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Synthesis of chiral oxa- and azacycle-fused anthraquinone derivatives

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ABSTRACT

A convenient protocol for the synthesis of chiral pyran and piperidine ring-fused anthraquinone derivatives has been developed from (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde using sequential applications of enyne metathesis, Diels–Alder reaction and aromatization as key steps.

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1. Introduction

Anthraquinones embellished with a carbocyclic or heterocyclic ring are important compounds due to their natural occurrence and impressive levels of biological activities including antiproliferative properties.[1] Anthracyclines[2] and anthrapyran antibiotics[3] broadly represent the two different classes of such compounds. Because of their importance, extensive synthetic efforts have been expended over several decades towards their syntheses. Moreover, a large number of simplified analogues of natural anthraquinones have been synthesized and evaluated.[4] A notable feature of some important members belonging to these two classes is the presence of a chiral side chain attached to the carbocyclic or heterocyclic ring appended to the anthraquinone nucleus, for example, in compounds such as doxorubicin[5] **1**, espicofulin[6] **2** and pluraflavin A[7] **3** (Fig. 1). In continuation of our work on the synthesis of analogues of anthracyclines,[8] herein we describe a synthetic route to two oxa- and azacycle-fused chiral anthraquinone derivatives of the type **4** which combines some of the structural features of **1–3**.

2. Results and discussion

Our synthesis started from (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde **5** (Scheme 1) which on treatment with allylzinc bromide, following literature precedent,[9] provided the known homoallyl alcohol **6** as the major product. The latter upon alkylation with propargyl bromide led to smooth formation of the corresponding ether **7**. We surmised that a metathesis reaction[10] of the oxygen-tethered enyne **7** should provide access to the corresponding vinylcycloalkene **9** onto which an anthraquinone moiety could possibly be built upon through a Diels–Alder reaction with 1,4-naphthoquinone. Accordingly, compound **7** was treated with Grubbs' first generation catalyst[11] benzylidene bistricyclohexylphosphinoruthenium(IV) dichloride **8** in refluxing benzene. The reaction proceeded well to provide the desired diene **9** as only isolable product but in somewhat moderate yield (58%). The Diels–Alder cycloaddition of vinylcycloalkenes has been extensively studied both as a convenient means for assembling complex architectures and a mechanistic probe for testing *endo–exo* selectivity.[12] We observed that cycloaddition of **9** with 1,4-naphthoquinone proceeded smoothly in refluxing toluene to provide the cycloadduct **10** in good yield but as an inseparable mixture of isomers, presumably as *exo*- and *endo*-diastereoisomers.[13] Moreover, compound **10** degraded considerably during attempted purification by silica gel chromatography. However, this mixture of isomers could be effectively aromatized by treatment with triethylamine in the presence of silica gel under aerobic conditions. The desired anthraquinone derivative **11** was obtained in a 47% yield over a two-step one-pot conversion. Deprotection of the cyclohexylidene group in compound **11** proceeded uneventfully under conventional conditions and the diol **12** was obtained as a yellowish amorphous powder in very good yield. The synthesis of the chiral anthrapyran derivative **12** proceeded in an overall yield of 10.1% over six steps starting from **5**.

We then concentrated on the preparation of an aza-analogue of compound **12** from the common intermediate **6**. Thus, the latter was converted to the corresponding mesylate **13** (Scheme 2) and thence to the azide **14** under conventional conditions. Reduction of the azido group in **14** with $LiAlH_4$ proceeded smoothly and the intermediate crude amine was treated with *p*-toluenesulfonyl chloride to prepare the corresponding *p*-toluenesulfonamide derivative **15** which was obtained in a combined yield of 74% over two steps. N-Alkylation of the latter with propargyl bromide using NaH as a base then neatly provided the *N*-tethered enyne derivative **16** in very good yield. The sequence of events described for the preparation of the anthrapyran derivative **12** from the enyne **7** was then repeated on compound **16**. Thus, ring-closing metathesis of **16** with the catalyst **8** proceeded sluggishly in refluxing benzene and the vinylcycloalkene derivative **17** was obtained as the only isolable product in an acceptable yield (64%).

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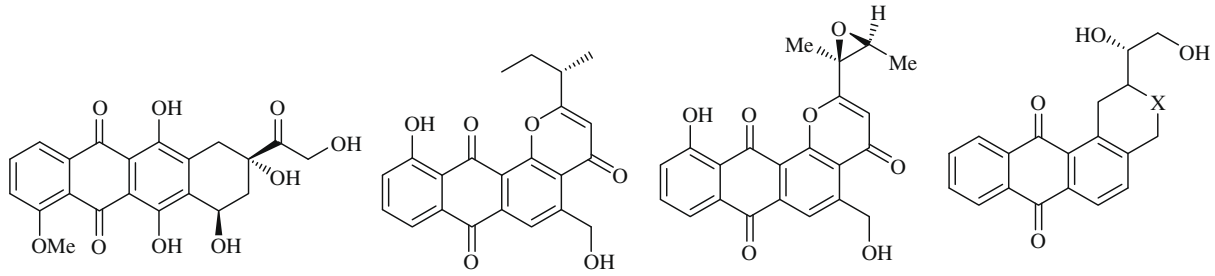
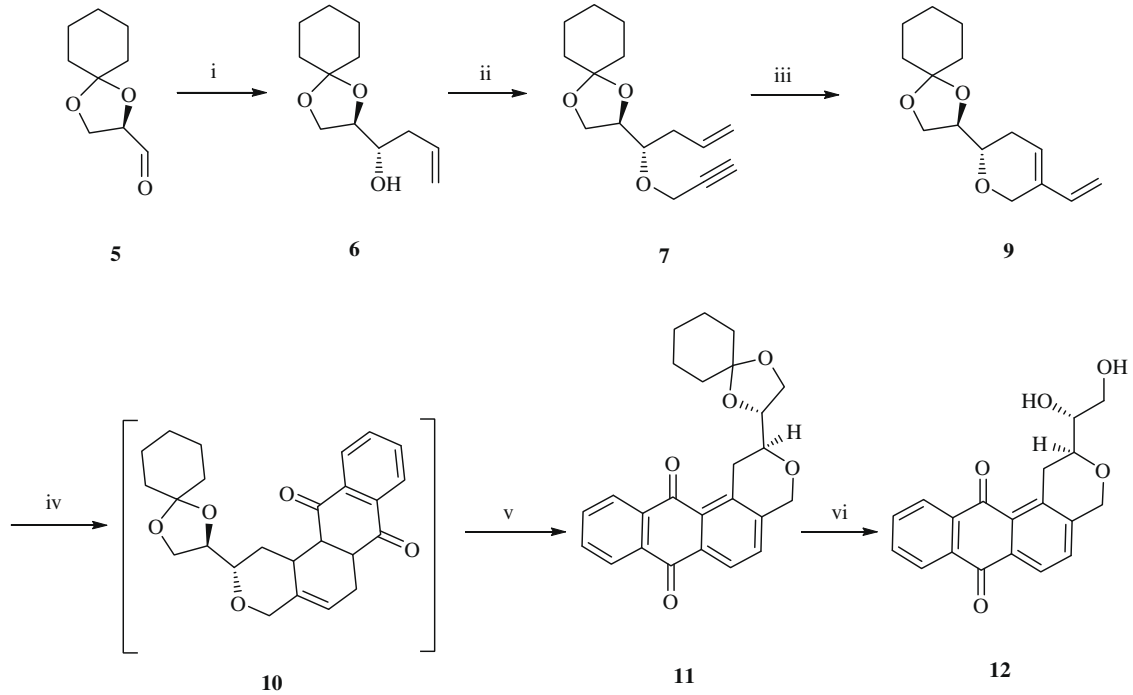


doxorubicin **1** espicufolin **2** pluraflavin A **3** **4**, X = O, NR

Figure 1.



Scheme 1. Reagents and conditions: (i) allyl zincbromide, THF, 0 °C to rt, 12 h; (ii) NaH, propargyl bromide, THF + DMSO, 0 °C to rt, 18 h; (iii) Grubbs' catalyst **8** (5 mol %), benzene, reflux, 20 h; (iv) 1,4-naphthaquinone, benzene, reflux, 24 h; (v) Et_3N, silica gel, O_2 (air),$CHCl_3$, rt, 7 h; (vi) HCl, THF, rt, 5 h.

Diels–Alder reaction of the latter with 1,4-naphthoquinone similarly provided the cycloadduct **18** also as a mixture of inseparable diastereomers. Subsequent aromatization of the latter using the Et_3N/silica gel protocol then neatly provided the corresponding anthraquinone derivative **19**. Acid-catalyzed deprotection of the cyclohexylidene moiety in the latter then liberated the diol **20**. The synthesis of the piperidine ring-fused anthraquinone derivative **20** from the common intermediate **6** proceeded in an overall yield of 9.5% over eight steps.

3. Conclusion

In brief, we have developed a concise synthetic route to chiral pyran and piperidine ring-fused anthraquinone derivatives of resemblance to some notable natural products. The methodology involves use of easily available starting materials, less expensive reagents and easy to perform experiments. The compounds prepared may prove to be biologically relevant and the methodology may prove to be adaptable for the synthesis of similar compounds.

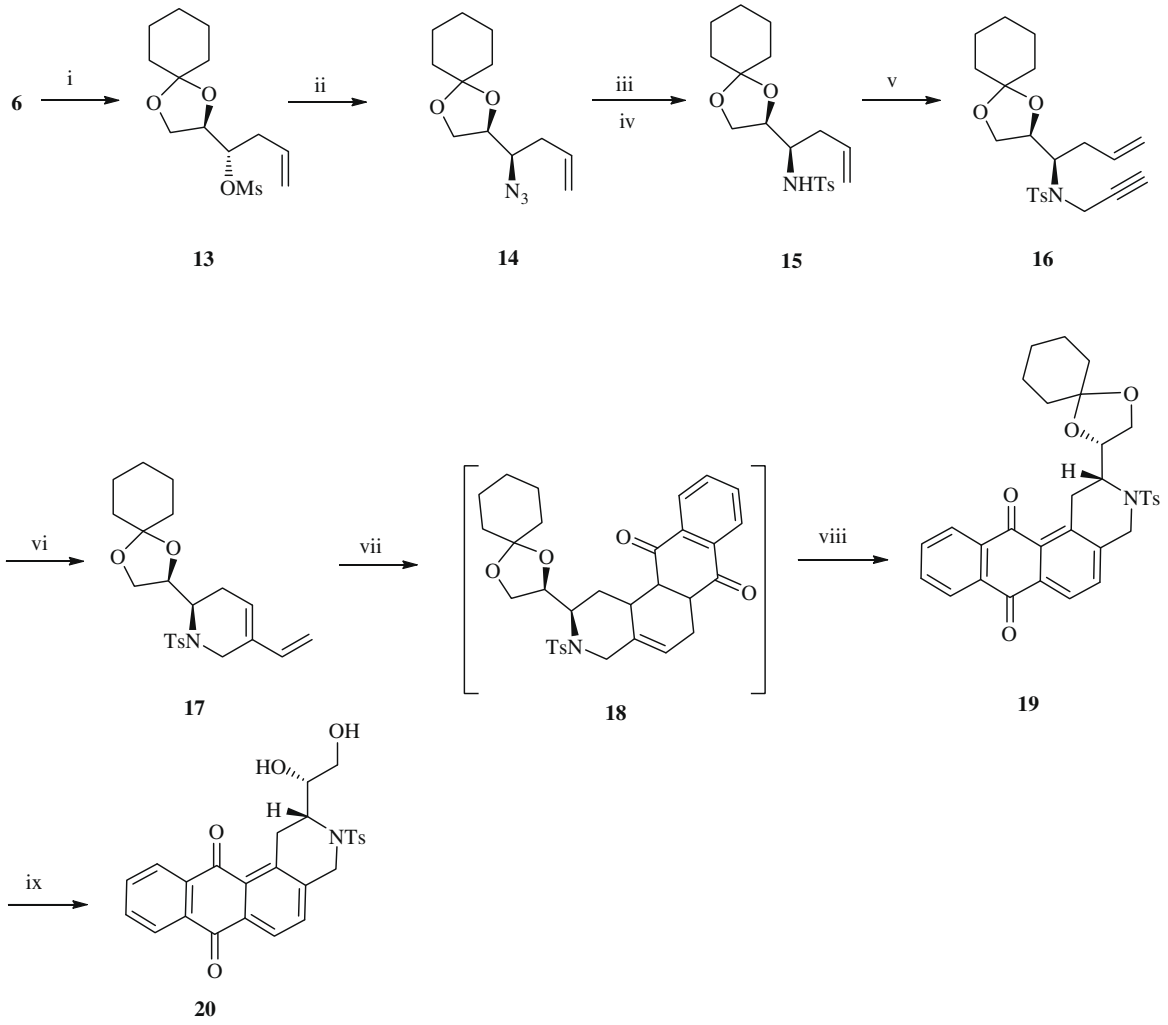
4. Experimental

4.1. General

Optical rotations were recorded in spectroscopic grade chloroform on a Jasco DIP-370 polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer Spectrum-1 spectrophotometer purchased through a DST-FIST grant. Proton and carbon NMR spectra were recorded on a Bruker DRX-300 spectrometer as a paid service from I.I.C.B., Kolkata. Chemical shifts are recorded relative to residual solvent or TMS as a standard. Mass spectra were recorded on a JEOL-JMS 600 instrument from I. I. C. B., Kolkata or IACS, Kolkata. Petroleum ether refers to the fraction boiling in the range 60–80 °C. Silica gel (60–120 mesh) for column chromatography was purchased from Spectrochem, India.

4.1.1. (1*S*)-1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-butenyl (2-propynyl) ether 7

A solution of **6** (0.40 g, 1.88 mmol) in dry THF (5 ml) was added dropwise to a stirred suspension of NaH (0.14 g, 5.83 mmol) in a



Scheme 2. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 24 h; (ii) NaN_3, DMF, 80 °C, 36 h; (iii) $LiAlH_4$, Et_2O, 0 °C to rt, 8 h; (iv) TsCl, pyridine, CH_2Cl_2, rt, 18 h; (v) NaH, propargyl bromide, THF + DMSO, 0 °C to rt, 18 h; (vi) Grubbs' catalyst **8** (5 mol %), benzene, reflux, 24 h; (vii) 1,4-naphthaquinone, benzene, reflux, 24 h; (viii) Et_3N, silica gel, O_2 (air), $CHCl_3$, rt, 7 h; (ix) HCl, THF, rt, 9 h.

mixture of anhydrous THF + DMSO (20 ml, 10:1) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and stirred for 40 min. A solution of propargyl bromide (0.34 g, 2.9 mmol) in anhydrous THF (2 ml) was then added dropwise to the reaction mixture at 0 °C and stirring was continued for 18 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C and then the reaction mixture was extracted with ethyl acetate (2 × 25 ml). The combined organic layer was washed with water (2 × 20 ml) and brine (20 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave the crude product which on chromatography (silica gel, ethyl acetate–petroleum ether, 1:19) provided the product **7** as a colourless liquid (0.367 g, 78%). $[\alpha]_D$ = +24 (*c* 0.13, $CHCl_3$). IR (neat): 3302, 2936, 2117, 1641, 1099 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.92–5.83 (1H, m), 5.15–5.07 (2H, m), 4.27 (2H, s), 4.07–3.99 (2H, m), 3.96–3.88 (1H, m), 3.70–3.59 (1H, m), 2.42 (1H, t, *J* = 2.5), 2.38–2.33 (2H, m), 1.61–1.56 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 117.6, 109.7, 80.0, 78.2, 76.6, 74.3, 65.9, 57.6, 36.2, 35.4, 34.9, 25.2, 24.0, 23.8. MS (TOF MS ES+): *m*/*z* (%) = 273 (M^++Na, 100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.19; H, 8.99.

4.1.2. (2*R*)-2-[(2*S*)-5-Vinyl-3,6-dihydro-2*H*-2-pyranyl]-1,4-dioxaspiro[4.5]decane 9

Grubbs' catalyst **8** (16 mg, 5 mol %) was added to a stirred solution of the propargyl ether **7** (0.10 g, 0.4 mmol) in dry degassed benzene (10 ml), under an argon atmosphere and the homogeneous mixture was heated at reflux for 20 h. It was then concentrated in vacuo to leave a crude product which on chromatography (silica gel, ethyl acetate–petroleum ether, 1:9) provided the product **9** as a colourless liquid (0.058 g, 58%). $[\alpha]_D$ = +12 (*c* 0.09, $CHCl_3$). IR (neat): 2935, 1651, 1606, 1101 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.25 (1H, dd, *J* = 11.0, 18.0), 5.85 (1H, br s), 4.94 (1H, d, *J* = 11.0), 4.89 (1H, d, *J* = 18.0), 4.45–4.26 (2H, m), 4.10–4.02 (3H, m), 3.95–3.93 (2H, m), 3.46–3.39 (1H, m), 1.59–1.40 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 134.7, 125.2, 110.8, 109.9, 77.5, 74.9, 66.9, 65.4, 36.4, 34.8, 28.0, 25.1, 24.0, 23.8. MS (TOF MS ES+): *m*/*z* (%) = 273 (M^++Na, 100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.26; H, 9.02.

4.1.3. (2*S*)-2-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]-1,4,7,12-tetrahydro-2*H*naphtho[2,3-*f*]isochromene-7,12-dione 11

A solution of the diene **9** (0.054 g, 0.22 mmol) and 1,4-naphthaquinone (0.041 g, 0.26 mmol) in anhydrous benzene (4 ml) was

heated at reflux for 24 h. It was then concentrated in vacuo to leave a crude product which was taken in anhydrous $CHCl_3$ (2 ml). The resulting solution was then stirred with silica gel (60–120 mesh, 1.5 g) and Et_3N (0.44 g, 4.3 mmol) under aerobic conditions for 7 h. It was then filtered and the filtrate was concentrated in vacuo to leave a crude product which on chromatography (silica gel, ethyl acetate–petroleum ether, 1:9) provided the product **11** as a pale yellow solid (0.041 g, 47%), mp 182–183 °C. $[\alpha]_D = -19$ (*c* 0.12, $CHCl_3$). IR (KBr): 2932, 1670, 1286 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.13 (2H, dd, *J* = 5.5, 8.5), 8.07 (1H, d, *J* = 8.0), 7.90–7.87 (2H, m), 7.56 (1H, d, *J* = 8.0), 4.93 (1H, d, *J* = 16.0) 4.86 (1H, d, *J* = 16.0), 4.13–4.09 (2H, m), 3.91 (1H, dd, *J* = 4.5, 7.5), 3.58–3.55 (2H, m), 3.07 (1H, dd, *J* = 11.5, 18.5), 1.61–1.51 (8H, m), 1.09–1.06 (2H, m). ^{13}C NMR (125 MHz, DMSO-d_6): δ 186.0, 184.1, 144.2, 137.4, 136.1, 135.8, 135.5, 134.5, 133.6, 132.1, 131.8, 128.4, 127.6, 126.4, 110.8, 78.7, 76.5, 69.3, 67.5, 37.4, 36.0, 32.4, 26.2, 25.2, 25.0. HRMS (FAB): *m*/*z* calcd for $C_{25}H_{24}O_5$ (M^+): 404.1624. Found: 404.1622.

4.1.4. (2*S*)-2-[(1*R*)-1,2-Dihydroxyethyl]-1,4,7,12-tetrahydro-2*H*-naphtho[2,3-*f*]isochromene-7,12-dione 12

A solution of the acetal derivative **11** (0.05 g, 0.12 mmol) in tetrahydrofuran (3 ml) was stirred with HCl (6 N, 3 ml) for 5 h at room temperature. It was then diluted with water (10 ml) and the precipitated solid was filtered, washed with H_2O (10 ml) and dried in vacuo. It was then recrystallized from methanol to provide the product **12** as a pale yellow solid (0.028 g, 71%), mp 235–237 °C. $[\alpha]_D = -6$ (*c* 0.75, DMF). IR (KBr): 3357, 1668, 1587, 1326, 1288 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.14 (2H, d, *J* = 2.0), 8.08 (1H, d, *J* = 8.0), 7.92–7.90 (2H, m), 7.58 (1H, d, *J* = 8.0), 4.98–4.92 (2H, m), 4.86–4.80 (1H, m), 4.59 (1H, t, *J* = 5.5), 3.62–3.57 (5H, m), 3.19 (1H, dd, *J* = 10.0, 19.0). ^{13}C NMR (100 MHz, DMSO-d_6): δ 184.5, 182.7, 142.9, 137.0, 134.5, 134.4, 133.9, 133.0, 132.1, 130.6, 130.1, 126.8, 126.1, 124.7, 74.6, 73.6, 67.9, 62.8, 29.4. MS (TOF MS ES+): *m*/*z* (%) = 347 (M^++Na, 100). Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.49; H, 5.12.

4.1.5. (1*S*)-1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-butenyl methanesulfonate 13

Methanesulfonyl chloride (0.6 ml, 7.75 mmol) was added dropwise to a stirred solution of the alcohol **6** (0.81 g, 3.82 mmol) and triethylamine (1.1 ml, 7.89 mmol) in dry dichloromethane (4 ml) under nitrogen at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 24 h. It was then diluted with H_2O (25 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic layer was washed successively with HCl (1 M, 2 × 50 ml), H_2O (2 × 50 ml) and brine (50 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude product which on chromatography (silica gel, ethyl acetate–petroleum ether, 1:19) provided the product **13** as a colourless liquid (0.964 g, 87%). $[\alpha]_D = +19$ (*c* 0.12, $CHCl_3$). IR (neat): 2938, 1364, 1177, 929 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.91–5.77 (1H, m), 5.23–5.17 (2H, m), 4.79 (1H, q, *J* = 6.0), 4.19 (1H, q, *J* = 6.5), 4.05 (1H, t, *J* = 8.5), 3.91 (1H, dd, *J* = 7.0, 8.0), 3.05 (3H, s), 2.52 (2H, t, *J* = 7.0), 1.59–1.40 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.0, 119.4, 110.4, 80.7, 75.3, 64.9, 38.8, 36.3, 36.0, 34.7, 25.0, 23.9, 23.7. MS (TOF MS ES+): *m*/*z* (%) = 313 (M^++Na, 100). Anal. Calcd for $C_{13}H_{22}O_5S$: C, 53.77; H, 7.64. Found: C, 53.91; H, 7.78.

4.1.6. (1*R*)-1-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-butenyl azide 14

Sodium azide (0.23 g, 3.54 mmol) was added to a stirred solution of the mesylate **13** (0.50 g, 1.72 mmol) in dry DMF (5 ml), under nitrogen and the reaction mixture was stirred at 80 °C for 36 h. It was allowed to come to room temperature, diluted with water (25 ml) and then extracted with diethyl ether (3 × 25 ml). The combined organic layer was washed successively with H_2O (2 × 25 ml) and brine (25 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified by column chromatography on silica gel (ethyl acetate–petroleum ether, 1:49) to provide the product **14** as a colourless liquid (0.29 g, 71%). $[\alpha]_D = -25$ (*c* 0.1, $CHCl_3$). IR (neat): 2937, 2112, 1102, 927 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.88–5.79 (1H, m), 5.22–5.14 (2H, m), 4.13 (1H, q, *J* = 6.5), 4.04 (1H, dd, *J* = 6.5, 8.5), 3.77 (1H, dd, *J* = 6.5, 8.0), 3.3 (1H, q, *J* = 6.5), 2.35–2.30 (2H, m), 1.72–1.57 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.3, 118.4, 110.5, 77.5, 66.0, 62.7, 36.0, 35.2, 34.7, 25.1, 23.9, 23.8. MS (TOF MS ES+): *m*/*z* (%) = 260 (M^++Na, 100).

4.1.7. (1*R*)-1-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-butenyl-4-methyl-1-benzene-sulfonamide 15

A solution of the azide **14** (2.37 g, 10.0 mmol) in dry ether (12 ml) was added dropwise over 25 min to a suspension of lithium aluminium hydride (0.76 g, 20 mmol) in dry ether (12 ml) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and stirred for 8 h. It was cooled to 0 °C and then slowly quenched with aqueous NaOH solution (2.5 M, 10 ml). The ether layer was separated and the thick aqueous layer was triturated with ether (25 ml). The combined organic extract was washed successively with H_2O (2 × 25 ml) and brine (25 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude product. The latter was dissolved in dichloromethane (50 ml) and then treated with *p*-toluenesulfonyl chloride (2.28 g, 12 mmol) and dry pyridine (1.5 ml, 18.5 mmol) at room temperature for 18 h. The reaction mixture was then washed successively with HCl (1 M, 2 × 25 ml), H_2O (2 × 25 ml) and brine (25 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified by column chromatography on silica gel (ethyl acetate–petroleum ether, 1:9) to provide the product **15** as a viscous liquid (2.70 g, 74% over two steps). $[\alpha]_D = +3.3$ (*c* 0.5, $CHCl_3$). IR (neat): 3286, 2934, 1642, 1330, 1162 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* = 8.0), 7.30 (2H, d, *J* = 8.0), 5.60–5.54 (1H, m), 5.00–4.94 (2H, m), 4.70 (1H, d, *J* = 7.5), 4.14 (1H, dt, *J* = 3.0, 6.5), 3.89 (1H, dd, *J* = 6.5, 8.5), 3.59 (1H, dd, *J* = 7.0, 8.5), 3.31–3.24 (1H, m), 2.43 (3H, s), 2.36–2.31 (1H, m), 2.19–2.17 (1H, m), 1.57–1.38 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 137.7, 133.3, 129.6, 127.0, 118.6, 109.8, 75.3, 65.5, 53.8, 37.2, 35.8, 34.4, 25.0, 23.9, 23.6, 21.5. MS (TOF MS ES+): *m*/*z* (%) = 388 (M^++Na, 100). Anal. Calcd for $C_{19}H_{27}NO_4S$: C, 62.44; H, 7.44; N, 3.83. Found: C, 62.59; H, 7.60; N, 4.01.

4.1.8. *N*1-{(1*R*)-1-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-butenyl-*N*1-(2-propynyl)-4-methyl-1-benzenesulfonamide 16

A solution of **15** (0.2 g, 0.55 mmol) in dry THF (1 ml) was added to a stirred suspension of NaH (0.02 g, 0.82 mmol) in a mixture of dry THF + DMSO (5 ml, 10:1), dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and stirred for 45 min. A solution of propargyl bromide (0.42 g, 3.5 mmol) in dry THF (1 ml) was then added dropwise at 0 °C and the reaction mixture was stirred for 18 h at room temperature. It was then slowly quenched with saturated aqueous NH_4Cl solution (5 ml) at 0 °C, diluted with H_2O (20 ml) and extracted with ethyl acetate (2 × 25 ml). The combined organic layer was washed with H_2O (2 × 20 ml) and brine (20 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure to leave a crude product which was purified by column chromatography on silica gel (ethyl acetate–petroleum ether, 1:19) to provide the product **16** as a colourless liquid (0.196 g, 89%). $[\alpha]_D = +27$ (*c* 0.1, $CHCl_3$). IR (neat): 3290, 2936, 2121, 1642, 1340, 1161 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (2H , d, *J* = 8.0), 7.26 (2H, d, *J* = 8.0 Hz), 5.71–5.60 (1H, m), 5.08–

4.99 (2H, m), 4.31 (2H, dd, J = 2.5, 6.0), 4.26–4.19 (1H, m), 3.98–3.87 (2H, m), 3.76 (1H, t, J = 8.0), 2.45–2.42 (5H, m), 2.12 (1H, t, J = 2.5), 1.61–1.36 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 137.4, 134.0, 129.1, 127.8, 118.0, 109.4, 79.5, 75.6, 72.8, 66.2, 58.3, 35.9, 34.6, 34.5, 34.1, 25.0, 23.8, 23.7, 21.4. MS (TOF MS ES+): m/z (%) = 426 (M^++Na, 100). Anal. Calcd for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.64; H, 7.37; N, 3.54.

4.1.9. (2*R*)-2-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-1-[(4-methylphenyl)sulfonyl]-5-vinyl-1,2,3,6-tetrahydropyridine 17

Catalyst **8** (15 mg, 5 mol %) was added to a stirred solution of the enyne **16** (0.15 g, 0.37 mmol) in dry and degassed benzene (10 ml) under an argon atmosphere and the homogeneous mixture was heated at reflux for 24 h. It was then concentrated in vacuo to leave a crude product which was purified by column chromatography on silica gel (ethyl acetate–petroleum ether, 1:19) to provide the product **17** as a colourless liquid (0.096 g, 64%). $[\alpha]_D$ = −41 (c 0.15, $CHCl_3$). IR (neat): 2935, 1652, 1334, 1161 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (2H, d, J = 8.0), 7.23 (2H, d, J = 8.0), 6.20 (1H, dd, J = 11.0, 18.0), 5.61 (1H, d, J = 3.5), 5.08–4.94 (2H, m), 4.37 (1H, d, J = 18.0), 4.21–4.05 (2H, m), 3.97 (1H, dd, J = 6.0, 8.0), 3.87–3.79 (1H, m), 3.69 (1H, dd, J = 6.0, 8.0), 2.42–2.31 (4H, m), 1.85 (1H, dd, J = 3.5, 19.0), 1.59–1.52 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 136.1, 132.3, 129.6, 129.4, 127.0, 124.5, 118.6, 111.6, 74.5, 66.5, 52.4, 40.5, 36.0, 34.7, 25.7, 25.1, 23.9, 23.8, 21.4. MS (TOF MS ES+): m/z (%) = 426 (M^++Na, 100). Anal. Calcd for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.59; H, 7.39; N, 3.58.

4.1.10. (2*R*)-2-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-[(4-methylphenyl)sulfonyl]-1,2,3,4,7,12-hexahydro-naphtho[2,3-*f*]isoquinolin-7,12-dione 19

A solution of the diene **17** (0.075 g, 0.186 mmol) and 1,4-naphthaquinone (0.032 g, 0.20 mmol) in dry benzene (4 ml) was heated at reflux for 24 h. It was then cooled and concentrated in vacuo to leave a crude product which was dissolved in dry chloroform (2 ml). The resulting solution was stirred with silica gel (60–120 mesh, 1.4 g) and Et_3N (0.50 ml, 3.6 mmol) under aerobic conditions for 7 h. It was then concentrated in vacuo to leave a crude product which was purified by column chromatography on silica gel (ethyl acetate–petroleum ether, 1:9) to provide the product **19** as a yellowish solid (0.049 g, 48%), mp 105–106 °C. $[\alpha]_D$ = +1 (c 0.1, $CHCl_3$). IR (KBr): 2934, 1668, 1360, 1161 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18–8.12 (2H, m), 8.08 (1H, d, J = 8.0), 7.74–7.68 (2H, m), 7.55 (2H, d, J = 8.0), 7.32 (1H, d, J = 8.0), 7.03 (2H, d, J = 8.0), 4.70 (1H, d, J = 17.0), 4.55 (1H, d, J = 17.0), 4.27–4.23 (1H, m), 4.11–4.02 (1H, m), 3.95–3.89 (1H, m), 3.86–3.84 (1H, m), 3.55 (1H, dd, J = 7.0, 18.5), 3.37 (1H, dd, J = 3.0, 18.5), 2.16 (3H, s), 1.59–1.48 (4H, m), 1.42–1.33 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3 (s), 183.0 (s), 143.4 (s), 140.6 (s), 136.8 (s), 136.5 (s), 134.7 (s), 134.3 (d), 134.0 (s), 133.8 (d), 132.5 (s), 131.3 (d), 131.0 (s), 129.5 (d), 127.4 (d), 127.3 (d), 126.7 (d), 125.7 (d), 110.3 (s), 76.7 (d), 66.3 (t), 52.8 (d), 45.7 (t), 35.9 (t), 34.7 (t), 28.4 (t), 25.1 (t), 23.9 (t), 23.8 (t), 21.3 (q). MS (TOF MS ES+): m/z (%) = 580 (M^++Na, 100). Anal. Calcd for $C_{32}H_{31}NO_6S$: C, 68.92; H, 5.60; N, 2.51. Found: C, 69.09; H, 5.71; N, 2.67.

4.1.11. (2*R*)-2-[(1*S*)-1,2-Dihydroxyethyl]-3-[(4-methylphenyl)-sulfonyl]-1,2,3,4,7,12-hexahydro-naphtho[2,3-*f*]isoquinolin-7,12-dione 20

A solution of the acetal derivative **19** (0.05 g, 0.09 mmol) in THF (3 ml) was stirred with HCl (6 N, 3 ml) for 9 h at room temperature. It was then diluted with H_2O (10 ml) and extracted with ethyl acetate (2 × 25 ml). The combined organic extract was washed sequentially with aqueous $NaHCO_3$ solution (10%, 2 × 20 ml), H_2O (20 ml) and brine (20 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified by column chromatography on silica gel (ethyl acetate–petroleum ether, 3:7) to provide the product **20** as a yellowish solid (0.033 g, 76%), mp 131–132 °C. $[\alpha]_D$ = +22 (c 0.1, $CHCl_3$). IR (KBr): 3425, 1670, 1592, 1327, 1284, 1159 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25–8.22 (1H, m), 8.19–8.16 (2H, m), 7.82–7.75 (2H, m), 7.56 (2H, d, J = 8.0), 7.45 (1H, d, J = 8.0), 7.10 (2H, d, J = 8.0), 4.79 (1H, d, J = 17.0), 4.66 (1H, d, J = 17.0), 4.31–4.25 (1H, m), 3.84–3.81 (1H, m), 3.69–3.59 (2H, m), 3.54 (1H, dd, J = 4.0, 18.0), 3.38 (1H, dd, J = 7.0, 18.0), 2.19 (3H, s), 1.83 (2H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.2, 182.8, 143.9, 140.3, 136.3, 135.7, 134.6, 134.3, 134.0, 133.9, 132.5, 131.5, 130.8, 130.0, 129.7, 127.2, 126.7, 125.9, 72.6, 63.3, 53.3, 46.0, 27.3, 21.3. MS (TOF MS ES+): m/z (%) = 477 (27), 499 (M^+−1+Na, 100), 500 (M^++Na, 47). Anal. Calcd for $C_{26}H_{23}NO_6S$: C, 65.39; H, 4.85; N, 2.93. Found: C, 65.56; H, 4.97; N, 3.14.

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