

2-[(4a*S*,9b*S*)-*rel*-6-Methoxy-4,4a-dihydro-9b*H*-spiro(dibenzo[*b*,*d*]-furan-3,2′-[1,3]dioxolane)-9b-yl]-*N*-methylethan-1-amine (16): A magnetically stirred solution of methyl ether **15** (237 mg, 0.50 mmol) in anhydrous methanol (30 mL) was treated with magnesium turnings (425 mg, 17.5 mmol) and sonicated for 2 h. Further magnesium turnings (100 mg, 4.38 mmol) were added, and the resulting mixture was sonicated for an additional 2 h. This second addition/ultrasonication process was repeated a further six times. Then the reaction mixture was quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with ethyl acetate (3× 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 90:12:2 v/v/v dichloromethane/methanol/triethylamine elution) to give, after concentration of the appropriate fractions (R_f = 0.4), amine **16** (131 mg, 83%) as colorless, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (m, 1 H), 6.79–6.70 (complex m, 2 H), 5.89 (d, J = 10.0 Hz, 1 H), 5.72 (d, J = 10.0 Hz, 1 H), 4.93 (t, J = 6.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.86 (s, 3 H), 2.65–2.45 (complex m, 2 H), 2.38 (s, 3 H), 2.23 (d, J = 6.3 Hz, 2 H), 1.89 (t, J = 7.9 Hz, 2 H) (signal due to NH group proton not observed) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 145.2, 133.2 (6), 133.3 (1), 127.7, 121.7, 115.3, 111.7, 104.1, 84.8, 65.1, 64.7, 56.0, 48.5, 47.5, 39.4, 36.3, 36.1 ppm. IR: ῡmax = 2951, 2922, 2849, 2849, 1617, 1590, 1491, 1458, 1281, 1205, 1120 cm^{-1}. MS (EI): m/z (%) = 317 (47) [M$^{+\cdot}$], 272 (100), 59 (81). HRMS (EI): calcd. for $C_{18}H_{23}NO_4$ 317.1627 [M$^{+\cdot}$]; found 317.1628.

***N*-{2-[(4a*S*,9b*S*)-*rel*-6-Methoxy-4,4a-dihydro-9b*H*-spiro(dibenzo-[*b*,*d*]furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*-methylformamide (17):** A magnetically stirred solution of amine **16** (100 mg, 0.32 mmol) in ethyl formate (5 mL) was heated at reflux for 6 h. Then the cooled reaction mixture was concentrated under reduced pressure to afford formamide **17** (109 mg, quant.) as a yellow, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$; mixture of rotamers): δ = 7.96 (s, 1 H), 6.87–6.60 (complex m, 3 H), 5.93 (m, 1 H), 5.80 (m, 1 H), 4.94 (m, 1 H), 4.05–3.95 (complex m, 4 H), 3.88 (s, 1.68 H), 3.86 (s, 1.32 H),

3.45–3.30 (complex m, 1 H), 3.13 (m, 1 H), 2.87 (s, 1.32 H), 2.80 (s, 1.68 H) 2.26 (m, 1 H), 2.16–2.08 (complex m, 1 H), 1.99–1.80 (complex m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; mixture of rotamers): δ = 162.7, 162.4, 146.4, 146.3, 145.5, 145.3, 132.7, 132.4, 132.1, 132.0, 129.1, 128.5, 122.2, 121.9, 115.3, 114.9, 112.0, 111.9, 104.3, 104.2, 84.6, 84.5, 65.1, 65.0, 64.8, 64.7, 56.0 (8), 56.0 (5), 48.6, 48.4, 45.6, 40.7, 39.0, 36.5, 36.4, 36.3, 34.7, 29.7 ppm. IR: $\tilde{\nu}_{max}$ = 2956, 2927, 2883, 1671, 1617, 1589, 1491, 1458, 1397, 1281, 1207, 1118, 1013 952, 732 cm^{-1}. MS (EI): *m*/*z* (%) = 345 (90) [M$^{+\cdot}$], 286 (93), 259 (100), 241 (50), 215 (63). HRMS (EI): calcd. for $C_{19}H_{23}NO_5$ [M$^{+\cdot}$] 345.1576; found 345.1578.

(4a*S*,8a*S*)-*rel*-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-one (18) [(±)-Narwedine]: A magnetically stirred solution of formamide **17** (31.0 mg, 0.09 mmol) and 2-chloropyridine (26 μL, 0.27 mmol) in anhydrous dichloromethane (3 mL) was cooled to –78 °C and then treated dropwise with a solution of Tf_2O (37 μL, 0.23 mmol) in anhydrous dichloromethane (0.7 mL). The resulting solution was warmed to 0 °C, stirred at this temperature for 0.5 h, then warmed to room temperature and stirred for a further 20 h. The resulting mixture was then cooled to 0 °C and treated, portionwise, with $NaBH(OAc)_3$. After 0.17 h at 0 °C the reaction mixture was warmed to room temperature and maintained at this temperature for 2 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-narwedine (**18**) (11.2 mg, 44%) as a light-brown solid m.p. 185–187 °C (ref.[6] m.p. 187–190 °C). ^{1}H NMR (800 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 10.4 Hz, 1 H), 6.70 (d, *J* = 8.1 Hz, 1 H), 6.66 (d, *J* = 8.1 Hz, 1 H), 6.04 (dd, *J* = 10.4 and 1.0 Hz, 1 H), 4.73 (m, 1 H), 4.11 (d, *J* = 15.5 Hz, 1 H), 3.84 (s, 3 H), 3.75 (d, *J* = 15.5 Hz, 1 H), 3.25 (t, *J* = 13.7 Hz, 1 H), 3.16 (m, 2 H), 2.75 (dd, *J* = 17.9 and 3.5 Hz, 1 H), 2.44 (s, 3 H), 2.28 (td, *J* = 13.7 and 3.5 Hz, 1 H), 1.86 (d, *J* = 13.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 147.2, 144.5, 144.2, 130.7, 129.5, 127.3, 122.2, 112.1, 88.1, 60.8, 56.2, 54.3, 49.1, 42.5, 37.5, 33.4 ppm. IR: ῡmax = 2926, 2848, 1683, 1622, 1507, 1437, 1280, 1223, 1166, 1145, 1050, 1031, 1008, 802, 771 cm^{-1}. MS (EI): *m*/*z* (%) = 285 (100) [M$^{+\cdot}$], 284 (98), 242 (47), 174 (42), 84 (68), 58 (82). HRMS (EI): calcd. for $C_{17}H_{19}NO_3$ [M$^{+\cdot}$] 285.1365; found 285.1363.

(4a*S*,6*R*,8a*S*)-*rel*-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol [(±)-1] [(±)-Galanthamine]: A magnetically stirred solution of (±)-narwedine [(±)-**18**] (12.0 mg, 0.042 mmol) in anhydrous THF (2 mL) was cooled to –78 °C and then treated with L-selectride (0.13 mL of a 1 M solution in THF, 0.13 mmol). The resulting mixture was maintained at –78 °C for 3 h and then treated with water (1 mL) and NaOH (1 mL of a 3 M aqueous solution) before being extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil subjected to flash chromatography (silica gel, 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-galanthamine [(±)-**1**] (10 mg, 83%) as a light-brown, waxy solid. ^{1}H NMR (800 MHz, $CDCl_3$): δ = 6.66 (d, *J* = 8.1 Hz, 1 H), 6.63 (d, *J* = 8.1 Hz, 1 H), 6.06 (ddd, *J* = 10.3, 1.4 and 0.7 Hz, 1 H), 6.01 (ddd, *J* = 10.3, 5.1 and 1.4 Hz, 1 H), 4.61 (m, 1 H), 4.14 (m, 1 H), 4.10 (d, *J* = 15.4 Hz, 1 H), 3.83 (s, 3 H), 3.70 (dd, *J* = 15.4 and 0.7 Hz, 1 H), 3.28 (t, *J* = 13.5 Hz, 1 H), 3.06 (d, *J* = 14.3 Hz, 1 H), 2.69 (ddt, *J* = 15.7, 3.3 and 1.4 Hz, 1 H), 2.41 (s, 3 H), 2.09 (td, *J* = 13.5 and 3.3 Hz, 1 H), 2.01 (ddd, *J* = 15.7, 5.1 and 2.5 Hz, 1 H), 1.59 (dd, *J* = 13.5 and 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0, 144.3, 133.2, 129.2, 127.8, 126.9, 122.3, 111.4, 88.9, 62.2, 60.7, 56.1, 54.0, 48.4, 42.2, 33.9, 30.1 ppm. IR: $\tilde{\nu}_{max}$ = 3339, 2917, 2835, 1958, 1623, 1590, 1506, 1438, 1281, 1230, 1202, 1166, 1046 cm^{-1}. MS (EI): *m*/*z* (%) = 287 (90) [M$^{+\cdot}$], 286 (100), 270 (22), 244 (41), 216 (50), 174 (47). HRMS (EI): calcd. for $C_{17}H_{21}NO_3$ [M$^{+\cdot}$] 287.1521; found 287.1521.

Supporting Information (see footnote on the first page of this article): Tabular comparisons of the ^{13}C NMR spectroscopic data acquired on compounds **18** and (±)-**1** with those reported in the literature. ^{1}H and ^{13}C NMR spectra of compounds **4**, **6**–**18** and (±)-**1** and a comparison of the ^{1}H NMR spectrum of synthetically derived (±)-galanthamine with that recorded on an authentic sample of (–)-galanthamine.

Acknowledgments

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. J. N. is grateful to the Australian Government for an APA scholarship. Professor Rod Bates (NTU, Singapore) is warmly thanked for stimulating discussions and helpful suggestions.

[1] For useful points-of-entry into the literature on the history, chemistry and pharmacology of galanthamine, see: a) M. Heinrich, H. L. Teoh, *J. Ethnopharmacol.* **2004**, *92*, 147; b) J. Marco-Contelles, M. do Carmo Carreiras, C. Rodríguez, M. Villarroya, A. G. García, *Chem. Rev.* **2006**, *106*, 116; c) L. Marco, M. do Carmo Carreiras, *Recent Pat. CNS Drug Discovery* **2006**, *1*, 105; d) M. Heinrich, *Alkaloids* **2010**, *68*, 157.

[2] For a fascinating commentary on its introduction into Japan, see: M. Takeda, T. Tanaka, M. Okochi, *Psychiatry Clin. Neurosci.* **2011**, *65*, 399.

[3] A. K. Hamouda, T. Kimm, J. B. Cohen, *J. Neurosci.* **2013**, *33*, 485 and references cited therein.

[4] a) M. I. Stanilova, E. D. Molle, S. G. Yanev, *Alkaloids* **2010**, *68*, 167; b) A. Schumann, L. Torras-Claveria, S. Berkov, D. Claus, A. Gerth, J. Bastida, C. Codina, *Biotechnol. Prog.* **2013**, *29*, 311; c) J. Eichhorn, T. Takada, Y. Kita, M. H. Zenk, *Phytochemistry* **1998**, *49*, 1037; d) S. Berkov, I. Ivanov, V. Georgiev, C. Codina, A. Pavlov, *Eng. Life Sci.* **2014**, *14*, 643.

[5] G. Appendino, *Angew. Chem. Int. Ed.* **2014**, *53*, 927; *Angew. Chem.* **2014**, *126*, 943.

[6] D. H. R. Barton, G. W. Kirby, *J. Chem. Soc.* **1962**, 806.

[7] See, for example: a) M. Node, S. Kodama, Y. Hamashima, T. Baba, N. Hamamichi, K. Nishide, *Angew. Chem. Int. Ed.* **2001**, *40*, 3060; *Angew. Chem.* **2001**, *113*, 3150; b) J. M. Reddy, K. V. Kumar, V. Raju, B. V. Bhaskar, V. Himabindu, A. Bhattacharya, V. Sundaram, R. Banerjee, G. M. Reddy, R. Bandichhor, *Synth. Commun.* **2008**, *38*, 2138; c) M. Node, T. Kajimoto, M. Ozeki, *Heterocycles* **2010**, *81*, 1061.

[8] a) K. Shimizu, K. Tomioka, S.-i. Yamada, K. Koga, *Heterocycles* **1977**, *8*, 277; b) S. Kodama, Y. Hamashima, K. Nishide, M. Node, *Angew. Chem. Int. Ed.* **2004**, *43*, 2659; *Angew. Chem.* **2004**, *116*, 2713.

[9] a) B. Küenburg, L. Czollner, J. Fröhlich, U. Jordis, *Org. Process Res. Dev.* **1999**, *3*, 425; b) L. Czollner, M. Treu, J. Froehlich, B. Kueenburg, U. Jordis, *ARKIVOC* **2001**, *1*, 191.

[10] a) B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785 and references cited therein; b) V. Satcharoen, N. J. McLean, S. C. Kemp, N. P. Camp, R. C. D. Brown, *Org. Lett.* **2007**, *9*, 1867; c) J.-Q. Chen, J.-H. Xie, D.-H. Bao, S. Liu, Q.-L. Zhou, *Org. Lett.* **2012**, *14*, 2714; d) Y. Zang, I. Ojima, *J. Org. Chem.* **2013**, *78*, 4013; e) J. Choi, H. Kim, S. Park, J. Tae, *Synlett* **2013**, *24*, 379.

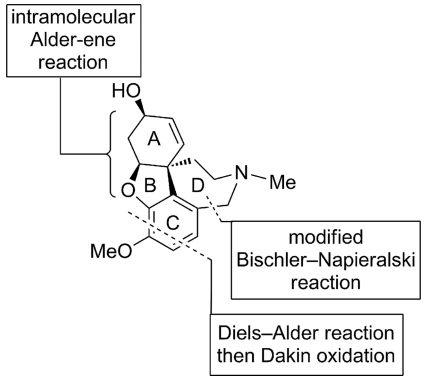
[11] See, for example: a) X.-D. Hu, Y. Q. Tu, E. Zhang, S. Gao, S. Wang, A. Wang, C.-A. Fan, M. Wang, *Org. Lett.* **2006**, *8*, 1823; b) T. Ishikawa, K. Kudo, K. Kuroyabu, S. Uchida, T. Kudoh, S. Saito, *J. Org. Chem.* **2008**, *73*, 7498; c) P. Magnus, N. Sane, B. P. Fauber, V. Lynch, *J. Am. Chem. Soc.* **2009**, *131*, 16045; d) J. H. Chang, H.-U. Kang, I.-H. Jung, C.-G. Cho, *Org. Lett.* **2010**, *12*, 2016; e) P. Chen, X. Bao, L.-F. Zhang, M. Ding, X.-J. Han, J. Li, G.-B. Zhang, Y.-Q. Tu, C.-A. Fan, *Angew. Chem. Int. Ed.* **2011**, *50*, 8161; *Angew. Chem.* **2011**, *123*, 8311; f) Y. Feng, Z.-X. Yu, *J. Org. Chem.* **2015**, *80*, 1952.
[12] a) T. Kato, H. Tanimoto, H. Yamada, N. Chida, *Heterocycles* **2010**, *82*, 563; b) N. Chida, T. Sato, *Chem. Rec.* **2014**, *14*, 592.
[13] M. G. Banwell, X. Ma, O. Karunaratne, A. C. Willis, *Aust. J. Chem.* **2010**, *63*, 1437.
[14] For some representative and seminal studies, see: a) S.-Y. Han, S. C. Mayer, E. J. Schweiger, B. M. Davis, M. M. Joullié, *Bioorg. Med. Chem. Lett.* **1991**, *1*, 579; b) A. Mary, D. Z. Renko, C. Guillou, C. Thal, *Tetrahedron Lett.* **1997**, *38*, 5151; c) H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen, M. D. Shair, *J. Am. Chem. Soc.* **2001**, *123*, 6740; d) P. Jia, R. Sheng, J. Zhang, L. Fang, Q. He, B. Yang, Y. Hu, *Eur. J. Med. Chem.* **2009**, *44*, 772; e) S. Santra, P. R. Andreana, *Angew. Chem. Int. Ed.* **2011**, *50*, 9418; *Angew. Chem.* **2011**, *123*, 9590; f) A. Yan, K. Wang, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3336.
[15] C. S. Beshara, A. Hall, R. L. Jenkins, K. L. Jones, T. C. Jones, N. M. Killeen, P. H. Taylor, S. P. Thomas, N. C. O. Tomkinson, *Org. Lett.* **2005**, *7*, 5729.
[16] C. A. Sperger, J. E. Tungen, A. Fiksdahl, *Eur. J. Org. Chem.* **2011**, 3719.
[17] A. Kamatami, L. E. Overman, *J. Org. Chem.* **1999**, *64*, 8743.
[18] A. L. Lehmann, A. C. Willis, M. G. Banwell, *Aust. J. Chem.* **2010**, *63*, 1665.
[19] B. M. Trost, C. Pedregal, *J. Am. Chem. Soc.* **1992**, *114*, 7292.
[20] L. Petit, M. G. Banwell, A. C. Willis, *Org. Lett.* **2011**, *13*, 5800.
[21] J. Liu, S. Ma, *Synthesis* **2013**, *45*, 1624.
[22] B. Nyasse, L. Grehn, U. Ragnarsson, *Chem. Commun.* **1997**, 1017.
[23] M. Movassaghi, M. D. Hill, *Org. Lett.* **2008**, *10*, 3485.
[24] W.-C. Shieh, J. A. Carlson, *J. Org. Chem.* **1994**, *59*, 5463.
[25] G. N. Trinadhachari, A. G. Kamat, K. R. Babu, P. D. Sanasi, K. J. Prabahar, *Tetrahedron: Asymmetry* **2014**, *25*, 117.
[26] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[27] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.

Received: March 19, 2015
Published Online: ■

EurJOC European Journal of Organic Chemistry

Natural Products

The first synthesis of the alkaloid galanthamine is reported in which the aromatic C-ring is assembled from non-aromatic precursors. This was accomplished by a Diels–Alder cycloaddition reaction. The diene used embodies the AB-ring system (and associated quaternary carbon centre) and was constructed by intramolecular Alder-ene and Tsuji–Trost-type chemistries. The D-ring was closed by a modified Bischler–Napieralski reaction.



Keywords: Natural products / Total synthesis / Alkaloids / Alder-ene reactions / Diels–Alder reactions / Cycloaddition

