Pergamon

Tetrahedron 57 (2001) 5173–5182

TETRAHEDRON

Formation of radicals by irradiation of alkyl halides in the presence of triethylamine. Application to the synthesis of (±)-bisabolangelone

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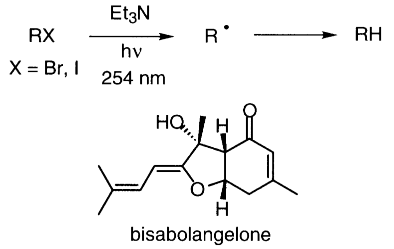
Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

Received 7 February 2001; revised 14 March 2001; accepted 15 March 2001

Abstract—The irradiation of unsaturated halides in the presence of triethylamine leads to the formation of the corresponding cyclized products. This photoreductive cyclization has been used to synthesize the bicyclic core of (±)-bisabolangelone.

Studies on the photochemistry of alkyl iodides have shown that the irradiation of alkyl halides in solution affords mixtures of radical and ionic products with the latter usually greatly predominant.[1] As the ionic products are usually obtained in high yield the reaction is of synthetic value.[2] On the contrary, alkyl bromides lead to radical-derived products in low yield.[3] If photochemically generated ketyl radicals are used as electron donors to halide derivatives,[4] reagents such as trialkyltin hydrides or trialkyldistannanes can be used for the subsequent reduction of C–Br and C–I bonds.[5] However, this reaction is troublesome as the separation of the products from trialkyltin derivatives is difficult. A partial solution to this problem has been found by using polymer-supported organotin compounds.[6]

Some years ago, we examined the photocyclization of unsaturated halides.[7] In this paper, we report that this photochemical reaction is a fast, convenient and chemoselective process that allows the formation of radicals either from alkyl bromides or alkyl iodides and that this reaction can be used in the synthesis of (±)-bisabolangelone (Scheme 1).



Scheme 1.

Irradiation of compounds **1** and **2** at 254 nm in acetonitrile (10^{-2} M), in the presence of triethylamine (10 equiv.) for 30 min leads to the formation of the cyclized product **7**[8] in, respectively, 94 and 90% yield. The reaction was generalized to compounds **3** and **4**. In the case of compound **3**, two products **8** and **8′**[8a] were formed in a ratio 85/15 and in 80% yield. The irradiation of compound **4** afforded compound **9**, the result of a **5**-*exo*-dig cyclization process, in 88% yield. It is worth noting that this photochemical process is chemoselective as the ester function of **4** was not reduced. Furthermore, when bromo ketone **5**[9] was irradiated, the only product that could be isolated, after 30 min, was ketone **10** (60%). The unsaturated tricyclic ketone **11** was obtained in 98% yield (based on the recovered starting material), when the unsaturated bromo oxanorbornanone **6** was irradiated at 5×10^{-2} M, for 30 min, in the presence of 5 equiv. of Et_3N. It is worth noting that no trace of alcohols[10] such as **5** and **6′** or an oxabridge opening products such as **5″** and **6″**[11] were detected when compounds **5** and **6** were irradiated in the presence of 5 equiv. of Et_3N for 30 min (Scheme 2).

Under these photochemical conditions, the reduction of a halide is faster than the reduction of a ketone. An amine–halide exciplex is probably formed which leads to a radical R˙ and a halide-anion. The radical can be trapped very efficiently by an internal π-bond system, or it can abstract a hydrogen atom from the resulting amino radical–cation intermediate[12] when no unsaturation is present (Scheme 3).

Due to the efficient formation of heterocyclic compounds

Keywords: radicals; photoreductive cyclization; bisabolangelone.

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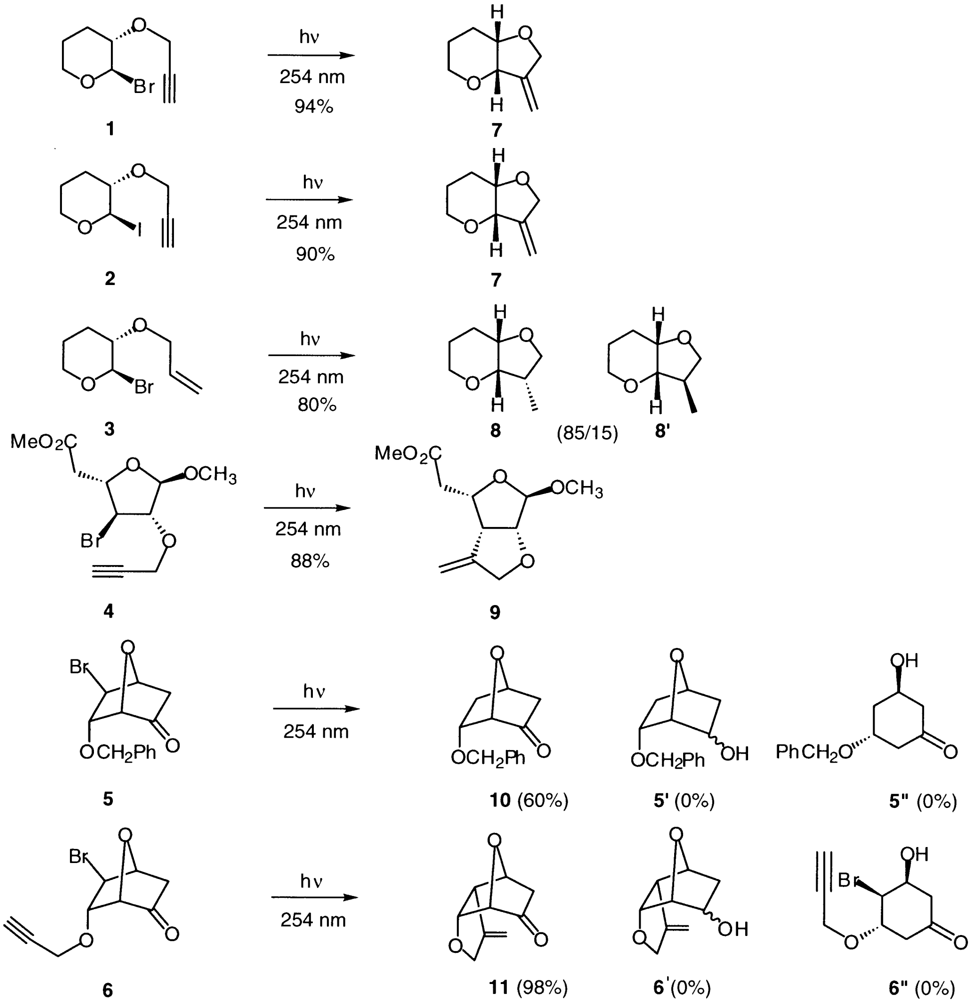
PII: S0040-4020(01)00357-X



Scheme 2. Irradiation of unsaturated halides in the presence of triethylamine.

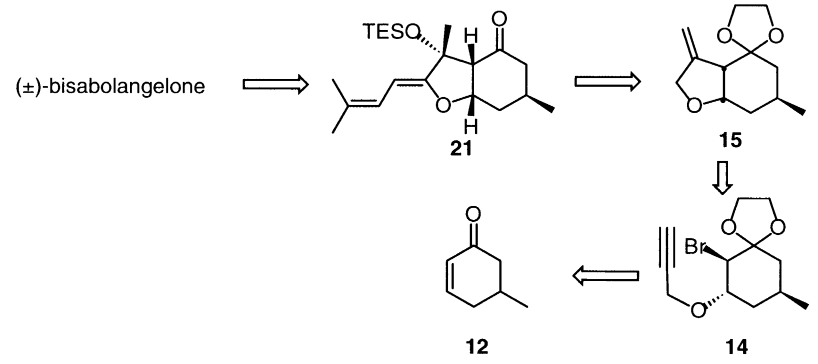
$$RX + Et_3N \xrightarrow[254\ nm]{h\nu} RX^{\bullet -}\ Et_3N^{\bullet +} \longrightarrow R^{\bullet} + X^{-}$$

$X = Br, I$

Scheme 3. Reduction of halides and the supposed mechanism.

from unsaturated halides when they are irradiated in the presence of Et_3N, the use of the photoreductive cyclization was envisaged as a key step in a formal total synthesis of (±)-bisabolangelone.

Bisabolangelone is a sesquiterpene which was isolated from umbelliferae such as *Angelica silvestris* L.,[13,14] *Angelica koreana* Max.,[15] *Angelica* spp.,[16] *Pimpinella major* Huds.[17] and *Angelica pubescens f. biserrata*.[18] The structure of bisabolangelone was established in 1966[14] and 1970.[15] This compound shows antifeeding properties against insects such as *Mythimna unipuncta* Haw. and *Leptinotarsa decemlineata* Say.[19,20] (±)-Bisabolangelone has been previously synthesized in 17 steps via intermediate **21** by using a dipolar 1,3-addition of acetonitrile oxide to



Scheme 4. Retrosynthetic analysis of (±)-bisabolangelone.

5-methylcyclohex-2-enone (**12**) and the cyclization of a γ-acetylenic alcohol as the key steps.[21]

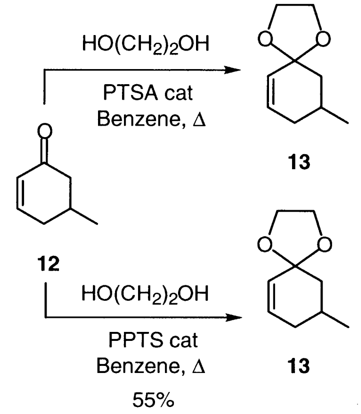
For our part, we envisaged the synthesis of the known intermediate **21** from the unsaturated halide **14**, as this compound possesses the functional groups appropriate for the synthesis of bisabolangelone (Scheme 4).

The transformation of 5-methylcyclohex-2-enone (**12**)[22] to bromo ether **14** was achieved in 2 steps. Treatment of ketone **12** with ethylene glycol in the presence of *p*-toluenesulfonic acid (PTSA) (0.01 equiv.), in refluxing benzene for 3 h,[23] afforded the expected 9-methyl-1,4-dioxaspiro[4.5]dec-6-ene (**13**) along with the undesired regioisomer **13′**. The formation of **13′** was avoided when **12** was treated with ethylene glycol in the presence of pyridinium *p*-toluenesulfonate [PPTS (0.005 equiv.)] in gently refluxing benzene for 6 h. Under these conditions, ketal **13** was isolated in 55% yield (Scheme 5).

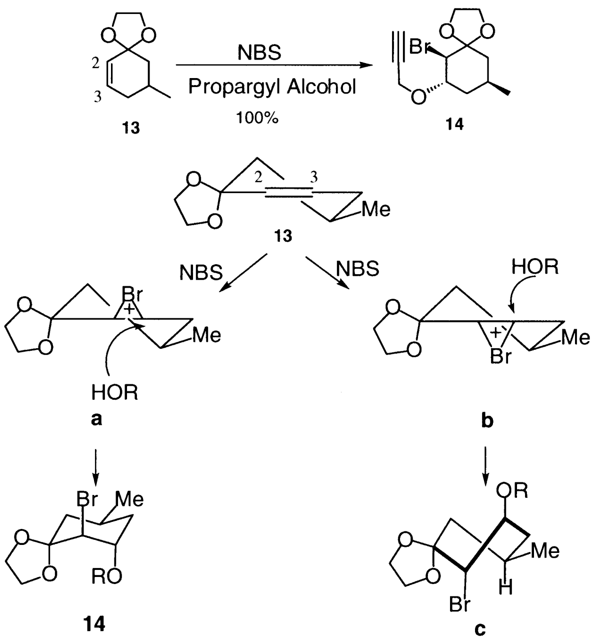
Ketal **13** reacted regioselectively and diastereoselectively (dr: 92:8) with *N*-bromosuccinimide (NBS) (1.25 equiv.) and propargyl alcohol (36 equiv.) to produce the bromo ether **14** in quantitative yield. The high regio- and diastereoselectivity can be explained by the formation of the bromonium intermediate **a** which is attacked in a *trans* diaxial fashion by propargyl alcohol on carbon C-3 due to the presence of the ketal. It is worth noting that intermediate **b** is not favored as the attack of **b** will lead to the twist intermediate **c** (Scheme 6).

The bicyclic structure of bisabolangelone was built up by irradiation of **14** in the presence of Et_3N (*hν*, 254 nm; Et_3N, 10 equiv.; CH_3CN, 10^{-2} M; 1 h). Under these conditions, a 5 *exo*-dig radical cyclization process takes place and affords the bicyclic compound **15** in 88% yield. In compound **15**, the relative *cis* stereochemistry between H-3a, H-7a and the methyl group on C-6, was confirmed by NOE experiments (Scheme 7).

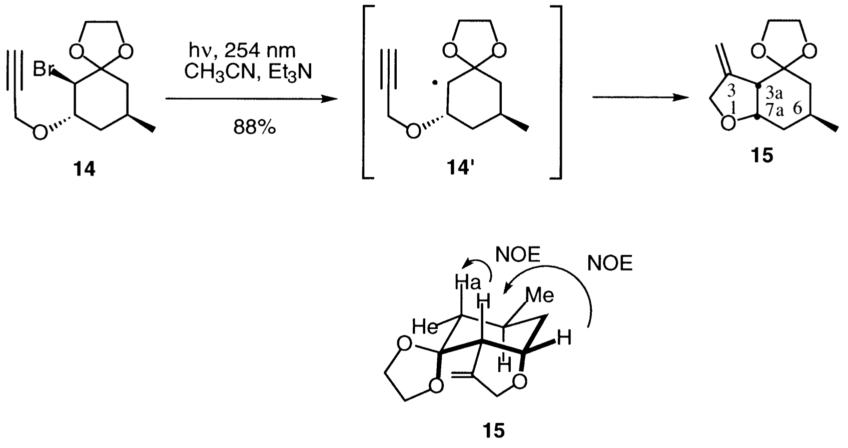
Ozonolysis of **15** in a mixture of CH_2Cl_2/MeOH (1/1) led to the corresponding ketone **16** (84% yield). The seleno compound **16f**, from alkylation–selenation of ketone **16**, was envisaged as a precursor of diene **17**. When **16** was treated with LDA (1.2 equiv., THF, −78°C) followed by



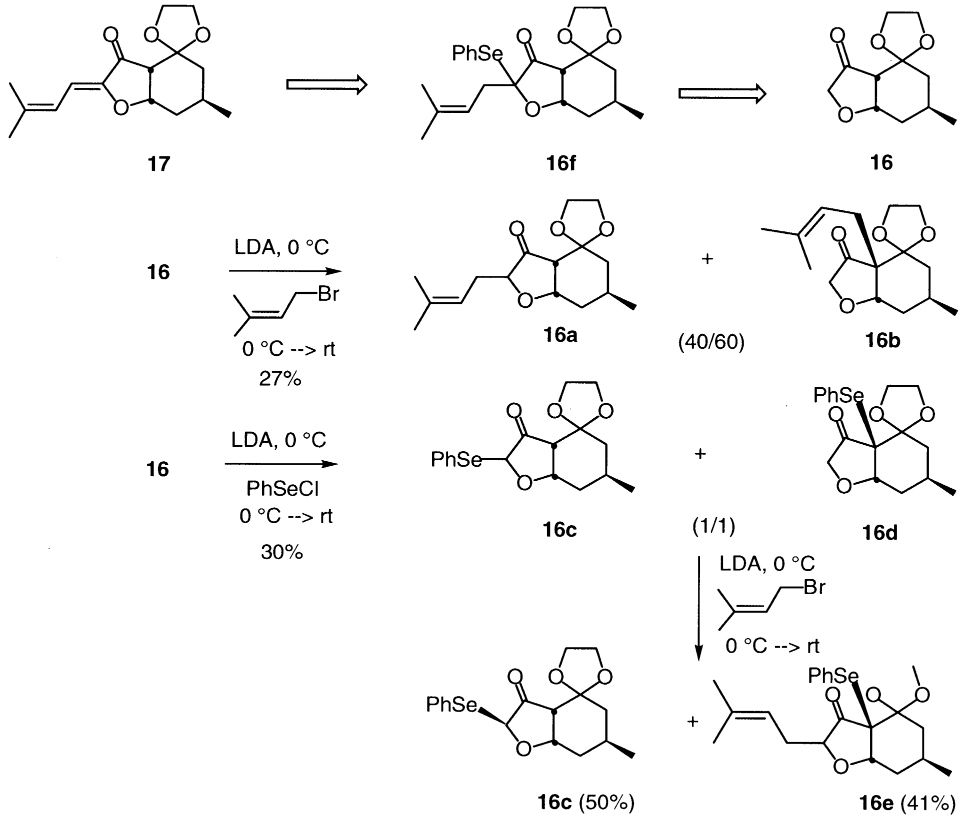
Scheme 5. Synthesis of ketal **13**.



Scheme 6. Attack of the bromonium intermediate **a** by propargyl alcohol.

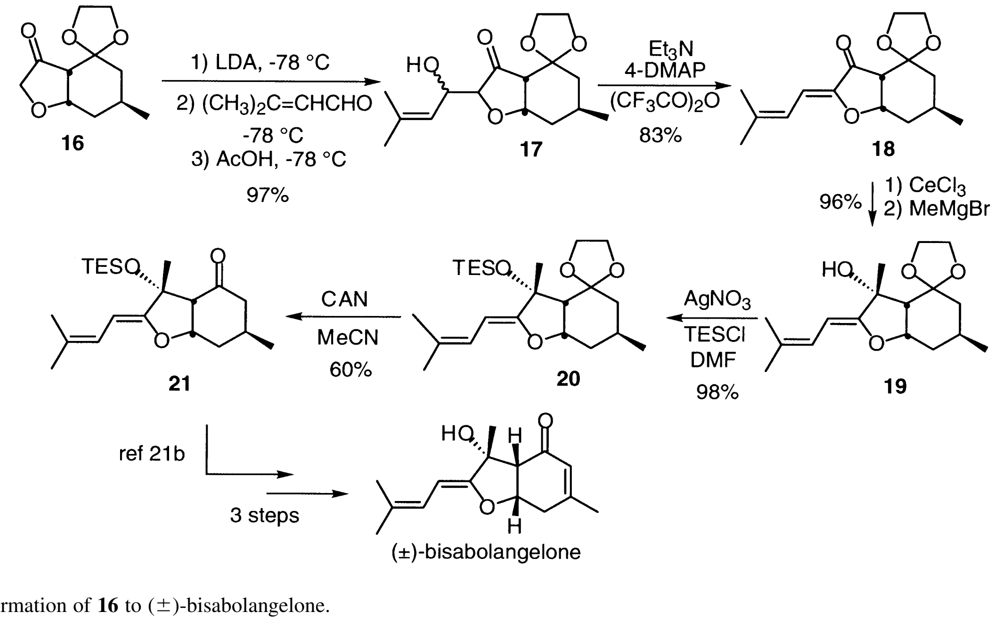


Scheme 7. Synthesis of compound **15** and NOE experiments.

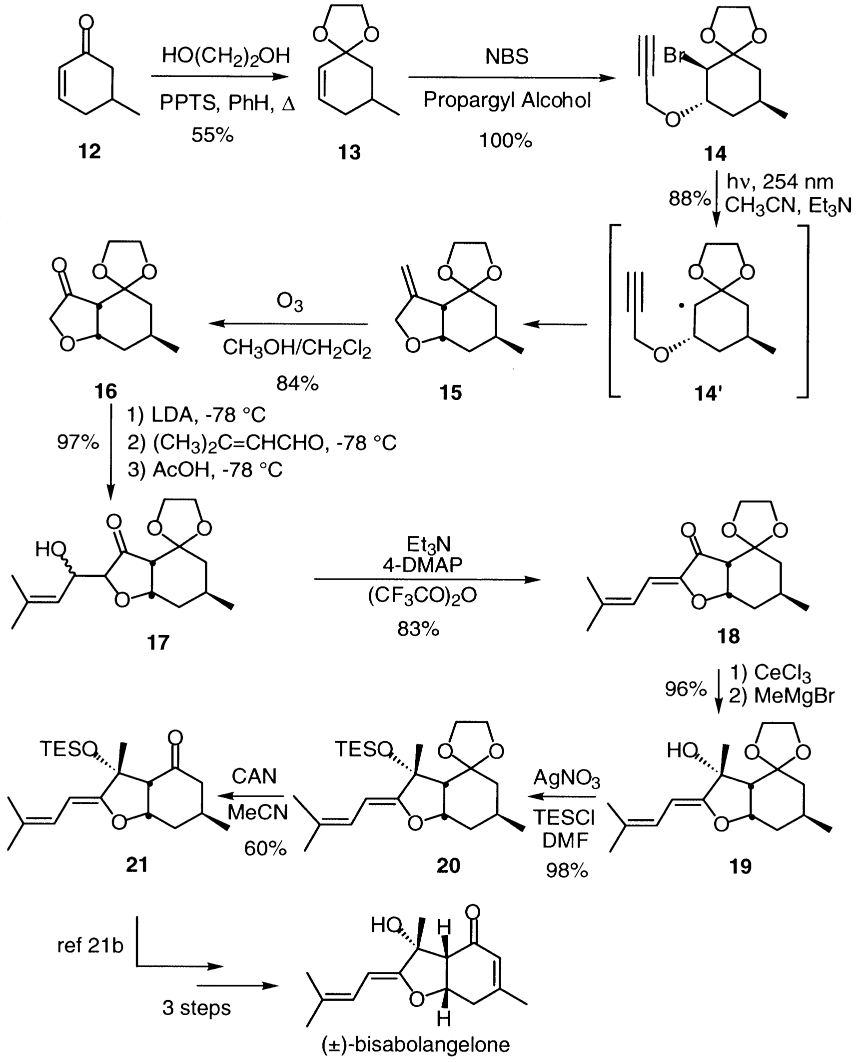


Scheme 8. Alkylation and selenation of **16**.

the addition of 4-bromo-2-methyl-2-butene in the presence of sodium iodide, the starting material **16** was entirely recovered. When the reaction was conducted at 0°C then warmed up to rt for 12 h, two inseparable compounds **16a** and **16b**, were isolated in 27% yield in the ratio 40/60. Due to the non-selective alkylation reaction, the selenation of **16** was achieved first. After treatment of ketone **16** with LDA (1.2 equiv., THF, 0°C), phenylselenyl chloride was added and the reaction mixture allowed to warm slowly to room temperature (12 h). Under these conditions, two seleno regioisomers **16c** and **16d** were isolated in 30% yield and in a ratio of 1:1. Treatment of this mixture with LDA (1.2 equiv., THF, 0°C) followed by the addition of 4-bromo-2-methyl-2-butene (0°C→rt; 12 h), led to the recovery of compound **16c** (50%) and to the formation of the alkylated product **16e** (41%) separable by chromatography. As the desired compound **16f** could not be prepared through seleno derivatives, an aldol condensation followed by a dehydration was envisaged as an alternative route (Scheme 8).



Scheme 9. Transformation of **16** to (±)-bisabolangelone.



Scheme 10. Synthesis of (±)-bisabolangelone.

The aldol condensation was achieved by treatment of ketone **16** with LDA (−78°C; 30 min; THF) followed by addition of 3-methyl-2-butenal (2 equiv.; −78°C; 15 min). After acidic work-up (AcOH, ether, −78°C), the condensation product **17** was isolated in 97% yield (based on the recovered starting material; conversion: 70%). Compound **17** was then treated with trifluoroacetic anhydride (3 equiv.) in the presence of Et_3N (6 equiv.) and a catalytic amount of 4-DMAP (0°C; 2 h; 0°C→rt; 20 h; then rt; 24 h) to produce diene **18** (83% yield).[24] The introduction of the methyl group at C-3 was achieved by addition of methylmagnesium bromide (7 equiv.) in the presence of $CeCl_3$ (6 equiv.), producing the tertiary alcohol **19** which was isolated in 96% yield. After silylation of the tertiary alcohol ($AgNO_3$; TESCl; DMF)[25] and deprotection of the ketal by using ceric ammonium nitrate (CAN)[26] (0.03 equiv.; CH_3CN; 60°C, borate–HCl buffer) ketone **21** was obtained with an overall yield of 58% for the two steps (Scheme 9).

The photoreductive cyclization of unsaturated halides affords heterocyclic compounds in good yields. By using this reaction as a key step, 5-methylcyclohex-2-enone was transformed to ketone **21** in nine steps with an overall yield of 18.5%. (Scheme 10). Since **21** has been converted to (±)-bisabolangelone,[21] the present synthesis constitutes a short formal total synthesis. It is worth noting that, as (*S*)-5-methylcyclohex-2-enone can be obtained in optically pure form,[27] natural (+)-bisabolangelone could be prepared efficiently by using our strategy.

1. Experimental

1.1. General procedures

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium/benzophenone ketyl immediately before use. Benzene, dichloromethane, acetonitrile, DMF, triethylamine and diisopropylamine were distilled from calcium hydride under argon. Moisture sensitive reactions were conducted in oven or flame-dried glassware under an argon atmosphere. Flash-chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck) and analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}). Melting points are uncorrected. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie in Paris. Mass spectra were obtained by GC/MS with electron impact ionization by using a 5971 Hewlett Packard instrument at 70 eV: only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. ^{1}H and ^{13}C spectra were respectively recorded on a Bruker AC 300 spectrometer at 300 and 75 MHz. Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at δ=7.27 for ^{1}H and to $CDCl_3$ at δ=77.1 for ^{13}C. ^{1}H NMR *J* values are given in Hz. IR spectra were recorded as neat films (NaCl cell) and KBr pellets for solids on a Perkin–Elmer 298 or FT-IR 1600. Compounds **4**,[28] **5**,[9] **6**,[28] **12**,[22] were prepared following known procedures.

1.1.1. *trans*-3-Bromo-2-(propargyloxy)tetrahydropyran (1).[29] To a solution of *N*-bromosuccinimide (1.28 g, 7.13 mmol, 1.2 equiv.) in propargyl alcohol (10 mL) at −30°C, a solution of dihydropyran (0.50 g, 0.54 mL, 5.90 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 2 h at −20°C and 12 h at rt, an aqueous solution of NaOH (1N, 10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×20 mL). The organic phase was washed with an aqueous NaOH solution (1N, 10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent in vacuo, the crude residue was purified by flash chromatography on silica gel (Et_2O/petroleum ether) to afford **1** (1.10 g, 5.02 mmol, 85% yield). Spectral data were consistent with those previously reported.[27] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.83 (d, *J*=3.7 Hz, 1H), 4.32 (dd, *J*=15.5, 2.6 Hz, 1H), 4.25 (dd, *J*=15.5, 2.6 Hz, 1H), 4.00 (dt, *J*=5.9, 4.0 Hz, 1H), 3.87 (ddd, *J*=11.8, 8.5, 3.3 Hz, 1H), 3.59 (m, 1H), 2.47 (t, *J*=2.6 Hz, 1H), 2.37 (m, 1H), 2.03–1.88 (m, 2H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.7, 78.7, 74.8, 62.1, 54.5, 48.5, 29.2, 22.5; EI MS *m/z* (relative intensity) 220–218 (M^+, 3), 165–163 (35), 136 (100).

1.1.2. *trans*-3-Iodo-2-(propargyloxy)tetrahydropyran (2). A similar procedure as for **1** was used. *N*-iodosuccinimide (1.60 g, 7.13 mmol, 1.2 equiv.), dihydropyran (0.50 g, 0.54 mL, 5.9 mmol), and propargyl alcohol (10 mL) afforded **2** (1.26 g, 4.7 mmol, 80% yield) after purification by flash chromatography on silica gel (Et_2O/petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.75 (d, *J*=2.6 Hz, 1H), 4.35 (dd, *J*=15.1, 2.6 Hz, 1H), 4.29 (dd, *J*=15.1, 2.6 Hz, 1H), 4.12 (dt, *J*=7.4, 4.4 Hz, 1H), 3.88 (td, *J*=11.0, 3.3 Hz, 1H), 3.63 (m, 1H), 2.46 (t, *J*=2.6 Hz, 1H), 2.38 (m, 1H), 1.89–1.76 (m, 2H), 1.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 96.6, 78.7, 74.8, 63.1, 54.6, 30.2, 28.1, 24.8; EI MS *m/z* (relative intensity) 266 (M^+, 3), 211 (12), 182 (47), 154 (100).

1.1.3. *trans*-3-Bromo-2-(allyloxy)tetrahydropyran (3).[30] Same procedure as for the preparation of **1** starting with dihydropyran (0.50 g, 0.54 mL, 5.9 mmol), *N*-bromosuccinimide (1.28 g, 7.13 mmol, 1.2 equiv.), and allyl alcohol (10 mL). Spectral data were consistent with those previously reported.[28] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.93 (dddd, *J*=17.3, 10.3, 5.9, 5.2 Hz, 1H), 5.33 (ddd, *J*=17.3, 3.3, 1.5 Hz, 1H), 5.21 (ddd, *J*=10.3, 2.9, 1.1 Hz, 1H), 4.66 (d, *J*=4.4 Hz, 1H) 4.26 (ddt, *J*=12.9, 5.2, 1.5 Hz, 1H); 4.05 (ddt, *J*=12.9, 6.3, 1.5 Hz, 1H), 4.03–3.89 (m, 2H); 3.59 (m, 1H), 2.41 (m, 1H), 2.00–1.89 (m, 2H), 1.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.8, 117.4, 100.0, 68.7, 62.5, 49.1, 30.1, 23.3; EI MS *m/z* (relative intensity) 222–220 (M^+,1), 181–179 (3), 165–163 (50), 135–133 (32), 55 (100).

1.2. General procedure for the irradiation

After dissolving the halide in freshly distilled CH_3CN (10^{-2} M), triethylamine (10 equiv.) was added. The resulting solution was irradiated in 10 mm ∅ quartz tubes in a merry-go-round apparatus equipped with eight low pressure Phillips TUV 15 lamps (λ_{irr}: 254 nm). After 30 min or 1 h at 25°C, the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel.

1.2.1. (±)-(3a*RS*,7a*SR*)-3-Methylidenehexahydro-4*H*-furo[2,3-*b*]pyran (7).[8] **7** was prepared by irradiation of **1** or **2**. Spectral data of **7** thus obtained were in good agreement with the reported data.[8b] Yield >90%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.15 (d, *J*=3.7 Hz, 1H), 5.06 (m, 1H), 4.96 (dd, *J*=5.3, 2.8 Hz, 1H), 4.58 (dq, *J*=12.9, 2.2 Hz, 1H), 4.49 (dq, *J*=12.9, 2.2 Hz, 1H), 3.86 (m, 1H), 3.44 (td, *J*=11.4, 2.6 Hz, 1H), 2.64 (m, 1H), 2.03 (m, 1H), 1.91 (m, 1H), 1.62 (m, 1H), 1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.7, 103.7, 101.4, 70.8, 64.4, 42.1, 22.2, 20.3; EI MS *m/z* (relative intensity) 140 (M^+,1), 111 (9), 94 (41), 79 (100).

1.2.2. (±)-(3a*RS*,7a*SR*)-3-Methylhexahydro-4*H*-furo[2,3-*b*]pyran (8) and (8′).[8a] Structural data of **8** and **8′** prepared by irradiation of **3** are identical to those previously reported in the literature.[8a] Yield: 80%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.29, 5.00 (d, *J*=3 Hz, 1H), 4.30–3.50 (m, 4H), 2.78–2.20 (m, 1H), 2.10–1.20 (m, 5H), 1.00, 0.97 (d, *J*=7.0 Hz, 3H); EI MS *m/z* (relative intensity) major isomer 142 (M^+, 13), 141 (100), 127 (2), 112 (21), 97 (52); minor isomer 142 (M^+, 12), 141 (100), 127 (2), 112 (19), 97 (34).

1.2.3. Methyl (±)-(3a*SR*,4*SR*,6*RS*,6a*RS*)-6-methoxy-3-methylidenehexahydrofuro[3,4-*b*]furan-4-acetate (9). Irradiation of (±)-**4**[28] (0.92 g, 3.0 mmol) afforded after flash chromatography (Et_2O, petroleum ether) **9** (0.60 g, 2.6 mmol, 88% yield). IR (neat) 1735, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.11 (m, 1H), 4.92 (m, 1H), 4.91 (s, 1H), 4.62–4.55 (m, 2H), 4.29–4.18 (m, 2H), 3.71 (s, 3H), 3.42 (dd, *J*=7.0, 6.9 Hz, 1H), 3.33 (s, 3H), 2.64 (dd, *J*=16.5, 7.3 Hz, 1H), 2.56 (dd, *J*=16.5, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 146.3, 108.4, 107.5, 88.2, 75.2, 72.3, 54.2, 51.6, 49.3, 35.9; EI MS *m/z* (relative intensity) 197 (M^+−31, 10), 168 (20), 165 (25), 126 (100), 108 (38). Anal. calcd for $C_{11}H_{16}O_5$ (228.24): C, 57.89; H, 7.07. Found: C, 58.18; H, 7.25.

1.2.4. (±)-(1*RS*,4*SR*,6*SR*)-6-*endo*-Benzyloxy-7-oxabicyclo[2.2.1]heptan-2-one (10). Irradiation of the 7-oxabicyclo[2.2.1]-heptan-2-one **5**[9] (0.100 g, 0.37 mmol) afforded after flash chromatography **10** (0.048 g, 0.22 mmol, 60% yield). IR (neat) 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.42 (m, 5H), 4.87 (dd, *J*=5.9, 5.5 Hz, 1H), 4.61 (d,

J=11.0 Hz, 1H), 4.47 (d, J=5.9 Hz, 1H), 4.44 (d, J=11.0 Hz, 1H), 4.26 (m, 1H), 2.57 (m, 1H), 2.38 (dddd, J=12.9, 9.6, 5.5, 2.6 Hz, 1H), 2.23 (d, J=17.6 Hz, 1H), 1.67 (dd, J=12.9, 2.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 208.4, 137.0, 128.4, 128.4, 128.0, 127.9, 126.9, 81.0, 76.3, 76.0, 72.1, 43.7, 36.4; EI MS m/z (relative intensity) 218 (M$^+$, 1), 200 (0.5), 190 (0.6), 172 (2), 91 (100).

1.2.5. (±)-(3a*SR*,4*SR*,7*SR*,7a*RS*)-3-Methylenehexahydro-4,7-epoxybenzofuran-6(7*H*)-one (11). Irradiation of compound **6**[28] (0.100 g, 0.41 mmol) in CH$_3$CN (5×10^{-2} M), for 30 min, in the presence of Et$_3$N (5 equiv.) afforded after flash chromatography (petroleum ether/AcOEt: 3/2) **11**(0.042 g, 0.25 mmol) (98% yield, based on recovered **6**). IR (neat) 1760, 1660, 1405 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.08 (dt, J=2.2, 2.1 Hz, 1H), 5.04 (td, J=2.4, 1.9 Hz, 1H), 4.92 (dddd, J=8.5, 5.4, 1.1, 0.6 Hz, 1H), 4.89 (ttd, J=5.9, 1.1, 1.0 Hz, 1H), 4.54 (m, 2H), 4.37 (dddd, J=5.4, 1.1, 1.1, 0.6 Hz, 1H), 3.64 (m, 1H, H-3a), 2.46 (ddddd, J=17.9, 5.9, 1.0, 0.9, 0.6 Hz, 1H), 2.35 (ddd, J=17.9, 1.0, 0.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 207.4, 145.0, 107.9, 84.5, 82.6, 78.7, 76.9, 51.8, 39.6; EI MS m/z (relative intensity) 166 (M$^+$, 6); 148 (2); 137 (11); 124 (12); 109 (36); 95 (100). HRMS calcd for C$_9$H$_{10}$O$_3$ 166.062992, found 166.06301.

1.3. Bisabolangelone intermediates

1.3.1. 9-Methyl-1,4-dioxaspirol[4.5]dec-6-ene (13). A solution of **12**[22] (3.3 g, 30.0 mmol, 1.0 equiv.), ethylene glycol (2.0 mL, 36.0 mmol, 1.2 equiv.), PPTS (0.038 g, 0.005 equiv.) in benzene (80 mL) was heated for 6 h under moderate reflux in a Dean–Stark unit. After cooling the reaction mixture at rt, a saturated aqueous NaHCO$_3$ solution (10 mL) was added. After dilution with Et$_2$O (100 mL), the organic layer was washed with brine (3×10 mL). After drying over MgSO$_4$, the solvent was removed in vacuo to afford an oil which was purified by flash chromatography on silica gel (Et$_2$O/petroleum ether: 1/4) to give **13** (1.34 g, 8.7 mmol) (55% yield, based on recovered **12**). R_f: 0.56 (Et$_2$O/petroleum ether: 1/4); IR (neat) 1655 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.87 (ddd, J=10.1, 5.3, 2.2 Hz, 1H), 5.51 (dm, J=10.1 Hz, 1H), 3.98–3.79 (m, 4H), 2.15–2.00 (m, 1H), 2.00–1.83 (m, 1H), 1.82–1.73 (m, 1H), 1.65–1.51 (m, 1H), 1.40 (t, J=13.1 Hz, 1H), 0.93 (d, J=6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 131.9, 127.0, 106.3, 64.4, 64.1, 41.8, 33.4, 27.7, 21.5; Anal. calcd for C$_9$H$_{14}$O$_2$: C, 70.10; H, 9.15. Found C, 69.81; H, 9.22.

1.3.2. 9-Methyl-1,4-dioxaspiro[4.5]dec-7-ene (13′). Following the same procedure as described above but with PTSA (0.01 equiv.) and under efficient reflux (3 h),[23] the desired compound **13** as well as **13′** were isolated. R_f: 0.58 (Et$_2$O/petroleum ether: 1/4); IR (neat) 1655 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.55 (br. s, 2H)), 4.05–3.90 (m, 4H), 2.50 (m, 1H), 2.35–2.10 (m, 2H), 1.86 (m, 1H), 1.40 (dd, J=12.9, 10.7 Hz, 1H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 132.7, 122.8, 108.1, 64.1, 64.1, 39.6, 35.3, 30.3, 20.9.

1.3.3. (±)-(6*RS*,7*SR*,9*SR*)-6-Bromo-9-methyl-7-(propargyloxy)-1,4-dioxaspiro[4.5]decane (14). To a solution of **13** (0.308 g; 2.0 mmol, 1.0 equiv.) in propargyl alcohol (4 mL), at 0°C, was added NBS (0.45 g, 2.50 mmol, 1.25 equiv.) in small portions. The reaction mixture was stirred at 0–10°C for 2 h. After removal of the excesss of propargyl alcohol in vacuo, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ solution (10 mL) and extracted with Et$_2$O (2×10 mL). The combined organic phases were dried over MgSO$_4$, filtered and evaporated. After filtration on silica gel of the crude reaction mixture (CH$_2$Cl$_2$), the solvent was removed in vacuo to afford **14** (0.576 g, 2.0 mmol, quantitative yield) as a colorless liquid which crystallizes when cooled. Compound **14** was used in the following step without further purification. Diastereomeric ratio (98:2) was measured by GC/MS analysis. R_f: 0.4 (Et$_2$O/petroleum ether: 1/2); IR (neat) 3290, 2120 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.25–4.21 (m, 2H), 4.11–3.90 (m), 2.44 (dd, J=2.6, 2.2 Hz, 1H)), 2.12–1.55 (m, 5H), 0.97 (d, J=7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 108.3, 79.6, 78.1, 74.6, 65.5, 64.6, 56.8, 53.9, 38.6, 33.8, 25.0, 20.9; EI MS m/z (relative intensity) 290–288 (M$^+$, 1), 275–273 (M$-$CH$_3$, 2), 235 (7), 233 (9), 209 (4), 179 (13), 155 (68), 113 (100). HRMS calcd for C$_{12}$H$_{18}$O$_3$Br 289.0439 (^{79}Br) 291.0420 (^{81}Br), found 289.0428 (^{79}Br) 291.0438 (^{81}Br).

1.3.4. (±)-(3a*RS*,6*SR*,7a*SR*)-6-Methyl-3-methylenehexahydrospiro[benzofuran-4(2*H*),2′-[1,3]dioxolane] (15). Irradiation of **14** at 254 nm (0.722 g, 2.5 mmol, 1.0 equiv.) for 1 h in CH$_3$CN (250 mL), in the presence of Et$_3$N (3.5 mL, 25.0 mmol, 10.0 equiv.) afforded after flash chromatography on silica gel (Et$_2$O/petroleum ether: 1/2) the bicyclic compound **15** (0.462 g, 2.2 mmol, 88% yield) as a colorless oil. R_f: 0.36 (Et$_2$O/petroleum ether: 1/2); IR (neat) 1670 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.03 (m, 1H), 4.83 (m, 1H), 4.36 (br. d, J=12.9 Hz, 1H), 4.10 (dm, J=12.9 Hz, 1H), 4.00 (m, 1H), 3.92–3.72 (m), 2.56 (br. d, J=4.4 Hz, 1H), 2.05–1.90 (m, 2H), 1.64 (dt, J=12.5, 2.2 Hz, 1H), 1.21–1.10 (m, 1H), 1.02 (t, J=12.5 Hz, 1H), 0.85 (d, J=6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 149.0, 109.8, 105.8, 78.8, 70.9, 65.9, 64.1, 51.0, 43.1, 35.6, 24.3, 21.6; EI MS m/z (relative intensity) 210 (M$^+$, 11), 195 (M$-$CH$_3$, 1), 181 (3), 167 (5), 148 (9), 139 (4), 122 (100), 113 (68), 86 (35).

1.3.5. (±)-(3a*RS*,6*SR*,7a*SR*)-6-Methyltetrahydrospiro-[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (16). Ozone was bubbled into a solution of **15** (0.483 g, 2.3 mmol, 1.0 equiv.) in methanol (15 mL) and CH$_2$Cl$_2$ (15 mL) at $-$78°C, until a light blue color was persistent (about 30 min). The resulting blue solution was purged with nitrogen until colorless, then the reaction was quenched with dimethyl sulfide (2 mL) at $-$78°C, and the resulting mixture was allowed to warm slowly to rt. After stirring for 30 min at rt, the mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (Et$_2$O/petroleum ether: 1/1) to afford ketone **16** (0.409 g, 1.93 mmol, 84% yield) as a colorless solid. Mp: 59–60°C; R_f: 0.40 (Et$_2$O/petroleum ether: 1/1); IR (neat): 1755 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.27 (m, 1H), 3.96 (br. d, J=16.6 Hz, 1H), 3.92–3.68 (m, 4H), 3.63 (d, J=16.6 Hz, 1H), 2.42 (d, J=5.1 Hz, 1H), 2.02 (m, 1H), 1.97 (dm, J=15.1 Hz, 1H), 1.62 (ddd, J=13.0, 2.6, 1.8 Hz, 1H), 1.19 (tdd, J=15.1, 3.5, 2.6 Hz, 1H), 0.99 (t, 1H, J=13.0 Hz, 1H), 0.85 (d, J=6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 214.1, 108.7, 77.5, 72.4, 65.3, 64.1, 52.6, 42.8, 35.4, 23.8, 21.4; EI MS *m/z* (relative intensity) 212 (M$^+$, 17), 197 (M−CH$_3$, 4), 183 (10), 155 (12), 139 (4), 127 (5), 113 (100), 99 (9), 86 (45), 69 (10), 68 (7); Anal. calcd for C$_{11}$H$_{16}$O$_4$: C, 62.25; H, 7.60. Found C, 62.32; H, 7.63.

1.3.6. (±)-6-Methyl-2-(3-methylbut-2-enyl)-tetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (16a) and (±)-6-methyl-3a-(3-methylbut-2-enyl)-tetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (16b). A solution of LDA was prepared by adding *n*-BuLi (0.96 mL, 2.5 M in hexanes, 2.4 mmol, 1.2 equiv.) to a solution of diisopropylamine (0.34 mL, 2.4 mmol, 1.2 equiv.) in THF (8 mL) at 0°C. After 15 min at 0°C, LDA was added to a solution of ketone **16** (0.424 g, 2.0 mmol, 1.0 equiv.) in THF (2 mL) at 0°C and stirred for 30 min before the addition of 4-bromo-2-methyl-2-butene (0.28 mL, 2.4 mmol, 1.2 equiv.). After 1 h at 0°C, the reaction mixture was allowed to warm up to rt for 12 h. A saturated aqueous NH$_4$Cl solution (10 mL) and Et$_2$O (50 mL) were added. The organic layer was separated, washed with brine (2×5 mL), and dried over MgSO$_4$. After filtration and evaporation of the solvent, the crude residue was purified. Flash chromatography on silica gel (AcOEt/petroleum ether: 1/9) afforded an inseparable mixture of **16a** and **16b** (0.15 g, 0.54 mmol, 27% yield) in a ratio (40/60) and ketone **16** (0.16 g, 0.76 mmol, 38% yield). **16a**+**16b**: R_f: 0.58 (AcOEt/petroleum ether: 1/6); IR (neat) 1765, 1755, 1670, 1630 cm^{-1}. **16a**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.25–5.17 (m, 1H), 4.51–4.45 (m, 1H), 4.08–3.72 (m, 5H), 2.53 (d, J=5.1 Hz, 1H), 2.35–2.00 (m, 4H), 1.75–0.80 (m, 9H), 0.95 (d, J=6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 215.3, 134.6, 119.1, 108.7, 81.5, 74.8, 65.4, 64.3, 53.1, 43.0, 35.6, 29.0, 25.7, 23.8, 21.6, 17.7; EI MS *m/z* (relative intensity) 280 (M$^+$, 5), 265 (M−CH$_3$, 1), 238 (5), 237 (16), 212 (26), 183 (7), 155 (73), 139 (8), 124 (8), 113 (100), 112 (23), 111 (17), 87 (12), 86 (18), 69 (29). **16b**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.97–4.88 (m, 1H), 4.20 (br. t, J=2.9 Hz, 1H), 4.11 (dd, J=16.7, 0.7 Hz, 1H), 4.08–3.72 (m, 4H), 3.66 (d, J=16.7 Hz, 1H), 2.77–2.66 (m, 1H), 2.35–2.00 (m, 3H), 1.75–0.80 (m, 9H), 0.96 (d, J=6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 216.6, 134.9, 119.1, 110.7, 80.5, 72.6, 64.9, 64.3, 55.3, 40.8, 34.4, 26.9, 25.7, 24.2, 21.5, 17.7; EI MS *m/z* (relative intensity) 280 (M$^+$, 3), 265 (M−CH$_3$, 1), 251 (1), 237 (1), 235 (1), 222 (3), 211 (13), 207 (3), 163 (3), 137 (4), 114 (9), 113 (100), 86 (29), 69 (12).

1.3.7. (±)-6-Methyl-2-(phenylseleno)-tetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (16c) and (±)-6-methyl-3a-(phenylseleno)-tetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (16d). A solution of LDA was prepared by adding *n*-BuLi (1.34 mL, 2.5 M in hexanes, 3.35 mmol, 1.2 equiv.) to a solution of diisopropylamine (0.47 mL, 3.36 mmol, 1.2 equiv.) in THF (10 mL) at 0°C. After 15 min at 0°C, the resulting solution of LDA was added to a solution of ketone **16** (0.593 g, 2.8 mmol, 1.0 equiv.) in THF (2 mL) at 0°C and after 30 min at 0°C, a solution of phenylselenyl chloride (0.804 g, 4.2 mmol, 1.5 equiv.) and NaI (0.021 g, 0.14 mmol, 0.05 equiv.) in THF (2 mL) was added. After 1 h at 0°C, the reaction mixture was allowed to warm slowly to rt (12 h). A saturated aqueous NH$_4$Cl solution (10 mL) and Et$_2$O (50 mL) were added. The organic layer was separated, washed with brine (2×5 mL), and dried over MgSO$_4$. After filtration and evaporation of the solvent, the crude residue was purified. Flash chromatography on silica gel (AcOEt/petroleum ether: 1/9) afforded an inseparable mixture of **16c** and **16d** (0.31 g, 0.84 mmol, 30% yield) in a ratio (50/50) and ketone **16** (0.220 g, 1.04 mmol, 37% yield). **16c**+**16d**: R_f: 0.55 (AcOEt/petroleum ether: 1/6). **16c**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.65–7.18 (m, 5H), 4.64 (m, 1H), 4.15–3.69 (m, 5H), 2.55 (d, J=5.2 Hz, 1H), 2.30–1.05 (m, 5H), 0.92 (d, J=6.2 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 208.8, 135.1, 128.9, 128.1, 127.9, 108.8, 84.6, 75.5, 65.5, 64.4, 52.6, 42.8, 34.8, 24.1, 21.4; EI MS *m/z* (relative intensity) 368 (M+1, 4), 280 (6), 211 (34), 157 (6), 113 (100), 86 (20), 77 (5). **16d**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.65–7.18 (m, 5H), 5.22–4.90 (m, 1H), 4.15–3.69 (m, 5H), 3.38 (d, J=16.6 Hz, 1H), 2.30–1.05 (m, 5H), 0.98 (d, J=6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 213.4, 137.6, 129.4, 129.2, 125.2, 110.9, 80.3, 68.4, 65.9, 65.0, 59.8, 41.1, 32.6, 24.2, 17.8; EI MS *m/z* (relative intensity) 368 (M+1, 2), 212 (13), 211 (100), 157 (7), 155 (11), 125 (21), 113 (17), 87 (28).

1.3.8. (±)-6-Methyl-2-(3-methylbut-2-enyl)-3a-(phenylseleno)-tetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (16e). A solution of LDA was prepared by adding *n*-BuLi (0.48 mL, 2.5 M in hexanes, 1.2 mmol, 1.2 equiv.) to a solution of diisopropylamine (0.17 mL, 1.2 mmol, 1.2 equiv.) in THF (6 mL) at 0°C. After 15 min at 0°C, the resulting solution of LDA was added to the mixture of regioisomers **16c** and **16d** (0.37 g, 1.0 mmol, 1.0 equiv.) in THF (4 mL) at 0°C and after 30 min, 4-bromo-2-methyl-2-butene (0.14 mL, 1.2 mmol, 1.2 equiv.) was added. After 1 h at 0°C, the cooling bath was removed and the reaction mixture was stirred for 12 h at rt. A saturated aqueous NH$_4$Cl solution (5 mL) and Et$_2$O (50 mL) were then added. The organic layer was separated and washed with brine (2×5 mL), and dried over (MgSO$_4$). After filtration and evaporation of the solvent, the crude residue was purified. Flash chromatography on silica gel (AcOEt/petroleum ether: 1/9) furnished **16e** (0.173 g, 0.41 mmol, 41% yield) and recovered **16c** (0.187 g, 0.50 mmol, 50% yield). R_f: 0.70 (AcOEt/petroleum ether: 1/6); IR (neat) 1760, 1580 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.68–7.55 (m, 2H), 7.32–7.23 (m, 3H), 5.07–4.97 (m, 1H), 4.64–4.54 (m, 1H), 4.17–3.63 (m, 5H), 2.70 (dd, J=14.9, 6.4 Hz, 1H), 2.24 (dd, J=14.9, 9.4 Hz, 1H), 2.19–2.00 (m, 2H), 1.76–1.10 (m, 3H), 1.73 (br. s, 3H), 1.62 (br. s, 3H), 0.95 (d, J=6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 211.2, 135.2, 134.7, 129.0, 128.9, 128.6, 118.8, 110.7, 85.3, 78.2, 65.0, 64.4, 56.1, 40.8, 33.7, 27.0, 25.8, 24.4, 21.5, 17.8.

1.3.9. (±)-(3a*RS*,6*SR*,7a*SR*)-2-(1-Hydroxy-3-methylbut-2-enyl)-6-methyltetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]dioxolan]-3(2*H*)-one (17). To a solution of diisopropylamine (0.348 mL, 2.49 mmol, 1.2 equiv.) in THF (32.6 mL), at 0°C, was added *n*-BuLi (0.995 mL, 2.5 M in hexanes, 2.49 mmol). The resulting solution was stirred 10 min at 0°C and cooled to −78°C and a solution of ketone **16** (0.440 g, 2.08 mmol, 1.0 equiv.) in THF (3.6 mL) was added dropwise. The resulting mixture was stirred for

30 min at −78°C and a solution of 3-methyl-2-butenal (0.34 mL, 4.15 mmol, 2 equiv.) was added dropwise. After 15 min at −78°C, the reaction mixture was quenched by addition of a solution of AcOH (0.15 mL, 2.49 mmol, 1.2 equiv.) in Et_2O (1.4 mL). The reaction mixture was then warmed up to rt and H_2O (3 mL) was added. The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic phases were washed with brine (3×15 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil which was purified by flash chromatography on silica gel (Et_2O/pentane: 1/1) to give ketone **16** (0.130 g, 0.61 mmol, 29.5% yield) and **17** (0.421 g, 1.42 mmol, 68.5% yield) as a mixture of two diastereomers in a ratio (50/50). R_f: 0.32 (Et_2O/pentane: 1/1); IR (neat) 3470, 1750, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.37 (dm, *J*=9.2 Hz, 0.5H), 5.29 (dm, *J*=9.2 Hz, 0.5H), 4.71–462 (m, 2×0.5H), 4.61–4.53 (m, 2×0.5H), 3.99–3.69 (m, 5H), 2.52 (br. d, *J*=6.1 Hz, 0.5H), 2.51 (m, 0.5H), 2.50 (br. d, *J*=6.1 Hz, 0.5H), 2.20 (m, 0.5H), 2.15–2.00 (m, 2H), 1.68 (m, 4H), 1.64 (d, *J*=1.5 Hz, 1.5H), 1.60 (d, *J*=1.1 Hz, 1.5H), 1.26–1.12 (m, 1H), 1.13 (td, *J*=12.9, *J*=3.3 Hz, 1H), 0.90 (d, *J*=6.6 Hz, 1.5H), 0.89 (d, *J*=6.6 Hz, 1.5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.3, 214.0, 137.0,123.2, 123.0, 108.8, 108.7, 83.9, 83.5, 77.2, 76.8, 69.4, 69.0, 65.4, 65.3, 64.3, 64.2, 53.5, 53.3, 53.1, 42.9, 35.8, 35.7, 25.8, 25.7, 23.7, 23.6, 21.4, 18.2; Anal. calcd for $C_{16}H_{24}O_5$: C, 64.85; H, 8.16. Found C, 64.37; H, 7.88.

1.3.10. (±)-(3a*RS*,6*SR*,7a*SR*)-6-Methyl-2-(3-methylbut-2-enylidene)-tetrahydrospiro[benzofuran-4(5*H*),2′-[1,3]-dioxolan]-3(2*H*)-one (18). The mixture of aldols **17** (0.222 g, 0.80 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (6 mL) and cooled at 0°C. Triethylamine (0.67 mL, 4.8 mL, 6 equiv.), a catalytic amount of 4-DMAP were added to the solution, and trifluoroacetic anhydride (0.34 mL, 2.4 mmol, 3 equiv.) in CH_2Cl_2 (3 mL) was then added dropwise at 0°C over a period of 30 min. The mixture was stirred at 0°C for 2 h and then warmed up to rt very slowly (20 h). After 24 h at rt, the reaction mixture was quenched by addition of a saturated aqueous $NaHCO_3$ solution (3 mL), water (3 mL) and Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Et_2O/pentane: 1/3) to give **18** (0.185 g, 0.67 mmol, 83% yield) as a white solid. Mp: 148–149°C; R_f: 0.60 (Et_2O/pentane: 1/3); IR (KBr) 1730, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.25 (d, 1H, *J*=12.1 Hz, 1H), 6.13 (dm, 1H, *J*=12.1 Hz, 1H), 4.58 (m, 1H), 4.07 (m, 1H), 3.92–3.74 (m, 3H), 2.72 (d, *J*=6.3 Hz, 1H), 2.25 (dm, *J*=14.7 Hz, 1H), 2.13 (m, 1H), 1.87 (br. s, 3H), 1.83 (br. s, 3H), 1.74 (dm, *J*=13.7 Hz, 1H), 1.44–1.10 (m, 2H), 0.99 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.5, 147.6, 142.7, 118.6, 109.0, 102.5, 77.7, 65.6, 64.4, 52.2, 43.1, 35.4, 26.5, 23.7, 21.4, 18.7; EI MS *m/z* (relative intensity) 279 (M+1, 8), 278 (M, 45), 263 (14), 155 (38), 139 (10), 113 (100), 96 (38), 81 (16). HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1520.

1.3.11. (±)-(3*RS*,3a*RS*,6*SR*,7a*SR*)-3,6-Dimethyl-2-(3-methylbut-2enylidene)hexahydrospiro[benzofuran-4(2*H*),2′-[1,3]dioxolan]-3-ol (19). Anhydrous $CeCl_3$[31] was dried just before use (vacuo ca. 0.1 Torr, 140°C, 2 h) and anhydrous THF (47 mL) freshly distilled was added with vigorous stirring. The resulting suspension was stirred overnight at rt, and a solution of **18** (0.242 g, 0.87 mmol, 1 equiv.) in THF (47 mL) was added. After 3 h at rt, methylmagnesium bromide (2.03 mL, 3 M in Et_2O, 6.09 mmol, 7 equiv.) was added with vigorous stirring at 0°C. After 15 min, the reaction was quenched with brine (10 mL) and diluted with Et_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic phases were washed with an aqueous saturated $NaHCO_3$ solution (15 mL) and brine (15 mL). After drying over $MgSO_4$ and evaporation of the solvent, the crude residue was purified by flash chromatography on silica gel (Et_2O/pentane: 1/1) to give **19** (0.245 g, 0.84 mmol, 96% yield) as a solid. Mp 151°C; R_f: 0.38 (Et_2O/pentane: 1/1); IR (KBr) 3510, 1680, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.05 (dm, *J*=11.4 Hz, 1H), 5.32 (d, *J*=11.4 Hz, 1H), 4.45 (m, 1H), 4.14–3.92 (m, 4H), 3.23 (br. s, 1H), 2.24 (d, *J*=5.2 Hz, 1H), 2.17 (dm, *J*=14.7 Hz, 1H), 1.98 (m, 1H), 1.84 (dm, *J*=13.6 Hz, 1H), 1.78 (br. s, 3H), 1.71 (br. s, 3H), 1.49 (br. s, 3H), 1.26 (m, 1H), 0.98 (dd, *J*=13.6, 11.8 Hz, 1H), 0.95 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.3, 130.1, 118.3, 110.2, 91.6, 79.0, 77.5, 64.1, 62.1, 51.0, 40.8, 35.9, 28.7, 25.9, 23.6, 21.1, 18.0; EI MS *m/z* (relative intensity) 295 (M+1, 19), 294 (M, 100), 277 (6), 276 (29), 189 (11), 162 (17), 161 (14), 155 (57), 154 (19), 153 (14), 139 (15), 125 (30), 113 (96), 112 (32), 111 (86), 95(21), 81 (14), 69 (22). HRMS calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1825.

1.3.12. (±)-(3*RS*,3a*RS*,6*SR*,7a*SR*)-3,6-Dimethyl-2-(3-methylbut-2-enylidene)-3-[(triethysilyl)oxy]-hexahydrospiro[benzofuran-4(2*H*),2′-[1,3]dioxolane (20). To a solution of alcohol **19** (0.176 g, 0.60 mmol, 1 equiv.) in DMF (4 mL) was added $AgNO_3$ (0.204 g, 1.2 mmol, 2 equiv.). When all the silver nitrate was dissolved (about 2 min), triethylsilyl chloride (0.20 mL, 1.2 mmol, 2 equiv.) was added dropwise. The reaction mixture was stirred for 1.5 h at rt, $AgNO_3$ (0.204 g, 1.2 mmol, 2 equiv.) and triethylsilyl chloride (0.20 mL, 1.2 mmol, 2 equiv.) were added again. After 1.5 h at rt, the reaction mixture was diluted with Et_2O (20 mL) and filtered into a cold (0°C) aqueous 5% $NaHCO_3$ solution (16 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic phases were washed with H_2O (3×10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil which was purified by flash chromatography on silica gel (Et_2O/pentane: 1/5) to afford **20** (0.220 g, 0.54 mmol, 90% yield) as an oil and alcohol **19** (0.014 g, 0.05 mmol, 8% yield). R_f: 0.68 (Et_2O/pentane: 1/5); IR (neat) 1665, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.97 (dm, *J*=11.0 Hz, 1H), 5.17 (d, *J*=11.0 Hz, 1H), 4.51 (m, 1H), 3.90–3.79 (m, 4H), 2.13–1.91 (m, 4H), 1.72 (br. s, 3H), 1.65 (m, 1H), 1.64 (br. s, 3H), 1.51 (s, 3H), 1.31 (m, 1H), 0.98 (d, *J*=7.0 Hz, 3H), 0.88 (t, *J*=7.9 Hz, 9H), 0.57 (q, *J*=7.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.5, 130.7, 118.4, 110.6, 94.3, 78.9, 77.7, 64.1, 63.6, 54.1, 38.9, 34.5, 26.7, 26.1, 25.9, 19.9, 17.9, 6.9, 6.5; EI MS *m/z* (relative intensity) 409 (M+1, 29), 408 (M, 96), 394 (14), 393 (49), 305 (7), 277 (8), 251 (10), 239 (10), 226 (19), 225 (100), 189 (40), 157 (30), 113 (32), 87 (14), 75 (14). HRMS calcd for $C_{23}H_{40}O_4Si$ 408.2696, found 408.2695.

1.3.13. (±)-(3*RS*,3a*RS*,6*SR*,7a*SR*)-3,6-Dimethyl-2-(3-methylbut-2-enylidene)-3-[(triethysilyl)oxy]-hexahydro-[benzofuran-4(2H)-one (21). Solid cerium ammonium nitrate (0.004 g, 0.03 equiv.) was added to a solution of ketal **20** (0.090 g, 0.22 mmol, 1 equiv.) in CH_3CN (0.4 mL) and borate–HCl buffered solution (Merck, pH 8, 0.5 mL). The resulting solution was heated at 60°C for 24 h. After cooling to rt, H_2O (1 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed under vacuo. The crude residue was purified by flash chromatography on silica gel to afford **21** (0.048 g, 0.13 mmol, 60% yield) as a colorless solid. Physical and spectral data are identical to those reported previously.[21b] Mp 64–65°C (lit.[21b] 65–66°C); R_f: 0.42 (Et_2O/petroleum ether: 1/5); IR (KBr) 1703, 1665, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.97 (dm, J=11.4 Hz, 1H), 5.22 (d, J=11.4 Hz, 1H), 4.66 (ddd, J=9.1, J=8.8 and 6.0 Hz, 1H); 2.64 (d, J=8.8 Hz, 1H), 2.47 (dd, J=16.2, 5.5 Hz, 1H), 2.33 (m, 1H), 2.14–2.02 (m, 2H), 1.89 (m, 1H), 1.74 (s, 3H), 1.66 (br. s, 3H), 1.50 (s, 3H), 0.90, (d, J=7.4 Hz, 3H), 0.83 (t, J=7.8 Hz, 9H), 0.53 (q, J=7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.1, 156.9, 132.5, 117.9, 95.9, 81.2, 78.0, 60.3, 48.0, 35.1, 26.1, 25.9, 24.9, 19.9, 18.0, 6.7, 6.1; EI MS m/z (relative intensity) 365 (M+1, 8), 364 (M, 27), 349 (9), 335 (21), 239 (9), 226 (21), 225 (100), 211 (4), 189 (5), 103 (8), 87 (7), 75 (11). HRMS calcd for $C_{21}H_{36}O_3Si$ 364.2434, found 364.2431.

Acknowledgements

Two of us (J.-L. R.) and (B. G.) thank the MRES for a grant.

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