Alkyne Zip Reaction in the Synthesis of a Taxoid C-Ring

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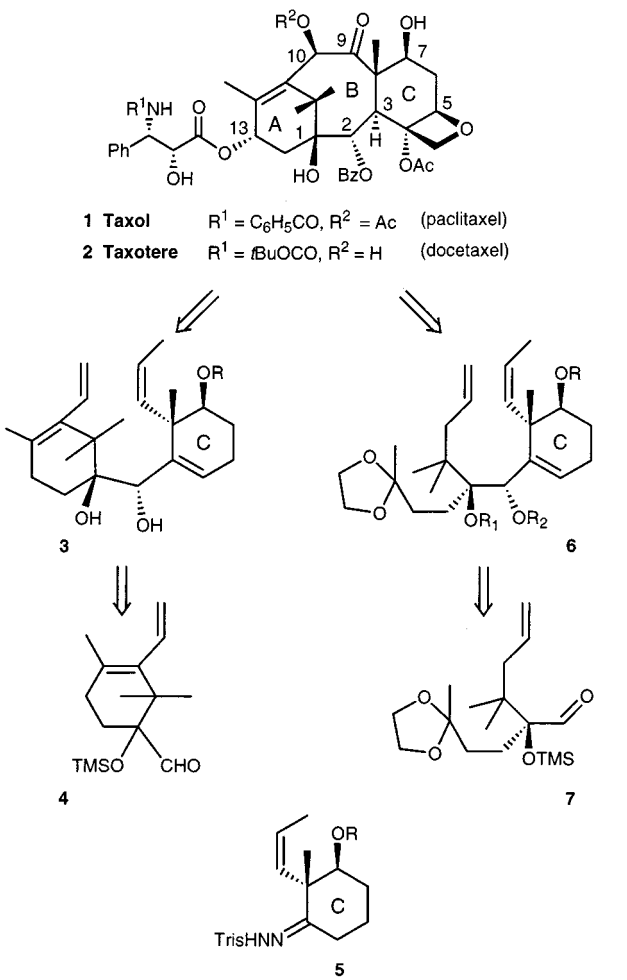
Hydrazone **30**, precursor of a taxoid C-ring, was synthesized in 7 steps from commercial 2-methyl-1,3-cyclohexanedione. An enantioselective approach to **30** was also investigated, using a reduction of diketone **11** with bakers' yeast to introduce enantioselectivity. During the alkyne isomerization step, anionic cyclizations of alkoxides and enolates onto the triple bond were observed, and a thorough study of these reactions is reported here.

Introduction

In our studies directed towards the total synthesis of antitumor agents taxol® (**1**) and taxotere® (**2**)[1,2] we planned a convergent retrosynthesis in which the key step was an olefin metathesis to form the B-ring of these molecules (Scheme 1). In a preceding paper,[3] we described the preparation of *seco*-taxane **3** by coupling the vinyllithium derived from hydrazone **5** with aldehyde **4**, by a Shapiro reaction. The diol formation was completely diastereoselective and adduct **3** was obtained with the desired stereochemistry for taxol at C-1 and C-2. Unfortunately, all attempts at metathesis with derivatives of diol **3** were unsuccessful.[4] We then turned our attention to a semiconvergent retrosynthesis, in which the A-ring would be assembled during the last steps by a pinacol coupling between ketone moieties at C11 and C12.[2e] Formation of the eight-membered B-ring would still be effected by an olefin metathesis reaction.[5] A similar Shapiro reaction between hydrazone **5** and acyclic aldehyde **7** was envisaged for the formation of *seco*-taxane **6** (Scheme 1).

We wish to describe here an efficient, enantioselective synthesis of ketone **8**, precursor of hydrazone **5**, from the easily accessible diketone **11** (Scheme 2). The nontrivial isomerization step of **10** into **9**, which led to side products through anionic cyclizations of alkoxide and enolate intermediates onto the alkyne function, is reported in detail.



Scheme 1

Results and Discussion

Alkylation of commercial 1,3-diketone **12** furnished diketo propargylic derivative **11** (Scheme 3).[6] The expected enantiopure hydroxy ketone **13** was obtained in >95% *ee* according to the method of Brooks,[7] by enantioselective reduction using bakers' yeast. The isolated yield of **13** on a large scale was only 33%, due to an arduous extraction followed by a difficult separation from the starting diketone, the other diastereomer (**13/14** = 3:1) and the diol resulting from overreduction.

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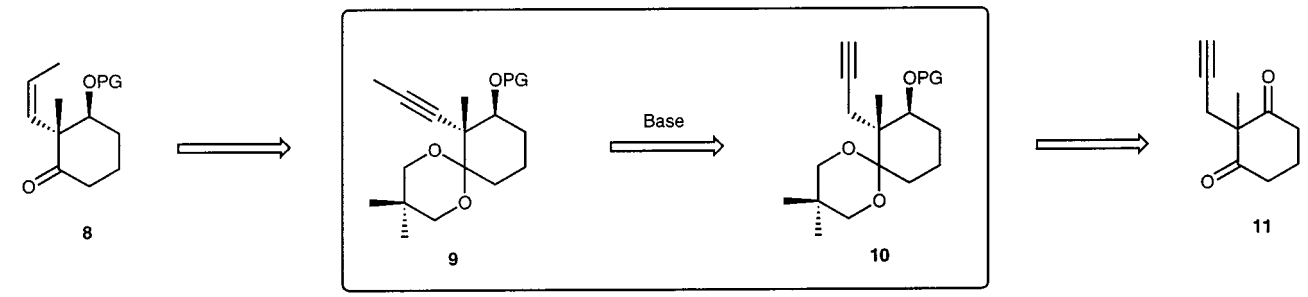
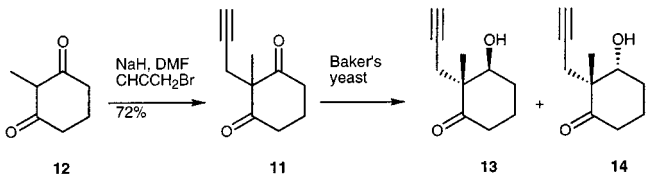
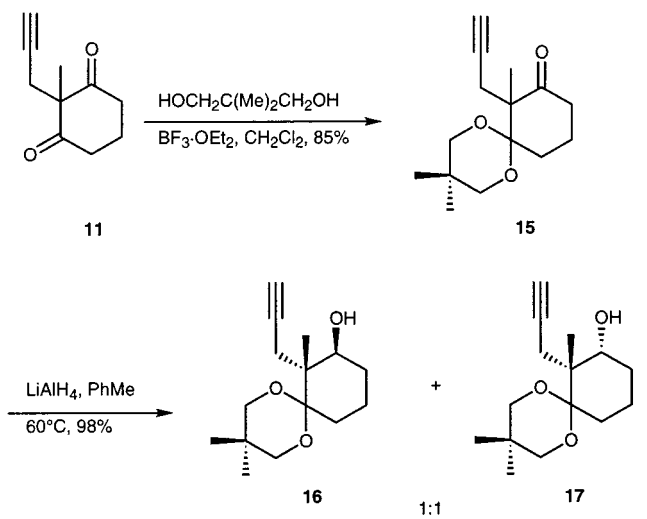


Scheme 2



Scheme 3

We therefore decided to look into an efficient preparation, from diketone **11**, of the racemic alkoxy derivative **10**, and to explore its conversion into **9**. Monoketalization of **11** gave ketone **15**; conversion did not exceed 70%, but the product crystallized out of the reaction mixture and it was possible to recycle the mother liquors, thus giving the desired product in 85% yield after 3 cycles. This monoketone was then reduced under various different conditions;[8] the best result was finally obtained with $LiAlH_4$ in toluene, furnishing a 1:1 mixture of the expected derivative **16** and its diastereomer **17** (Scheme 4). Both structures were assigned by extensive NMR study.

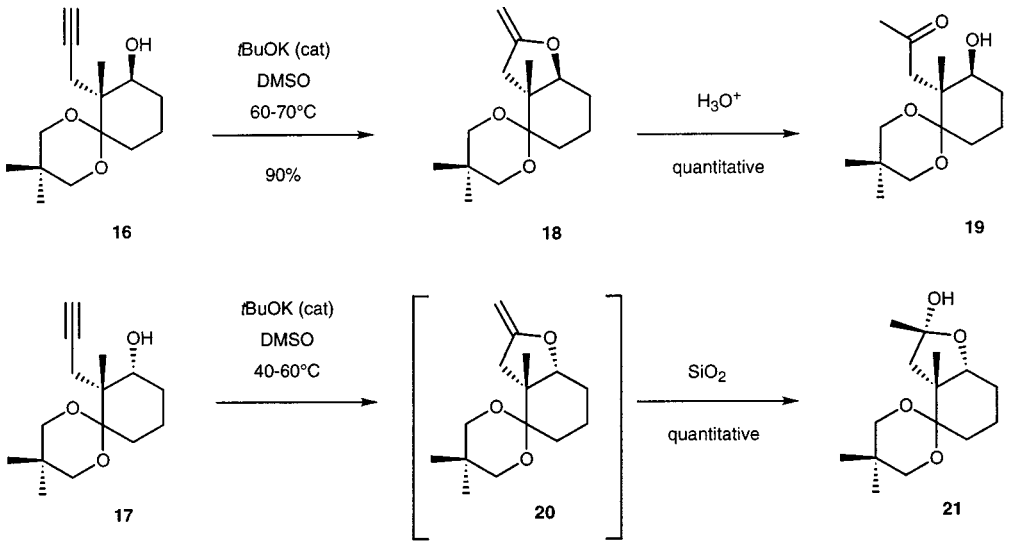


Scheme 4

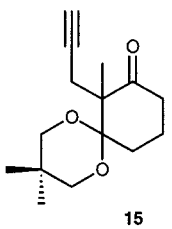
When treated with a catalytic amount of *t*BuOK in DMSO,[9] alcohol **16** did not produce the expected isomerized alkyne. However, enol ether **18** could be isolated in 90% yield after rapid flash chromatography (Scheme 5). Hydrolysis of **18** in acidic media led to hydroxy ketone **19** (existing in an open form). The same treatment was also applied, at a slightly lower temperature, to isomer **17**, and resulted in an unstable product which, after hydrolysis on silica gel, produced lactol **21**.[10] Hence, the intermediate product was assigned, from its ^1H and ^{13}C NMR spectra, as enol ether **20**. The mechanism leading to these products is discussed later in this paper.

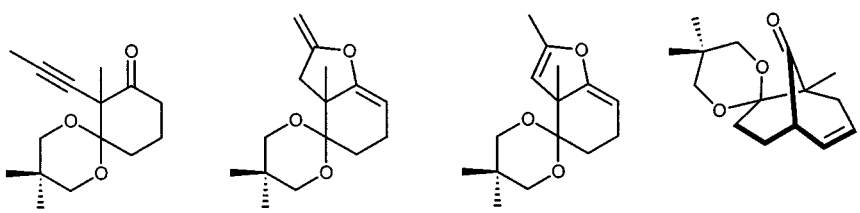
In order to avoid the anionic cyclization of the alkoxide onto the alkyne during the basic treatment needed for the isomerization, we decided to protect the free alcohol as a silyl ether. However, the only reaction observed on treatment of the corresponding TBS ether with *t*BuOK in DMSO was deprotection of the silyl ether, followed by anionic cyclization of the resulting alkoxide. We next examined the case of ketone **15**.[11] Treatment of **15** with *t*BuOK in DMSO at room temperature required a stoichiometric amount of base, and afforded the cyclic products **23**, **24**, and **25**. The desired acetylenic isomer **22** was not detected (Scheme 6). Use of KH in DMF led to compounds **23**, **24**, and **25** in poor yields, because of extensive degradation. However, when this reaction was carried out under the same conditions, except with diisopropylamine added as a proton source, acetylenic product **22** was produced in 52% yield. Compounds **23** and **24** were isolated in 8% and 4% yields, respectively, while bicyclo derivative **25** was not detected in this case. Having revealed the importance of the proton source, we reverted to the previous conditions (*t*BuOK in DMSO), with addition of *t*BuOH. Under these conditions, reaction was complete within one hour; the expected acetylenic product **22** was obtained, but only in a 35% yield, along with 35% of **23**. The moderate yields observed for these reactions are due to degradation of compound **22** in basic media; **22** has a half-life of 6 hours at room temperature under *t*BuOK/DMSO conditions (none of the other isomers **23**, **24**, **25**, or even **15** were detected in this case).

Formation of compounds **18** and **20** can be explained by attack of the oxygen atom of the intermediate alkoxides onto the triple bond. Cyclizations of alcohols on triple bonds have been thoroughly studied. The method most often used to effect such a reaction involves either stoichiometric salts of (for example) Ag, Hg, or W,[12] or catalytic amounts of palladium catalysts.[13] An anionic cyclization similar to ours had already been reported by Heathcock in the synthesis of dihydromevinolin[14] and a mechanism has been proposed, for the case of a phenolate, by Kirby.[15] However, this reaction has seldom been used, although it does not require any expensive or toxic reagent and it proceeds under mild conditions.



Scheme 5





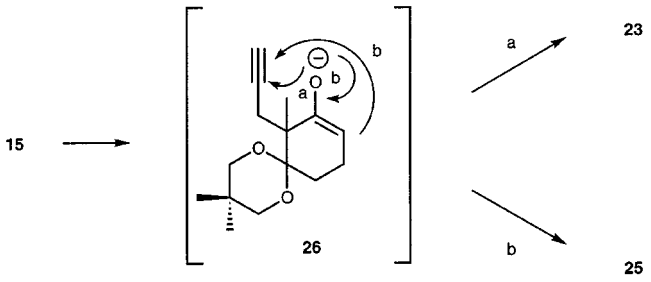
Conditions	22	23	24	25
*t*BuOK / DMSO, 20°C	/	50%	10%	7%
KH / DMF, 40°C	/	6%	20%	15%
KH / DMF / DIPA, 40°C	**52%**	**8%**	**4%**	/
*t*BuOK/ *t*BuOH / DMSO, 20°C	35%	35%	/	/

Scheme 6

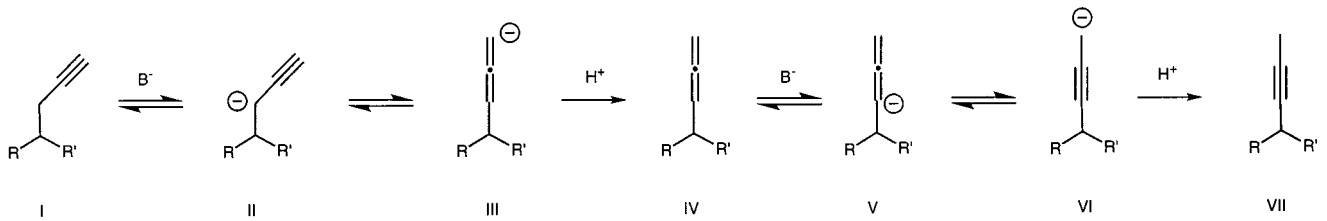
Compound **23** results from a cyclization of the oxygen atom of the intermediate enolate **26** onto the triple bond.[16] Endocyclic alkene **24** is not a product of cyclization of the isomerized alkyne **22** (vide supra), but might derive from an isomerization of a precursor of **23**, or from direct isomerization of **23** (Scheme 7, path a). All attempts to induce isomerization of **23** into **24** resulted either in degradation or in recovery of the starting material,[17] and we therefore suppose isomerization occurs on the intermediate vinylic anion before reprotonation. For the methyl-1-bicyclo[3.3.1]-nonane **25**, we also assume intermediate formation of the enolate, followed by C-cyclization on the triple bond (Scheme , path b). To the best of our knowledge, such an anionic C-cyclization of an enolate is unprecedented.

We have shown that addition of a proton source prevents these cyclization reactions and promotes triple bond isomerization. This could be rationalized with the mechanism proposed below. A proton source appears to be necessary to shift the I−II−III anionic equilibrium towards formation of allene IV; the second anionic equilibrium V−VI might then lead after protonation to the expected isomeric compound VII (Scheme 8).[18]

In order to achieve an efficient preparation of the target ketone **8**, we decided to protect the secondary alcohol of **16**

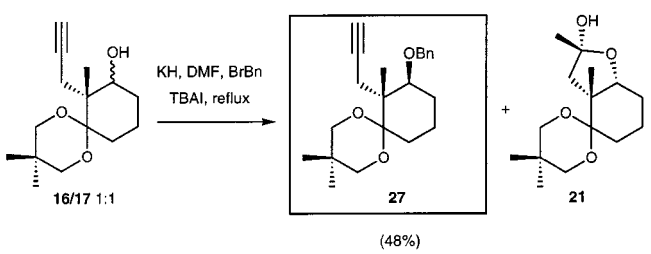


Scheme 7



Scheme 8

with a benzyl ether: a group commonly used for the C7 alcohol function of taxol.[2a] Protection proved to be tricky; use of NaH in THF led to less than 10% conversion into the protected product, while use of KH in DMF led to complete cyclization. Finally, however, protection of a 1:1 mixture of the two alcohols **16** and **17** using KH and BnBr in refluxing THF with a catalytic amount of TBAI was found to deliver benzyl derivative **27**, as a pure isomer, in 48% yield (Scheme 9). This result clearly illustrates the difference in reactivity between the two diastereomers; under these conditions, isomer **17** produces lactol **21**, while the alkoxide derived from isomer **16** does not cyclize and can hence be protected in very good yield. This route proved to be practical on large scale (e.g., 10 g) as the laborious separation of **16** and **17** by column chromatography was avoided (see the Experimental Section for details).

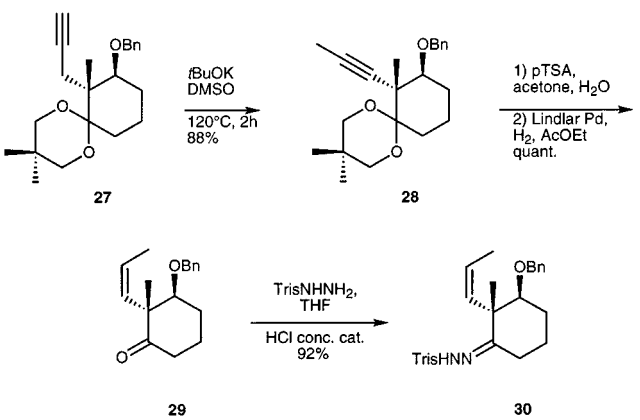


Scheme 9

Compound **27** required drastic conditions (stoichiometric *t*BuOK, 120 °C in DMSO) for isomerization, but the expected acetylenic derivative **28** was produced in 88% yield after purification. The desired ketone **29** was obtained after hydrolysis of the ketal moiety and partial hydrogenation of the triple bond with Lindlar's catalyst (Scheme 10). Hydrazone **30** was then obtained in 92% yield.

It is noteworthy that *t*BuOH did not facilitate the isomerization of **27** much (a temperature of 120 °C was still necessary). However, in the presence of *t*BuOH, a substoichiometric amount of *t*BuOK was sufficient and the reaction was much cleaner, with fewer side products resulting from DMSO decomposition. The harsh conditions required for the isomerization process might be attributed to the difference in conformation between the sp^2 and sp^3 substituted cyclohexanes, which might position the methylene moiety of the propargyl side chain in a hindered position.

In conclusion, we have shown that anionic cyclizations of an alkoxide or an enolate onto a triple bond constitute an



Scheme 10

easy route to furan derivatives, and proved that this reaction could be utilized advantageously for the diastereoselective synthesis of derivative **27**, by differentiating between diastereomers **16** and **17**. We have also demonstrated that the isomerization of alkyne **27** to give alkyne **28** can be effected, although under harsh conditions, leading to a C-ring precursor for the synthesis of taxol®.

Experimental Section

General Remarks: All air- and/or water-sensitive reactions were carried out under argon atmosphere with dry, freshly distilled solvents, using standard syringe-cannula/septa techniques. All corresponding glassware was oven-dried (110 °C) and/or carefully dried in line with a flameless heat gun.

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker WP 200 (200 MHz) or on a Bruker AM 400 (400 MHz) instrument. The chemical shifts are expressed in parts per million = referenced to

residual chloroform (δ = 7.27). H,H-COSY and H,H-NOESY experiments were routinely performed to ascertain H−H connectivities and configuration assignments, respectively. ^{13}C NMR spectra were recorded on the same instruments at 50.3 MHz and 100.6 MHz, respectively. ^{13}C NMR chemical shifts are expressed in parts per million (ppm), reported from the central peak of deuteriochloroform (δ = 77.14). *J*-modulated spin-echo technique (*J*-mod) experiments were used for evaluating CH multiplicities.

Mass spectra (MS) were obtained on a Hewlett−Packard HP 5989B spectrometer, either by direct introduction (chemical ionisation, CI, NH_3) or by GC/MS coupling with a Hewlett-Packard HP 5890 chromatograph. − Infrared spectra (IR) were obtained on a Perkin−Elmer FT 1600 instrument, using NaCl salt plates (thin film) and are reported in terms of absorption frequency ($\tilde{\nu}$, cm^{-1}). − Microanalyses were performed by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, C.N.R.S., F-91198, Gif sur Yvette. − Flash chromatography was performed on E. Merck silica gel Si 60 (40−63 mm, ref. 9385).

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone, methanol from magnesium methoxide.

3,3,7-Trimethyl-7-prop-2-ynyl-1,5-dioxaspiro[5.5]undecan-8-one (15): To a solution of diketone **11** (17.1 g, 0.10 mmol) and 2,2-dimethylpropane-1,3-diol (15.6 g, 0.15 mmol) in CH_2Cl_2 (300 mL) was added $BF_3{\cdot}OEt_2$ (1.2 mL, 10 mol-%). The pink solution was stirred at 20 °C for 2 h, quenched with triethylamine (10 mL), and concentrated in vacuo. The resulting crude solid was triturated with ether (50 mL), and filtered. The white paste was successively washed with ethanol (2 × 25 mL) and ether (50 mL) to yield 13.3 g (51%) of **15** as a white solid. Repetition of the above procedure on the mother liquors yielded successively 5.7 g (22%) and 2.9 g (11%) of **15** (total yield 84%). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.62 (t, 2 H, *J* = 11.4 Hz, 2-H_a, 4-H_a), 3.34 (dt, 2 H, *J* = 11.0, 2.5 Hz, 2-H_b, 4-H_b), 2.83 (dd, 1 H, *J* = 17.0, 2.7 Hz, 1′-H), 2.58 (dd, 1 H, *J* = 17.0, 2.8, 1′-H), 2.53−2.36 (br. m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 1.95 (t, 1 H, *J* = 2.7, 3′-H), 1.68 (m, 2 H, CH_2), 1.37 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 0.72 (s, 3 H, CH_3-3). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 209.7 (8), 101.9 (6), 81.7 (2′), 58.0 (7), 70.2 (2, 4), 70.1 (3′), 36.8 (9), 29.7 (3), 23.3, 22.3 (2 C, CH_3-3), 22.3 (1′), 21.1 (10, 11), 16.1 (CH_3-7). − IR (thin film): 3239, 2870, 1717, 1395, 1124, 1080. − MS (CI, NH_3): *m*/*z* 268 (MNH_4^+), 251 (MH^+).

(7*R,8*S**)-3,3,7-Trimethyl-7-prop-2-ynyl-1,5-dioxaspiro[5.5]undecan-8-ol (16). Starting from Ketone 15. − Sodium Borohydride Reduction:** To a solution of **15** (300 mg, 1.2 mmol) in MeOH/CH_2Cl_2, 2:1, (10 mL) was added portionwise sodium borohydride (90 mg, 2.4 mmol). The resulting solution was stirred at 20 °C for 4 h, then diluted with ether (50 mL) and quenched with a saturated, aqueous NH_4Cl solution (5 mL). The phases were separated, and the organic layer was washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 10:90) to yield 66 mg (22%) of pure **16** as a white solid (m.p. 95−97 °C), 157 mg (52%) of pure **17** as a white solid (m.p. 110−112 °C) and 40 mg (13%) of a mixture of **16** and **17**.

Lithium Aluminium Hydride Reduction: See preparation of compound **27**.

From Alcohol 13: To a solution of hydroxy ketone **13** (500 mg, 3.0 mmol) and 2,2-dimethyl-1,3-propanediol (626 mg, 6.0 mmol) in CH_2Cl_2 (10 mL) over 3-Å molecular sieves was added $BF_3{\cdot}OEt_2$ (37 μL, 0.3 mmol). The resulting mixture was stirred at 20 °C for 15 h, then filtered, diluted with ether (100 mL), and quenched with a saturated, aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with ether (50 mL), and the combined organic layers were washed successively with water (2 × 10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: Et_2O/petroleum ether, 30:70) to yield 541 mg (71%) of **16** and 96 mg (19%) of recovered starting material **13**. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.01 (dt, 1 H, *J* = 6.9, 3.6 Hz, 8-H), 3.66 (d, 1 H, *J* = 11.3 Hz, 2,4-H_a), 3.61 (d, 1 H, *J* = 11.4 Hz, 2,4-H_a), 3.36 (dd, 1 H, *J* = 11.3, 2.6 Hz, 2,4-H_b), 3.26 (dd, 1 H, *J* = 11.4, 2.4 Hz, 2,4-H_b), 3.30 (brs, 1 H, OH), 2.56 (d, 2 H, *J* = 2.4 Hz, 1′-H), 2.04 (t, 1 H, *J* = 2.8 Hz, 3′-H), 1.76−1.41 (br. m, 6 H, CH_2), 1.25, 1.17 (2s, 6 H, CH_3-3, CH_3-7), 0.72 (s, 3 H, CH_3-3). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 101.0 (6), 82.8 (2′), 73.5 (8), 70.8, 69.8, 69.1 (2, 4, 3′), 46.0 (7), 29.8 (3), 28.6 (1′), 23.9 (9), 23.3, 22.2 (2C, CH_3-3), 21.1 (10), 17.2 (11), 14.4 (CH_3-7). − IR (thin film): 3519, 3305, 2953, 2869, 2114, 1470, 1395, 1122, 1066, 1027. − MS (CI, NH_3): *m*/*z* 270 (MNH_4^+), 253 (MH^+), 235. − $C_{15}H_{24}O_3$ (252.4): calcd. C 71.39, H 9.58; found C 71.22, H 9.53.

(7*R,8*R**)-3,3,7-Trimethyl-7-prop-2-ynyl-1,5-dioxaspiro[5.5]undecan-8-ol (17). − From Alcohol 14:** To a solution of hydroxy ketone **14** (300 mg, 1.8 mmol) and 2,2-dimethyl-1,3-propanediol (375 mg, 3.6 mmol) in CH_2Cl_2 (6 mL) over 3 Å molecular sieves was added $BF_3{\cdot}OEt_2$ (20 μL, 0.15 mmol). The resulting mixture was stirred at 20 °C for 15 h, then filtered, diluted with ether (50 mL) and quenched with a saturated, aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with ether (50 mL), and the combined organic layers were washed successively with water (2 × 10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 30:70) to yield 320 mg (70%) of **17** and 59 mg (20%) of recovered starting material **14**. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.89 (dt, 1 H, *J* = 10.9, 3.0 Hz, 8-H), 3.69 (d, 1 H, *J* = 17.5 Hz, 2,4-H_a), 3.66 (d, 1 H, *J* = 17.3 Hz, 2,4-H_a), 3.57 (brd, 1 H, *J* = 10.9 Hz, OH), 3.37 (dd, 1 H, *J* = 10.3, 2.6 Hz, 2,4-H_b), 3.27 (dd, 1 H, *J* = 10.3, 2.6 Hz, 2,4-H_b), 3.07 (dd, 1 H, *J* = 16.7, 2.8 Hz, 1′-H), 2.54 (dt, 1 H, *J* = 14.0, 2.9 Hz, 9-H_{eq}), 2.50 (dd, 1 H, *J* = 16.7, 2.7 Hz, 1′-H), 1.96 (t, 1 H, *J* = 2.7 Hz, 3′-H), 1.78−1.51 (br. m, 4 H, H-10, 11-H), 1.37 (td, 1 H, *J* = 13.9, 4.5 Hz, 9-H_{ax}), 1.15 (s, 3 H, CH_3-3), 1.12 (d, 3 H, *J* = 0.6 Hz, CH_3-7), 0.72 (s, 3 H, CH_3-3). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 101.4 (6), 82.8 (2′), 72.6 (8), 69.7, 69.6, 69.1 (2, 4, 3′), 45.0 (7), 29.8 (3), 28.2 (1′), 23.3, 22.2 (2C, CH_3-3), 21.6, 21.1 (9, 10), 19.0 (CH_3-7), 16.5 (11). − IR (thin film): 3498, 3228, 2958, 2869, 2114, 1469, 1444, 1417, 1114, 1067, 1014, 913. − MS (CI, NH_3): *m*/*z* 270 (MNH_4^+), 253 (MH^+), 235. − $C_{15}H_{24}O_3$ (252.4): calcd. C 71.39, H 9.58; found C 71.27, H 9.59.

(3a*R,7a*S**)-3a,3′,3′-Trimethyl-2-methylene-2,3,5,6,7,7a-hexahydrospiro[benzofuran-4,2′-[1,3]dioxane] (18):** To a solution of **16** (50 mg, 0.2 mmol) in DMSO (1 mL) was added *t*BuOK (4 mg, ca. 0.2 equiv.). The resulting mixture was stirred at 60 °C for 15 h, then cooled to room temperature, diluted with ether (50 mL) and quenched with a saturated, aqueous NH_4Cl solution (5 mL). The layers were separated, and the organic layer was washed with water (3 × 5 mL) and brine (10 mL), then dried with $MgSO_4$ and concentrated in vacuo. The crude product was quickly purified by flash chromatography on silica gel (Et_2O/petroleum ether, 50:50) to yield 45 mg (90%) of **18**. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.26 (s, 1 H, CH_2-2), 3.98 (dd, 1 H, *J* = 18.2, 8.4 Hz, 7a-H), 3.95 (s, 1 H, CH_2-2), 3.63 (d, 1 H, *J* = 15.1 Hz, 4′,6′-H_a), 3.60 (d, 1 H, *J* = 14.6 Hz, 4′,6′-H_a), 3.35 (dd, 1 H, *J* = 15.0, 1.3 Hz, 4′,6′-H_b), 3.30

(dd, 1 H, J = 14.7, 1.2 Hz, 4′,6′-H_b), 3.05 (d, 1 H, J = 17.2 Hz, 3-H), 2.51 (d, 1 H, J = 16.7 Hz, 5-H), 2.16 (d, 1 H, J = 17.0 Hz, 3-H), 1.88 (m, 1 H, 7-H), 1.69 (m, 1 H, 6-H), 1.60 (m, 1 H, 7-H), 1.30 (br. m, 2 H, H-5, 6-H), 1.12 (s, 3 H, CH_3-5′), 0.96 (s, 3 H, CH_3-3a), 0.73 (s, 3 H, CH_3-5′). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 162.2 (2), 99.8 (4), 82.0 (7a), 81.3 (CH_2-2), 70.2, 70.0 (4′, 6′), 49.0 (3a), 36.6 (3), 30.1 (5′), 23.8 (5), 22.9, 22.0 (2C, CH_3-5′), 21.7 (7), 19.5 (6), 14.5 (CH_3-3a). − MS (CI, NH_3): m/z 252 (M^+), 209, 141, 122, 109.

(2*R,3a*R**,7a*R**)-2-Hydroxy-2,3a,3′,3′-tetramethyl-2,3,5,6,7,7a-hexahydrospiro[benzofuran-4,2′-[1,3]dioxane] (21):** To a solution of **17** (60 mg, 0.2 mmol) in DMSO (1 mL) was added *t*BuOK (5 mg, ca. 0.2 equiv.). The resulting mixture was stirred at 40 °C for 5 h, then cooled to room temperature, diluted with ether (50 mL) and quenched with a saturated, aqueous NH_4Cl solution (5 mL). The layers were separated, and the organic layer was washed with water (3 × 5 mL) and brine (10 mL), then dried with $MgSO_4$ and concentrated in vacuo. The crude product was diluted with CH_2Cl_2, and stirred with SiO_2 (500 mg) for 1 h, then filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (Et_2O/petroleum ether, 50:50) to yield 57 mg (95%) of **21**. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.21 (d, 1 H, J = 0.8 Hz, OH), 3.78−3.61 (bm, 3 H, 2′,4′-H_a, 7a-H), 3.41 (dd, 1 H, J = 18.7, 2.6 Hz, 2′,4′-H_e), 3.33 (dd, 1 H, J = 18.5, 2.6 Hz, 2′,4′-H_e), 2.68 (d, 1 H, J = 14.3 Hz, 3-H), 2.57 (m, 1 H, CH_2), 1.97 (m, 1 H, CH_2), 1.73 (d, 1 H, J = 14.2 Hz, 3-H), 1.67−1.49 (bm, 4 H, CH_2), 1.46 (d, 2 H, J = 0.9 Hz, CH_3-2), 1.22 (s, 3 H, CH_3-3′), 1.07 (s, 3 H, CH_3-3a), 0.75 (s, 3 H, CH_3-3′). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 103.5 (2), 102.0 (4), 83.5 (7a), 69.6, 69.2 (2′, 4′), 49.5 (3), 43.1 (3a), 29.6 (3′), 27.5 (CH_3-2), 25.3, 22.1 (5, 7), 23.5, 21.9, 20.7 (CH_3-3′, CH_3-3a), 17.3 (6). − IR (film): ṽ (cm^{-1}) 3394, 2950, 2670, 1463, 1394, 1377, 1265, 1110, 1054, 958, 892. − MS (IC, NH_3): m/z 253 (MH^+ − H_2O), 237, 141, 122.

Procedures for Anionic Cyclizations. − With KH/DMF: To a suspension of degreased KH (35% in oil, 70 mg, 1.2 equiv.) at room temperature in dry DMF (2.5 mL) was added, portionwise over 5 min, **15** (125 mg, 0.5 mmol). The resulting pink mixture was then stirred at 40 °C for 5 h, during which time it turned brown. It was then diluted with ether (50 mL) and quenched with water (5 mL). The layers were separated, and the organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting crude product was then purified by flash chromatography (Et_2O/petroleum ether, 10:90 → 20:80), giving successively **23** (8 mg, 6%), **24** (25 mg, 20%), **25** (19 mg, 15%), and **15** (15 mg, 12%).

With KH/DMF/DIPA: To a suspension of degreased KH (35% in oil, 125 mg, 1.2 equiv.) at room temperature in dry DMF (10 mL) was added diisopropylamine (285 µL, 2.0 mmol, 2.0 equiv.), dropwise over 5 min, and **15** (250 mg, 1.0 mmol), portionwise. The resulting orange mixture was then stirred at 60 °C for 15 h, during which time it turned brown. It was then diluted with ether (100 mL) and quenched with water (10 mL). The layers were separated, and the organic layer was washed with water (3× 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting crude product was then purified by flash chromatography (Et_2O/petroleum ether, 10:90 → 20:80), giving successively **23** (20 mg, 8%), **24** (10 mg, 4%), **22** (130 mg, 52%), and **15** (26 mg, 10%).

With *t*BuOK/DMSO: To a solution of **15** (100 mg, 0.4 mmol) at room temperature in dry DMSO (2 mL) was added, portionwise over 2 min, *t*BuOK (54 mg, 0.5 mmol, 1.2 equiv.). The resulting brown mixture was stirred at 20 °C for 12 h. It was then diluted with ether (50 mL) and quenched with water (5 mL). The layers were separated, and the organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting crude product was then purified by flash chromatography (Et_2O/petroleum ether, 10:90 → 20:80), giving successively **23** (50 mg, 50%), **24** (10 mg, 10%), and **25** (7 mg, 7%).

With *t*BuOK/*t*BuOH/DMSO: To a solution of **15** (100 mg, 0.4 mmol) and *t*BuOH (375 µL, 4.0 mmol, 10 equiv.) at room temperature in dry DMSO (2 mL) was added, portionwise over 2 min, *t*BuOK (54 mg, 0.5 mmol, 1.2 equiv.). The resulting brown mixture was stirred at 20 °C for 2 h. It was then diluted with ether (50 mL) and quenched with water (5 mL). The layers were separated, and the organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting crude product was then purified by flash chromatography (Et_2O/petroleum ether, 10:90 → 20:80), giving successively **23** (35 mg, 35%) and **22** (35 mg, 35%).

3,3,7-Trimethyl-7-prop-1-ynyl-1,5-dioxaspiro[5.5]undecan-8-one (22): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.73 (d, 1 H, J = 11.4 Hz, 2′,4′-H_a), 3.47 (d, 1 H, J = 11.3 Hz, 2′,4′-H_a), 3.45 (dd, 1 H, J = 11.3, 2.6 Hz, 2′,4′-H_e), 3.28 (dd, 1 H, J = 11.2, 2.6 Hz, 2′,4′-H_e), 2.95 (td, 1 H, J = 13.6, 7.2 Hz, 6-H), 2.67 (dt, 1 H, J = 14.2, 3.0 Hz, 5-H), 2.23 (brd, 1 H, J = 14.0 Hz, 5-H), 2.13 (td, 1 H, J = 13.7, 4.3 Hz, 6-H), 1.80 (s, 3 H, CH_3−CC-2), 1.49 (dt, 1 H, J = 13.2, 4.5 Hz, 4-H), 1.43 (dt, 1 H, J = 13.4, 4.5 Hz, 4-H), 1.40, 1.12, 0.69 (3s, 9 H, CH_3-2, CH_3-3′). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 205.9 (1), 101.7 (3), 81.0, 79.2 (CC-2), 70.8, 70.0 (2′, 4′), 55.6 (2), 36.3 (6), 29.6 (3′), 22.9, 22.0 (CH_3-3′), 22.3, 18.5 (4, 5), 14.9 (CH_3-2), 3.8 (CH_3−CC-2). − IR (film): ṽ (cm^{-1}) 2956, 2869, 2248, 1731, 1454, 1396, 1365, 1237, 1178, 1133, 1084. − MS (IC, NH_3): m/z 251 (MH^+), 180, 164, 141.

3a,3′,3′-Trimethyl-2-methylene-3,3a,5,6-tetrahydro-2*H*-spiro-[benzofuran-4,2′-[1,3]dioxane] (23): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.82 (t, 1 H, J = 3.5 Hz, 7-H), 4.42 (t, 1 H, J = 2.2 Hz, CH_2-2), 4.06 (t, 1 H, J = 2.0 Hz, CH_2-2), 3.75 (d, 1 H, J = 11.3 Hz, 2′,4′-H_a), 3.67 (d, 1 H, J = 11.3 Hz, 2′,4′-H_a), 3.44 (dd, 1 H, J = 11.3, 2.7 Hz, 2′,4′-H_e), 3.37 (dd, 1 H, J = 11.3, 2.7 Hz, 2′,4′-H_e), 3.25 (dt, 1 H, J = 14.8, 1.8 Hz, 3-H), 2.20 (d, 1 H, J = 14.7 Hz, 3-H), 2.64 (dd, 1 H, J = 14.5, 6.1 Hz, 5-H_e), 2.18 (dddd, 1 H, J = 17.2, 6.9, 3.8, 1.1 Hz, 6-H_e), 2.04 (dddd, 1 H, J = 17.2, 11.1, 6.8, 3.2 Hz, 6-H_a), 1.58 (ddd, 1 H, J = 14.5, 11.1, 7.0 Hz, 5-H_a), 1.23 (d, 3 H, J = 1.5 Hz, CH_3-3a), 1.15, 0.75 (2s, 6 H, CH_3-3′). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 160.0, 157.7 (2, 8), 98.7 (4), 92.1 (7), 83.2 (CH_2-2), 71.0, 70.3 (2′, 4′), 47.6 (3a), 34.5 (3), 29.9 (3′), 22.9, 22.8, 22.0 (CH_3-3′, CH_3-3a), 20.5, 18.5 (5, 6). − IR (film): ṽ (cm^{-1}) 2953, 2868, 1725, 1472, 1395, 1254, 1194, 1111, 1054, 954.

2,3a,3′,3′-Tetramethyl-5,6-dihydro-3a*H*-spiro[benzofuran-4,2′-[1,3]-dioxane] (24): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.05 (t, 1 H, J = 1.1 Hz, 3-H), 4.95 (t, 1 H, J = 3.6 Hz, 7-H), 3.72 (d, 1 H, J = 11.2 Hz, 2′,4′-H_a), 3.58 (d, 1 H, J = 11.3 Hz, 2′,4′-H_a), 3.44 (dd, 1 H, J = 11.3, 2.6 Hz, 2′,4′-H_e), 3.39 (dd, 1 H, J = 11.2, 2.6 Hz, 2′,4′-H_e), 2.61 (ddd, 1 H, J = 14.6, 7.3, 1.3 Hz, 5-H_e), 2.23 (dddd, 1 H, J = 17.5, 7.9, 3.2, 1.6 Hz, 6-H_e), 2.12 (dddd, 1 H, J = 17.4, 9.9, 7.4, 4.1 Hz, 6-H_a), 1.61 (ddd, 1 H, J = 14.6, 9.8, 8.0 Hz, 5-H_a), 1.90 (d, 3 H, J = 1.3 Hz, CH_3-2), 1.19, 1.16, 0.75 (3s, 9 H, CH_3-3′, CH_3-3a). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 159.3 (7a), 152.1 (2), 103.9 (3), 99.1 (4), 94.1 (7), 70.9, 70.7 (2′, 4′), 53.4 (3a), 29.9 (3′), 25.1 (CH_3-2), 22.8, 22.0 (CH_3-3′), 20.4, 19.0 (5, 6), 13.7 (CH_3-3a). − IR (film): ṽ (cm^{-1}) 2954, 2865, 1715, 1664, 1471, 1454, 1434, 1394, 1348, 1258, 1211, 1134, 1092, 1043, 935, 912, 821.

(1*R,5*S**)-1,3′,3′-Trimethylspiro[bicyclo[3.3.1]non-6-en-4,2′-[1,3]-dioxane]-9-one (25):** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.77 (dt, 1 H, *J* = 11.4, 3.6 Hz, 8-H), 5.62 (ddt, 1 H, *J* = 11.4, 6.4, 2.0 Hz, 7-H), 3.76 (d, 1 H, *J* = 11.2 Hz, 2′,4′-H_a), 3.57 (d, 1 H, *J* = 11.2 Hz, 2′,4′-H_a), 3.48 (dd, 1 H, *J* = 11.2, 2.3 Hz, 2′,4′-H_e), 3.36 (dd, 1 H, *J* = 11.2, 2.3 Hz, 2′,4′-H_e), 3.01 (ddd, 1 H, *J* = 19.0, 3.5, 1.7 Hz, 4-H), 2.89 (dd, 1 H, *J* = 5.9, 3.5 Hz, 6-H), 2.72−2.69 (m, 1 H, 5-H), 2.12 (dt, 1 H, *J* = 19.0, 2.5 Hz, 4-H), 1.79 (dd, 1 H, *J* = 13.5, 4.1 Hz, 9-H), 1.70 (dt, 1 H, *J* = 13.5, 3.5 Hz, 9-H), 1.61−1.58 (m, 1 H, 5-H), 1.22, 1.15, 0.72 (3s, 9 H, CH_3-2′,4′,2). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 129.4, 127.6 (7, 8), 103.3 (3), 70.6, 69.7 (2′, 4′), 55.6 (2), 46.6 (6), 40.5 (9), 29.6 (3′), 26.3 (4), 23.2, 22.2 (CH_3-3′), 19.6 (5), 15.2 (CH_3-2). − IR (film): $\tilde{\nu}$ (cm^{-1}) 2955, 2869, 1726, 1442, 1395, 1369, 1307, 1209, 1102, 1065, 1038, 908.

(7*R,8*S**)-8-Benzyloxy-3,3,7-trimethyl-7-prop-2-ynyl-1,5-dioxaspiro[5.5]undecane (27):** To a suspension of $LiAlH_4$ (380 mg, 10 mmol, 0.5 equiv.) in toluene (60 mL) was added, portionwise over 15 min, ketone **15** (5.0 g, 20 mmol). The resulting mixture was heated for 1 h at 70 °C (reaction was monitored by TLC with MeOH/CH_2Cl_2, 2:98 as eluent) and then cooled to 0 °C, and treated with methanol (10 mL, added carefully). The mixture was diluted with ether (100 mL), and stirred overnight with a saturated, aqueous Na,K-tartrate solution (Rochelle's salt, 40 mL). The layers were separated, the aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed successively with water (50 mL) and brine (50 mL), then concentrated in vacuo and dried with $MgSO_4$. The crude product of the reaction was diluted with THF (40 mL), and added by cannula to a suspension of KH (880 mg, 22 mmol, 1.1 equiv, from 2.5 g of a 35% suspension of KH in mineral oil) in THF (40 mL) at room temperature. Benzyl bromide (2.9 mL, 1.2 equiv.) and $(NBu)_4I$ (ca 500 mg, 10% weight) were added, and the reaction mixture was heated at reflux for 2 h. It was cooled to room temperature, and quenched with a saturated, aqueous NH_4Cl solution. The layers were separated, the aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed successively with 1 N HCl (2 × 50 mL), water (50 mL), and brine (50 mL), then concentrated in vacuo and dried with $MgSO_4$. Purification by flash chromatography (Et_2O/petroleum ether, 10:90) yielded 3.3 g of **27** (48%) as a colourless oil. − ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43−7.25 (br. m, 5 H, Ar-H), 4.60 (s, 2 H, Ar−CH_2−O), 3.74 (dd, 1 H, *J* = 10.6, 4.5 Hz, 8-H), 3.69 (d, 1 H, *J* = 11.3 Hz, 2,4-H_a), 3.58 (d, 1 H, *J* = 11.6 Hz, 2,4-H_a), 3.35 (dd, 1 H, *J* = 11.5, 2.5 Hz, 2,4-H_b), 3.33 (dd, 1 H, *J* = 11.6, 2.4 Hz, 2,4-H_b), 2.78 (dd, 1 H, *J* = 17.0, 2.7 Hz, 1′-H), 2.65 (dd, 1 H, *J* = 17.0, 2.6 Hz, 1′-H), 2.50 (m, 1 H, CH_2), 2.00 (m, 1 H, CH_2), 1.94 (t, 1 H, *J* = 2.7 Hz, 3′-H), 1.61−1.19 (m, 4 H, CH_2), 1.26 (s, 3 H, CH_3-3), 1.08 (s, 3 H, CH_3-7), 0.73 (s, 3 H, CH_3-3). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.0 (*C*−CH_2−O-8), 128.3, 127.9, 127.3 (5C, Ar), 101.6 (6), 85.4 (2′), 80.4 (8), 72.1, 70.3, 69.7, 68.1 (4C, CH_2−O-8, 3′, 2, 4), 48.0 (7), 29.9 (3), 26.6 (1′), 23.9, 22.7 (2C, CH_3-3), 23.3 (11), 21.6, 18.7 (2C, 9, 10), 15.0 (CH_3-7). − IR (thin film): 3299, 2952, 2865, 2115, 1720, 1453, 1394, 1362, 1210, 1163, 1111, 1090, 1047, 1027, 969. − MS (CI, NH_3): *m*/*z* 360 (MNH_4^+), 343 (MH^+), 257, 235, 197, 150.

(7*R,8*S**)-8-Benzyloxy-3,3,7-trimethyl-7-prop-1-ynyl-1,5-dioxaspiro[5.5]undecane (28):** To a solution of **27** (430 mg, 1.2 mmol) in DMSO (5 mL) with *t*BuOH (1.5 mL) was added *t*BuOK (40 mg, 30 mol-%), and the resulting mixture was stirred at 120 °C for 2 h. It was then cooled to room temperature, diluted with ether (100 mL) and quenched with a saturated, aqueous NH_4Cl solution. The layers were separated, the aqueous layer was extracted with ether (2× 50 mL), and the combined organic layers were washed successively with water (3 × 10 mL) and brine (20 mL), then concentrated in vacuo and dried with $MgSO_4$. Purification by flash chromatography (Et_2O/petroleum ether, 10:90) yielded 380 mg of **28** (88%) as a colourless oil. − ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43 (d, 2 H, *J* = 7.3 Hz, Ar-H), 7.34 (t, 2 H, *J* = 7.4 Hz, Ar-H), 7.27 (m, 1 H, Ar-H), 4.86 (d, 1 H, *J* = 11.7 Hz, Ar−CH_2−O), 4.66 (d, 1 H, *J* = 11.7 Hz, Ar−CH_2−O), 3.75 (dd, 1 H, *J* = 11.1, 4.7 Hz, 8-H), 3.70 (d, 1 H, *J* = 11.5 Hz, 2,4-H_a), 3.60 (d, 1 H, *J* = 11.5 Hz, 2,4-H_a), 3.47 (m, 2 H, H_b-2, 4-H_b), 2.48 (d, 1 H, *J* = 11.7 Hz, CH_2), 1.91 (s, 3 H, CH_3-2′), 1.84 (m, 1 H, CH_2), 1.55 (m, 1 H, CH_2), 1.37, 1.26 (2s, 6 H, CH_3-3, CH_3-7), 1.46−1.21 (br. m, 3 H, CH_2), 0.75 (s, 3 H, CH_3-3). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 139.6 (*C*−CH_2−O-8), 128.1, 127.5, 127.1 (5C, Ar), 100.8 (2C, 6, 1′), 83.5 (2′), 81.2 (8), 73.2, 70.3, 69.7 (CH_2−O-8, 2, 4), 47.7 (7), 30.1 (3), 26.7 (11), 22.8, 22.1 (CH_3-3), 20.8 (9), 18.2 (10), 16.0 (CH_3-7), 3.9 (CH_3-2′). − IR (thin film): 3062, 3029, 2952, 2864, 2237, 1496, 1454, 1395, 1364, 1334, 1281, 1216, 1184, 1127, 1089, 969, 910. − MS (CI, NH_3): *m*/*z* 360 (MNH_4^+), 343 (MH^+), 257, 235, 141, 108, 91. − $C_{22}H_{30}O_3$ (342.5): calcd. C 77.15, H 8.82; found C 77.24, H 8.83.

(7*R,8*S**)-8-Benzyloxy-3,3,7-trimethyl-7-prop-1-enyl-1,5-dioxaspiro[5.5]undecane (29):** A solution of **28** (420 mg, 1.6 mmol) in 20 mL of AcOEt was stirred vigorously under a hydrogen atmosphere with a catalytic amount of Lindlar catalyst (40 mg, 10% weight) for 2 h. The resulting suspension was then filtered through a pad of Celite and concentrated in vacuo. Purification by flash chromatography (Et_2O/petroleum ether, 20:80) yielded 410 mg (98%) of **29** as a colourless oil. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.35−7.25 (bm, 5 H, Ar-H), 5.49 (dq, 1 H, *J* = 11.3, 7.0 Hz, 2′-H), 5.40 (dq, 1 H, *J* = 11.4, 1.3 Hz, 1′-H), 4.59, 4.37 (2d, 2 H, *J* = 12.1 Hz, O−CH_2-Ar), 3.68 (m, 1 H, 3-H), 2.66 (m, 1 H, 6-H), 2.28 (m, 1 H, CH_2), 1.98 (m, 3 H, CH_2), 1.82 (m, 1 H, CH_2), 1.48 (dd, 3 H, *J* = 7.0, 1.3 Hz, CH_3-2′), 1.26 (s, 3 H, CH_3-2). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 213.1 (1), 138.1 (O−CH_2−C), 133.1 (1′), 128.0, 127.9, 127.2, 126.6 (6 C, 2′, Ar), 85.8 (O−CH_2−Ar), 70.5 (3), 55.6 (2), 38.7 (6), 23.8, 21.8 (4, 5), 19.1 (CH_3-3′), 13.2 (CH_3-2). − IR (film): $\tilde{\nu}$ (cm^{-1}) 2941, 1715, 1653, 1455, 1374, 1313, 1103, 949, 801. − MS (IC, NH_3): *m*/*z* 276 (MNH_4^+), 259 (MH^+), 241, 167, 151, 108, 91.

Triisopropylbenzenesulfonyl Hydrazone 30 Derived from Ketone 29: To a solution of **29** (420 mg, 1.6 mmol) and triisopropylbenzenesulfonylhydrazine (600 mg, 2.0 mmol, 1.25 equiv.) in 4 mL of THF was added ten drops of concentrated HCl. The resulting solution was stirred at room temperature for 1 h, then diluted with ether (80 mL) and quenched with a saturated, aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the organic layer was washed successively with water (2 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo at 40 °C. The resulting crude product was recrystallized from petroleum ether to give 590 mg (68%) of trisylhydrazone **30** as a white solid (m.p. 35−37 °C). Purification of the mother liquors by flash chromatography (Et_2O/petroleum ether, 20:80) yielded a further 210 mg (24%) of **30**. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (brs, 1 H, NH), 7.29−7.20 (m, 5 H, Ar-H), 7.16 (s, 2 H, Ar), 5.35 (dq, 1 H, *J* = 11.6, 7.2 Hz, 2′-H), 5.21 (dq, *J* = 11.6, 1.7 Hz, 1′-H), 4.50 (d, 1 H, *J* = 12.2 Hz, O−CH_2−Ar), 4.32 (d, 1 H, *J* = 12.2 Hz, O−CH_2−Ar), 4.26 (sept, 2 H, *J* = 6.7 Hz, CH−Ar), 3.40 (brs, 1 H, 3-H), 2.92 (sept, 1 H, *J* = 6.9 Hz, CH−Ar), 2.52 (dt, 1 H, *J* = 14.0, 4.1 Hz, CH_2), 1.97 (td, 1 H, *J* = 12.5, 5.9 Hz, CH_2), 1.90−1.64 (br. m, 4 H, CH_2), 1.29, 1.28, 1.28, 1.26 [$(CH_3)_2$−CH−Ar], 1.19 (dd, 3 H, *J* = 7.4, 1.8 Hz, CH_3-2′), 1.17 (s, 3 H, CH_3-2). − ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 160.8 (1),

152.7, 151.4 (Ar), 138.7 (O−CH_2−C), 134.2 (1′), 132.1 (Ar), 128.0, 127.4, 127.2, 126.0 (Ar), 123.4 (2′), 84.4 (O−CH_2−Ar), 71.1 (3), 50.0 (2), 34.1 (*C*H−Ar), 29.7 (*C*H−Ar), 24.7, 23.4 ((*C*H_3)$_2$−CH−Ar), 24.5, 23.4, 20.0 (4, 5, 6), 21.0 (CH_3-2′), 13.0 (CH_3-2). − IR (film): $\tilde{\nu}$ (cm^{-1}) 2959, 1600, 1455, 1361, 1318, 1164, 1107. − MS (IC, NH_3): *m*/*z* 539 (MH^+), 449, 300, 276, 259, 151, 108, 91.

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