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Enantioselective Synthesis of the Hydroazulene Core of 3α-Hydroxy-15-rippertene

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Dedicated to Professor Hans J. Schäfer on the occasion of his 70th birthday

Keywords: Hydroazulenes / Hydroboration / Ring expansion / Organocopper compounds / Aldol reactions

As part of a project directed toward the total synthesis of the tetracyclic diterpene 3α-hydroxy-15-rippertene, a constituent of the defense secretion of higher termites, a fast access to two advanced hydroazulene key intermediates has been achieved by starting from (–)-isopulegol. A regio- and diastereoselective formal hydromethallylation and a regioselective ring expansion served as the key steps in the formation of the seven-membered ring. Completion of the bicyclic title compounds was then achieved by cyclopentene annulation through diastereoselective conjugate addition of organocuprates and subsequent intramolecular aldol condensations.

Introduction

The defense secretion of the nasute termite soldiers contains structurally unique bi- to tetracyclic diterpenes derived from cembrene A dissolved in monoterpene hydrocarbons.[1] The biological effects of these diterpenes are currently only poorly investigated due to the low quantities isolated. However, several tricyclic trinervitane diterpenes showed interesting antimicrobial activities in recent studies.[2] Due to their complex architecture, the tetracyclic termite diterpenes are attractive synthetic targets. So far, the total synthesis of a single naturally occurring kempane, kempene-2,[3] has been achieved in racemic form, and many advanced synthetic investigations directed to this class of natural products have been reported.[4,5]

We recently reinitiated our studies toward the enantioselective total synthesis of the diterpene 3α-hydroxy-15-rippertene (**1**) that has been isolated from the defense secretion of the higher termites *Nasutitermes rippertii* and *Nasutitermes ephratae* by Prestwich[6] (Figure 1). Several years ago, we accomplished the first enantioselective construction of the tetracyclic skeleton of **1** starting from the sesquiterpene lactone (–)-α-santonin.[5] Herein we disclose a concise synthetic sequence to two advanced key intermediates **4a** and **4b** containing the complete hydroazulene moiety of **1** by commencing with (–)-isopulegol (**6**) as the chiral source. As outlined in Figure 1, a domino Heck cyclization[7] of enol triflate **3** is envisioned to generate the tetracyclic ring system, and the hydroazulenes **4a** and **4b** represent suitable precursors for this intermediate; **4a** and **4b**, in turn, should be available from the cycloheptenone **5** by cyclopentene annulation, while **5** can be retrosynthetically traced back to (–)-isopulegol (**6**) by a sequence of chain elongation, oxidation and ring expansion.

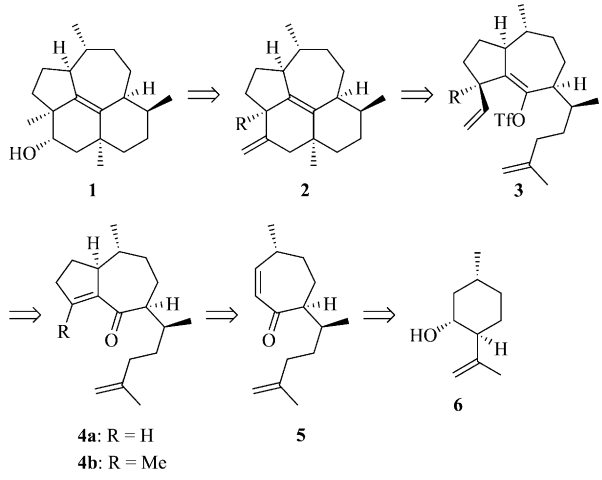

Figure 1. Retrosynthetic analysis.

Results and Discussion

Preparation of **5** from **6** started with a high-yielding synthesis of the alcohol **8** according to a methodology developed by Knochel (Scheme 1).[8] To this end, a completely diastereoselective hydroboration of the silyl-protected[9] (–)-

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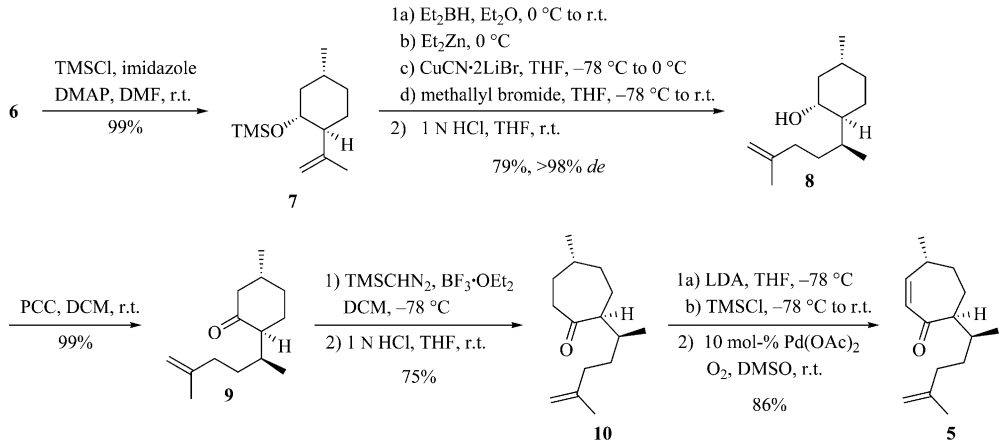


Scheme 1. Synthesis of cycloheptenone **5**.

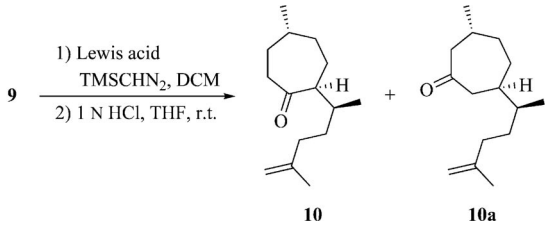
isopulegol derivative **7** was effected with diethylborane followed by a boron/zinc exchange reaction with diethylzinc to generate a diorganozinc species. Hydroboration of **7** follows the stereochemical course already observed with **6**[10] through minimization of allylic strain.[11] After copper-induced allylic substitution with methallyl bromide and deprotection of the intermediate silyl ether with aqueous HCl,[12] the enantiomerically pure alcohol **8** was isolated in excellent yield with >98% *de* (GC). PCC oxidation[13] of **8** to give the ketone **9** and a Lewis acid catalyzed ring expansion of **9** with (trimethylsilyl)diazomethane[14] afforded the cycloheptanone **10** after hydrolysis of the trimethylsilyl enol ether intermediate. Subsequent reconversion of **10** into the TMS enol ether[15] and oxidation of this compound according to the Saegusa–Ito method[16] in DMSO with oxygen as the stoichiometric oxidant then smoothly furnished the cycloheptenone **5**. An attempt at a one-pot conversion of ketone **9** to give **5** was less efficient due to partial hydrolysis of the silyl enol ether in the course of the trifluoroborane-triggered ring enlargement.

During optimization of the ring expansion with (trimethylsilyl)diazomethane, we found that the ratio of cycloheptanones **10/10a** showed a marked dependence on the nature of the Lewis acid applied (Table 1).[17] Gratifyingly, the desired regioisomer **10** could be isolated in 75% yield with the aid of trifluoroborane–diethyl ether followed by hydrolysis.

For construction of the hydroazulenes **4a**,**b** from **5** we used a conjugate addition followed by either an acetal cleavage/aldol or an oxidation/aldol sequence. The first route commenced with a diastereoselective copper-catalyzed 1,4-addition[18] of the acetal-protected Grignard species **11** or **13**, respectively, to cycloheptenone **5** (Scheme 2).[19] A conjugate addition *trans* to the allylic methyl group in **5** to give **12** and **14**, respectively, was proven by NOESY experiments.

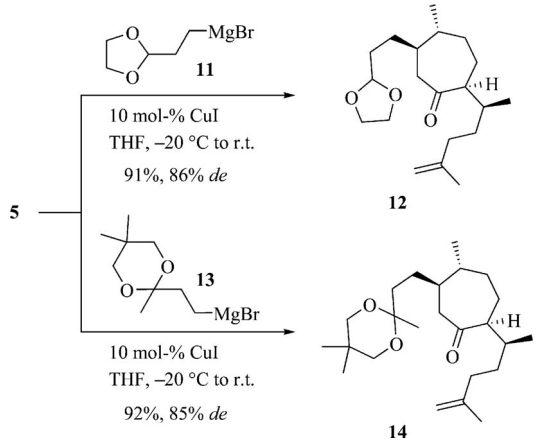
Finally, the hydroazulenes **4a** and **4b** could be generated by palladium-catalyzed acetal cleavage[20] and subsequent aldol condensations under basic conditions[21,22] (Scheme 3). For **4b**, an alternative combination of PPTS-induced deblocking[23] of **14** and aldol condensation without purification of diketone **16** turned out to be more productive. Whereas acetals similar to **12** have been converted

Table 1. Ring expansion with various Lewis acids.



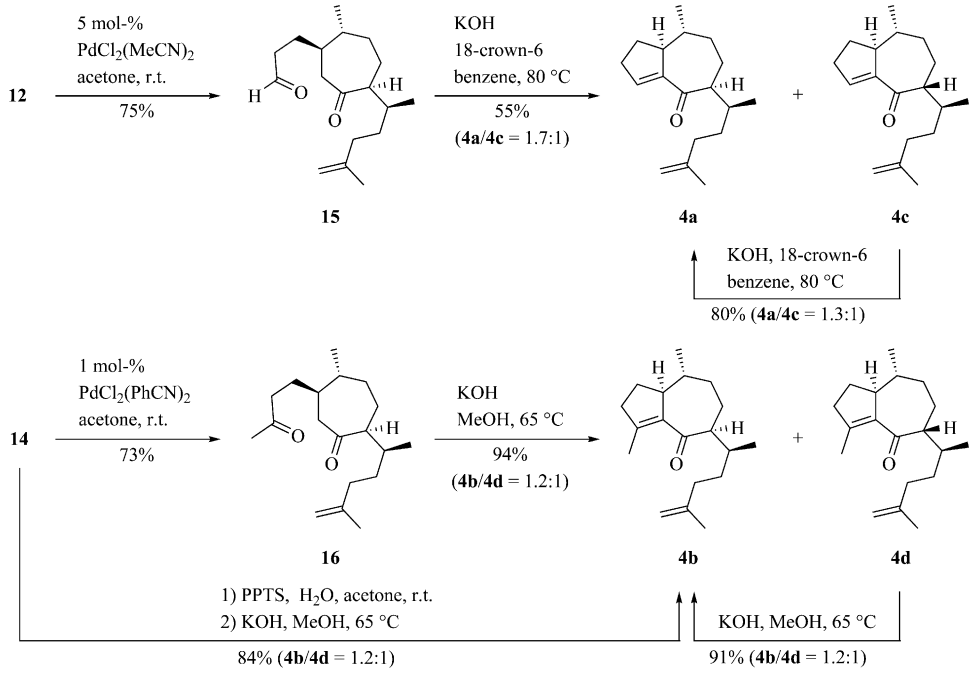
Entry[a]	Lewis acid	Conditions	Yield	Ratio **10/10a**[a]
1	Me_3Al	–78 °C to room temp., 16 h	66%	1:1
2	Me_2AlCl	–78 °C, 1 h	78%	6:1
3	$EtAlCl_2$	–78 °C, 1 h	57%	1:1
4	$BF_3{\cdot}OEt_2$	–78 °C, 1 h	90%	5:1

[a] Ratio of isolated isomers.



Scheme 2. Copper-catalyzed 1,4-addition.

into hydroazulene enones with aqueous HCl in a one-pot procedure,[19,24] all attempts to use this methodology for the preparation of hydroazulene **4a** by varying the acid concentration, temperature and solvent met with failure in our hands. In addition, an acid-catalyzed shift of the terminal double bond took place at higher temperature, e.g. in refluxing THF. Only the palladium-catalyzed transacetaliza-



Scheme 3. Acetal cleavage and aldol condensation.

tion reaction[20] gave rise to aldehyde **15** in good yield. Due to 1,4-addition of the solvent methanol, the conditions applied for cyclization of ketone **16** could not be transferred to the production of enone **4a** from aldehyde **15**. Eventually, the desired aldol condensation of **15** was attained by using KOH in the presence of the phase-transfer catalyst 18-crown-6 in benzene with the aid of a Dean–Stark trap.[22] Unfortunately, the strongly basic conditions required for cyclization caused a significant epimerization α to the ketone function for both **4a** and **4b**. Gratifyingly, however, the two resultant epimeric mixtures could be readily separated by flash chromatography, which allowed a high-yielding equilibration of the undesired isomers **4c** and **4d** under conditions analogous to those used during their formation from **15** and **16**.

The relative configuration of isomers **4a**–**d** was established by 2D NMR measurements through the NOESY results summarized in Figure 2.

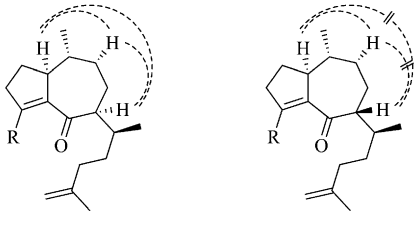
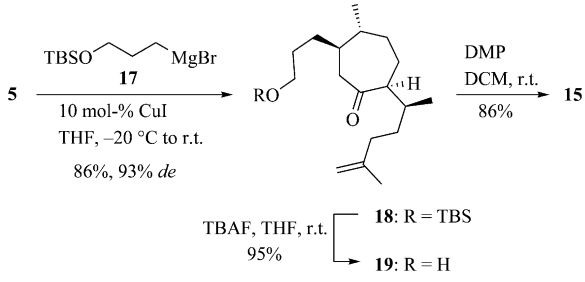


Figure 2. Results of NOESY experiments.

In order to reduce the time needed for the preparation of aldehyde **15** from **5** and to facilitate its purification, we additionally developed the alternative route to **15** depicted in Scheme 4. This sequence commenced again with a copper-catalyzed conjugate addition[18,19] of the TBS-protected Grignard species **17**[25] to cycloheptenone **5**, which succeeded with high stereochemical control (93% *de*) in 86% yield. Desilylation of **18** with TBAF[26] had to be monitored very carefully by TLC, because longer reaction times led to an epimerization α to the carbonyl group. After oxidation[27] of alcohol **19** with the Dess–Martin periodinane (DMP), aldehyde **15** was isolated in an overall yield of 70% over 3 steps in a total reaction time of 8 h. Compared to the acetal cleavage sequence, which produces **15** in an overall yield of 68% (2 steps) from **5** in 3 d, this oxidation route is now our preferred pathway, since it also delivers the aldehyde **15** with an improved purity of >99% (GC).



Scheme 4. Alternative route to aldehyde **15**.

Conclusions

The synthetic sequence reported herein permits a fast access to the hydroazulenes **4a** and **4b**, two advanced intermediates for the enantioselective total synthesis of 3α-hydroxy-15-rippertene (**1**). Studies toward completion of the synthesis according to the strategy illustrated in Figure 1 are currently in progress.

Experimental Section

General Remarks: NMR spectra were recorded with Bruker ASP-500 (^{1}H: 500.13 MHz; ^{13}C: 125.77 MHz). The chemical shifts are reported in ppm and refer to the applied NMR solvent (for $CDCl_3$: ^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.0 ppm). The assignment of the signals resulted from two-dimensional NMR methods (COSY, HSQC, HMBC, NOESY). The coupling constants (*J*) are given in Hertz (Hz). Resonance patterns are reported with the following notations: br. (broad), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The multiplicities of the ^{13}C NMR signals were determined by DEPT spectra. FT-IR spectra were recorded with Nicolet 205 FT-IR and Nicolet Avatar 360 FT-IR instruments, and only the most significant absorption bands are given in cm^{-1}. Mass spectra were recorded by GC/MS coupling with Hewlett Packard 5890 II and Agilent 6890N instruments by using the mass-selective detectors Hewlett Packard 5972 and Agilent 5973N (EI, 70 eV). Specific rotations were determined at 589 nm with Perkin–Elmer 241 and 341 LC instruments and refer to the given temperature. Thin-layer chromatography (TLC) was carried out by using TLC aluminum sheets with silica gel 60 F_{254} purchased from Merck. Flash column chromatography[28] was performed by using silica gel 60 (40–60 mesh) as the stationary phase purchased from Merck. All eluant mixtures are given in vol.-%. All solvents used for flash chromatography were distilled prior to use (ethyl acetate from tartaric acid, diethyl ether from KOH). Unless otherwise noted, solvents and reagents were of reagent grade, purchased from ABCR, Acros, Aldrich, Fluka, Merck, Lancaster, and used without further purification. Tetrahydrofuran and diethyl ether were first distilled from CaH_2 and finally dried with sodium/potassium alloy. Dichloromethane was first distilled and then finally dried with aluminum oxide (basic) using a cartridge device.[29] Triethylamine and chlorotrimethylsilane were distilled from calcium hydride. Methanol was dried with magnesium turnings. Copper cyanide was dried at 0.05 mbar and 160 °C for 3 d, and lithium bromide was dried at 0.1 mbar and 120 °C for 2 h. All reactions were carried out in heat gun dried flasks under argon unless otherwise stated. Diethylzinc and triethylborane were transferred to the Schlenk flask by using heat gun dried glass syringes, which were cooled down under argon. The excess of diethylzinc and triethylborane was removed from the reaction mixture under reduced pressure and condensed in a safety flask cooled down to –78 °C. After complete removal of the pyrophoric liquids from the reaction mixture, the safety flask was flushed with argon, and the residue was diluted with THF and carefully hydrolyzed with ethanol at –78 °C and finally treated with water.

Silyl Ether 7: (–)-Isopulegol (**6**) (15.0 g, 97.2 mmol, 1.0 equiv.) was dissolved in DMF (200 mL) and subsequently treated with imidazole (13.2 g, 0.195 mol, 2.0 equiv.), 4-(dimethylamino)pyridine (200 mg, 1.64 mmol, 0.02 equiv.) and chlorotrimethylsilane (18.5 mL, 15.9 g, 0.146 mol, 1.5 equiv.) at room temperature. After 16 h, the reaction mixture was poured into diethyl ether/pentane/H_2O (1:1:1) (1500 mL). The organic layer was washed with water (3 × 300 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by distillation under reduced pressure afforded **7** (21.9 g, 99%) as a colorless liquid. B.p. 86 °C (13 mbar). $[\alpha]_D^{25}$ = –37.3 (*c* = 1.12, in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2955, 2924, 1250, 1009, 885 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.75 (s, 1 H), 4.72 (s, 1 H), 3.45 (ddd, *J* = 10.3, 10.3, 4.4 Hz, 1 H), 1.91–1.86 (m, 1 H), 1.86–1.82 (m, 1 H), 1.68 (s, 3 H), 1.63–1.58 (m, 2 H), 1.45–1.40 (m, 1 H), 1.34–1.26 (m, 1 H), 1.06–0.99 (m, 1 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 0.87–0.85 (m, 1 H), 0.06 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 147.94 (s), 110.78 (t), 73.69 (d), 53.09 (d), 45.16 (t), 34.36 (t), 31.68 (d), 30.46 (t), 22.24 (q), 21.17 (q), 0.45 (q) ppm. GC-MS (EI): *m*/*z* (%) = 226 (3) [M$^+$], 143 (100). $C_{13}H_{26}OSi$ (226.43): calcd. C 68.96, H 11.57; found C 68.72, H 11.79.

Alcohol 8: Preparation of diethylborane (solution in diethyl ether): To a solution of borane–dimethyl sulfide complex (4.75 mL, 50.0 mmol, 1.0 equiv.) in diethyl ether (21 mL) at 0 °C was added triethylborane (14.5 mL, 0.1 mol, 2.0 equiv.). After 30 min at 0 °C, the diethylborane solution is ready for use. Alkene **7** (6.50 g, 28.7 mmol, 1.0 equiv.) was placed in a Schlenk flask and treated through cannula dropwise with the diethylborane solution (14.4 mL, 57.4 mmol, 2.0 equiv.) at 0 °C. After the reaction mixture was stirred at room temperature for 2 d, the solvent was removed in vacuo (0 °C, 0.1 mbar) for 30 min. Diethylzinc (5.74 mL, 57.4 mmol, 2.0 equiv.) was added with a heat gun dried glass syringe (cooled down under argon) at 0 °C, and the mixture was stirred at this temperature for 2 h. The excess diethylzinc and formed triethylborane was distilled off under reduced pressure (0 °C, 0.1 mbar) for 4 h. The residue was dissolved in THF (20 mL), cooled down to –78 °C and treated with a solution of copper cyanide (2.57 g, 28.7 mmol, 1.0 equiv.) and lithium bromide (4.99 g, 57.4 mmol, 2.0 equiv.) in THF (30 mL). The reaction mixture was allowed to warm to 0 °C for 30 min and, after a color change from olive-green to black, immediately cooled back to –78 °C and treated with methallyl bromide (11.6 g, 86.1 mmol, 3.0 equiv.). The reaction mixture was allowed to warm to room temperature overnight and poured into an aqueous saturated solution of NH_4Cl (500 mL). The aqueous layer was extracted with diethyl ether (3 × 500 mL). The combined organic phases were washed with brine (80 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude silyl ether was dissolved in THF (200 mL) and treated at room temperature with aqueous HCl (1 N) (50 mL). After 1 h, the reaction mixture was neutralized with an aqueous saturated solution of $NaHCO_3$ (50 mL), and the aqueous layer was extracted with diethyl ether (5 × 100 mL). The combined organic phases were washed with brine (80 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (dichloromethane) gave **8** (4.75 g, 79%) as a colorless oil. R_f = 0.36 (dichloromethane). $[\alpha]_D^{25}$ = –51.3 (*c* = 1.01, in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3363, 2952, 2927, 2921, 884 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.69 (s, 1 H), 4.67 (s, 1 H), 3.46 (ddd, *J* = 10.4, 10.4, 4.3 Hz, 1 H), 2.13–2.07 (m, 1 H), 1.97–1.87 (m, 3 H), 1.71 (s, 3 H), 1.66–1.60 (m, 2 H), 1.58–1.51 (m, 1 H), 1.44–1.38 (m, 1 H), 1.31 (br. s, OH), 1.16–1.06 (m, 2 H), 1.03–0.97 (m, 1 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 0.95–0.89 (m, 1 H), 0.87–0.78 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 147.61 (s), 109.62 (t), 71.05 (d), 50.75 (d), 45.08 (t), 36.30 (t), 34.68 (t), 31.60 (d), 31.20 (d), 29.27 (t), 24.53 (t), 22.50 (q), 22.18 (q), 17.78 (q) ppm. GC-MS (EI): *m*/*z* (%) = 210 (2) [M$^+$], 81 (100). $C_{14}H_{26}O$ (210.36): calcd. C 79.94, H 12.46; found C 79.65, H 12.73.

Cyclohexanone 9: Pyridinium chlorochromate (5.33 g, 24.7 mmol, 2.0 equiv.) was suspended in dichloromethane (60 mL) and treated with a solution of alcohol **8** (2.60 g, 12.4 mmol, 1.0 equiv.) in dichloromethane (20 mL) at room temperature. After 16 h, the reaction mixture was diluted with diethyl ether (20 mL) and passed through a pad of silica gel by using diethyl ether as eluant. Evaporation of the solvent afforded **9** (2.55 g, 99%) as a colorless and analytically pure oil. R_f = 0.46 (diethyl ether/pentane, 1:5). $[\alpha]_D^{25}$ = –38.7 (*c* = 1.04, in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2955, 2929, 2871, 1712, 884 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.66 (s, 1 H), 4.65 (s, 1 H), 2.35–2.31 (m, 1 H), 2.13–2.00 (m, 3 H), 1.98–1.81 (m, 5 H), 1.71 (s, 3 H), 1.54–1.48 (m, 1 H), 1.46–1.38 (m, 1 H), 1.36–1.30 (m, 1 H), 1.18–1.10 (m, 1 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz,

3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 212.02 (s), 146.35 (s), 109.55 (t), 55.26 (d), 50.84 (t), 35.66 (t), 35.18 (d), 33.98 (t), 30.92 (t), 30.76 (d), 27.91 (t), 22.41 (q), 22.25 (q), 17.36 (q) ppm. GC-MS (EI): *m*/*z* (%) = 208 (5) [M^+], 96 (100). $C_{14}H_{24}O$ (208.34): calcd. C 80.71, H 11.61; found C 80.77, H 11.66.

General Procedure for the Ring Expansion of Ketone 9: To a solution of the Lewis acid (aluminum Lewis acids were used as solutions in hexanes) in dichloromethane (0.13 M, 1.5 equiv.) cooled down to –78 °C was added dropwise a solution of ketone **9** in dichloromethane (0.31 M, 1.0 equiv.), followed by a solution of (trimethylsilyl)diazomethane (2 M in hexane, 1.5 equiv.). After the given reaction time, an aqueous saturated solution of $NaHCO_3$ was added, and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude silyl enol ether was dissolved in THF (0.12 M) and treated at room temperature with aqueous HCl (1 N) (0.25 mL per mL THF). After 1 h, the reaction mixture was neutralized with an aqueous saturated solution of $NaHCO_3$, and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) gave **10** and **10a** as colorless oils as listed in Table 1.

Cycloheptanones 10 and 10a: To a solution of boron trifluoride–diethyl ether (1.32 g, 9.30 mmol, 1.18 mL, 1.5 equiv.) in dichloromethane (70 mL) cooled down to –78 °C was added dropwise a solution of ketone **9** (1.29 g, 6.19 mmol, 1.0 equiv.) in dichloromethane (20 mL), followed by a solution of (trimethylsilyl)diazomethane (4.65 mL, 2 M in hexane, 9.30 mmol, 1.5 equiv.). After 1 h, an aqueous saturated solution of $NaHCO_3$ (6 mL) was added, and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic phases were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude silyl enol ether was dissolved in THF (50 mL) and treated at room temperature with aqueous HCl (1 N) (12.5 mL). After 1 h, the reaction mixture was neutralized with an aqueous saturated solution of $NaHCO_3$ (12.5 mL), and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) gave **10** (1.03 g, 75%) and **10a** (205 mg, 15%) as colorless oils (**10**/**10a** = 5:1). Data for **10**: R_f = 0.50 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = –115.0 (*c* = 1.05, in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2954, 2929, 2871, 1699, 885 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.67 (s, 1 H), 4.64 (s, 1 H), 2.58 (ddd, *J* = 12.8, 12.8, 2.9 Hz, 1 H), 2.30 (ddd, *J* = 12.7, 6.3, 2.4 Hz, 1 H), 2.24–2.20 (m, 1 H), 2.05–2.00 (m, 1 H), 1.95–1.70 (m, 5 H), 1.69 (s, 3 H), 1.57–1.50 (m, 2 H), 1.48–1.41 (m, 1 H), 1.26–1.17 (m, 2 H), 1.00–0.94 (m, 1 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 217.03 (s), 145.95 (s), 109.82 (t), 58.53 (d), 42.08 (t), 36.99 (t), 36.91 (d), 35.52 (d), 35.14 (t), 33.83 (t), 31.26 (t), 27.38 (t), 23.46 (q), 22.37 (q), 17.26 (q) ppm. GC-MS (EI): *m*/*z* (%) = 222 (2) [M^+], 96 (100). $C_{15}H_{26}O$ (222.37): calcd. C 81.02, H 11.79; found C 80.97, H 11.97. Data for **10a**: R_f = 0.36 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = +54.4 (*c* = 1.01, in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2958, 2919, 2873, 1701, 885 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.67 (s, 1 H), 4.64 (s, 1 H), 2.38–2.28 (m, 4 H), 2.06–2.00 (m, 1 H), 1.96–1.90 (m, 1 H), 1.86–1.77 (m, 2 H), 1.71–1.66 (m, 2 H), 1.69 (s, 3 H), 1.47–1.28 (m, 3 H), 1.27–1.16 (m, 2 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 214.36 (s), 145.90 (s), 109.87 (t), 51.80 (t), 45.93 (t), 40.52 (d), 38.73 (t), 38.55 (d), 35.70 (t), 33.84 (t), 32.17 (d), 31.75 (t), 24.10 (q), 22.39 (q), 15.04 (q) ppm. GC-MS (EI): *m*/*z* (%) = 222 (7) [M^+], 55 (100). $C_{15}H_{26}O$ (222.37): calcd. C 81.02, H 11.79; found C 81.06, H 11.98.

Cycloheptenone 5: To a solution of diisopropylamine (1.67 mL, 1.21 g, 11.9 mmol, 1.5 equiv.) was added dropwise BuLi (6.21 mL, 1.6 M in hexane, 9.93 mmol, 1.25 equiv.) at 0 °C. After 30 min, the reaction mixture was cooled down to –78 °C and treated slowly with a solution of ketone **9** (1.77 g, 7.95 mmol, 1.0 equiv.) in THF (16 mL). After 90 min, chlorotrimethylsilane (1.51 mL, 1.29 g, 11.9 mmol, 1.5 equiv.) was added, and the reaction mixture was stirred for another 90 min. For workup, the solution was passed through a pad of basic aluminum oxide by using diethyl ether as eluant. Evaporation of the solvent afforded the crude silyl enol ether (2.34 g, 100%), which was used without further purification in the next step. To a solution of the crude silyl enol ether (2.34 g, 7.94 mmol, 1.0 equiv.) in DMSO (160 mL) was added $Pd(OAc)_2$ (178 mg, 0.793 mmol, 0.1 equiv.) at room temperature, and a slow stream of oxygen was passed through the reaction mixture. After 16 h, the solution was poured into a cold solution (0 °C) of diethyl ether/H_2O (1:1) (400 mL), and the aqueous layer was extracted with diethyl ether (4 × 150 mL). The combined organic phases were subsequently washed with H_2O and brine (150 mL each), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) to furnish **5** (1.50 g, 86%) as a colorless oil. R_f = 0.43 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = –25.0 (*c* = 1.14, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2960, 2930, 2872, 1651, 882 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 6.12 (ddd, *J* = 12.6, 3.5, 1.5 Hz, 1 H), 5.81 (dd, *J* = 12.6, 2.6 Hz, 1 H), 4.66 (s, 1 H), 4.63 (s, 1 H), 2.48–2.41 (m, 2 H), 2.04–1.97 (m, 2 H), 1.94–1.85 (m, 3 H), 1.67 (s, 3 H), 1.53–1.42 (m, 2 H), 1.31–1.19 (m, 2 H), 1.05 (d, *J* = 7.2 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 208.39 (s), 147.66 (d), 145.97 (s), 129.32 (d), 109.79 (t), 59.82 (d), 39.14 (d), 36.15 (d), 35.55 (t), 32.96 (t), 31.06 (t), 24.17 (t), 22.33 (q), 21.49 (q), 17.37 (q) ppm. GC-MS (EI): *m*/*z* (%) = 220 (7) [M^+], 124 (100). $C_{15}H_{24}O$ (220.35): calcd. C 81.76, H 10.98; found C 81.82, H 11.14.

General Procedure for the Conjugate Addition of Alkyl Bromides to Cycloheptenone 5: Magnesium (2.5 equiv.) was suspended in THF (0.23 mL per mmol), and some crystals of iodine and 3 drops of alkyl bromide (1.35 equiv.) were added at room temperature. The reaction mixture was stirred and eventually heated (max. 60 °C) until the color disappeared and the solution turned cloudy. Subsequently, the mixture was diluted with THF (1.13 mL per mmol Mg) and the remaining alkyl bromide was added within 1 h by using a syringe pump. After 15 min at room temperature, the mixture was cooled down to 0 °C, stirred for 20 min, cooled down to –20 °C and treated with copper(I) iodide (0.13 equiv.). After 5 min at –20 °C, a solution of cycloheptenone **5** in THF (1.33 mL per mmol, 1.0 equiv.) was added within 90 min by using a syringe pump. After the addition, the mixture was stirred at –20 °C for 15 min, warmed to 0 °C and stirred for 15 min before warming to room temperature. After 30 min, the solution was poured into a rapidly stirred 4:1 mixture of saturated aqueous ammonium chloride solution and aqueous ammonium hydroxide (25%) (13 mL per mmol **5**) and diethyl ether (17 mL per mmol **5**) until a clear phase separation appeared. The organic phase was separated, washed twice with ammonia buffer (13 mL per mmol **5**), once with brine (13 mL per mmol **5**), dried with $MgSO_4$, filtered and concentrated under reduced pressure.

1,4-Adduct 12: According to the general procedure for conjugate addition, **12** (531 mg, 91%, 86% *de*) was obtained from cyclohep-

tenone **5** (400 mg, 1.82 mmol) after purification of the crude product by flash column chromatography on silica gel (diethyl ether/pentane, 1:1) as a colorless oil. R_f = 0.58 (diethyl ether/pentane, 1:1). $[\alpha]_D^{25}$ = –94.1 (*c* = 1.05, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2955, 2928, 2874, 1698, 885 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.82–4.80 (m, 1 H), 4.67 (s, 1 H), 4.64 (s, 1 H), 3.95–3.91 (m, 2 H), 3.90–3.71 (m, 2 H), 2.52 (dd, *J* = 11.1 Hz, 1 H), 2.18–2.10 (m, 2 H), 2.06–1.89 (m, 3 H), 1.82–1.77 (m, 1 H), 1.68 (s, 3 H), 1.74–1.54 (m, 5 H), 1.48–1.16 (m, 5 H), 1.03–0.93 (m, 1 H), 0.91 (d, *J* = 6.1 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 216.49 (s), 145.79 (s), 109.92 (t), 104.50 (d), 64.87 (t), 64.84 (t), 58.93 (d), 45.56 (t), 43.87 (d), 40.34 (d), 35.80 (d), 35.44 (t), 34.78 (t), 31.29 (t), 30.13 (t), 28.69 (t), 27.15 (t), 22.36 (q), 21.24 (q), 17.32 (q) ppm. GC-MS (EI): *m*/*z* (%) = 322 (3) [M^+], 73 (100). $C_{20}H_{34}O_3$ (322.48): calcd. C 74.49, H 10.63; found C 74.35, H 10.75.

1,4-Adduct 14: According to the general procedure for conjugate addition, **14** (785 mg, 92%, 85% *de*) was obtained from cycloheptenone **5** (497 mg, 2.26 mmol) after purification of the crude product by flash column chromatography on silica gel (diethyl ether/pentane, 1:3) as a colorless oil. R_f = 0.48 (diethyl ether/pentane, 1:3). $[\alpha]_D^{25}$ = –77.5 (*c* = 1.02, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2955, 2928, 2866, 1698, 884 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.67 (s, 1 H), 4.63 (s, 1 H), 3.37–3.55 (m, 4 H), 2.53 (dd, *J* = 11.3, 11.3 Hz, 1 H), 2.17–2.09 (m, 2 H), 2.02–1.91 (m, 3 H), 1.82–1.77 (m, 1 H), 1.68 (s, 3 H), 1.73–1.65 (m, 2 H), 1.62–1.55 (m, 3 H), 1.42–1.34 (m, 3 H), 1.32 (s, 3 H), 1.25–1.16 (m, 2 H), 0.98 (s, 3 H), 1.02–0.96 (m, 1 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.86 (s, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 216.71 (s), 145.76 (s), 109.91 (t), 98.85 (s), 70.29 (t), 58.93 (d), 45.70 (t), 44.20 (d), 40.32 (d), 35.78 (d), 35.50 (t), 34.76 (t), 34.13 (t), 31.26 (t), 29.88 (s), 27.99 (t), 27.11 (t), 22.74 (q), 22.45 (q), 22.35 (q), 21.29 (q), 20.42 (q), 17.32 (q) ppm. GC-MS (EI): *m*/*z* (%) = 378 (0.3) [M^+], 129 (100). $C_{24}H_{42}O_3$ (378.59): calcd. C 76.14, H 11.18; found C 76.23, H 11.24.

1,4-Adduct 18: According to the general procedure for conjugate addition, **18** (893 mg, 86%, 93% *de*) was obtained from cycloheptenone **5** (577 mg, 2.62 mmol) after purification of the crude product by flash column chromatography on silica gel (diethyl ether/pentane, 1:15) as a colorless oil. R_f = 0.26 (diethyl ether/pentane, 1:15). $[\alpha]_D^{25}$ = –81.5 (*c* = 1.10, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2952, 2928, 2857, 1699, 1254, 885 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.68 (s, 1 H), 4.65 (s, 1 H), 3.58–3.56 (m, 2 H), 2.53 (dd, *J* = 11.0, 11.0 Hz, 1 H), 2.18–2.10 (m, 2 H), 2.05–1.90 (m, 3 H), 1.83–1.78 (m, 1 H), 1.69 (s, 3 H), 1.68–1.55 (m, 4 H), 1.46–1.38 (m, 2 H), 1.34–1.18 (m, 4 H), 1.04–0.97 (m, 1 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 0.87 (s, 9 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.02 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 216.87 (s), 145.86 (s), 109.91 (t), 63.16 (t), 58.96 (d), 45.70 (t), 44.04 (d), 40.34 (d), 35.84 (d), 35.55 (t), 34.81 (t), 31.33 (t), 30.81 (t), 29.00 (t), 27.16 (t), 25.92 (q), 22.40 (q), 21.26 (q), 18.29 (s), 17.35 (q), –5.31 (q) ppm. GC-MS (EI): *m*/*z* (%) = 394 (1) [M^+], 75 (100). $C_{24}H_{46}O_2Si$ (394.71): calcd. C 73.03, H 11.75; found C 73.37, H 11.98.

Oxo Aldehyde 15: To a solution of dioxolane **12** (531 mg, 1.65 mmol, 1.0 equiv.) in acetone (165 mL) was added bis(acetonitrile)dichloridopalladium(II) (21 mg, 80.9 μmol, 0.05 equiv.) at room temperature. After 2 d, the solvent was removed under reduced pressure, and the residue was filtered through a short pad of silica gel by using diethyl ether as eluant. Evaporation of the solvent and purification of the crude product by flash column chromatography on silica gel (diethyl ether/pentane, 1:3) yielded **15** (342 mg, 75%) as a colorless oil. R_f = 0.48 (diethyl ether/pentane, 1:1). $[\alpha]_D^{25}$ = –86.1 (*c* = 1.05, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2930, 2870, 1724, 1697, 883 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.77 (s, 1 H), 4.68 (s, 1 H), 4.64 (s, 1 H), 2.56–2.88 (m, 2 H), 2.44–2.38 (m, 1 H), 2.16–2.09 (m, 2 H), 2.06–1.90 (m, 4 H), 1.84–1.77 (m, 1 H), 1.69 (s, 3 H), 1.65–1.54 (m, 2 H), 1.52–1.36 (m, 2 H), 1.35–1.17 (m, 3 H), 1.05–0.97 (m, 1 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 0.83 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 216.85 (s), 201.91 (d), 145.76 (s), 109.95 (t), 58.94 (d), 45.17 (t), 43.74 (d), 40.86 (t), 40.54 (d), 35.74 (d), 35.31 (t), 34.74 (t), 31.29 (t), 27.09 (t), 26.50 (t), 22.38 (q), 21.26 (q), 17.33 (q) ppm. GC-MS (EI): *m*/*z* (%) = 278 (1) [M^+], 96 (100). $C_{18}H_{30}O_2$ (278.43): calcd. C 77.65, H 10.86; found C 77.68, H 10.98.

Hydroxy Ketone 19: To a solution of the silyl ether **18** (780 mg, 1.89 mmol, 1.0 equiv.) in THF (33 mL) was added TBAF (3.03 mL, 1 M in THF, 3.03 mmol, 1.6 equiv.) at room temperature. After 90 min, the reaction mixture was poured into diethyl ether/H_2O (1:1) (50 mL), and the aqueous layer was extracted with diethyl ether (4 × 50 mL). The combined organic phases were washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 2:1) afforded **19** (524 mg, 95%) as a colorless oil. R_f = 0.30 (diethyl ether/pentane, 2:1). $[\alpha]_D^{25}$ = –94.1 (*c* = 1.02, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3395, 2933, 2873, 1693, 885 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.68 (s, 1 H), 4.64 (s, 1 H), 3.65–3.58 (m, 2 H), 2.53 (dd, *J* = 11.0, 11.0 Hz, 1 H), 2.19–2.10 (m, 2 H), 2.06–1.89 (m, 3 H), 1.83–1.72 (m, 1 H), 1.69 (s, 3 H), 1.67–1.52 (m, 4 H), 1.51–1.38 (m, 2 H), 1.35–1.17 (m, 4 H), 1.04–0.93 (m, 1 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.83 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 216.85 (s), 145.80 (s), 109.91 (t), 62.98 (t), 58.97 (d), 45.56 (t), 44.05 (d), 40.50 (d), 35.79 (d), 35.45 (t), 34.76 (t), 31.29 (t), 30.77 (t), 29.05 (t), 27.13 (t), 22.37 (q), 21.28 (q), 17.33 (q) ppm. GC-MS (EI): *m*/*z* (%) = 280 (2) [M^+], 96 (100). $C_{18}H_{32}O_2$ (280.45): calcd. C 77.09, H 11.50; found C 76.92, H 11.37.

Oxidation of Alcohol 19: To a solution of alcohol **19** (500 mg, 1.78 mmol, 1.0 equiv.) in dichloromethane (20 mL) was added Dess–Martin periodinane (1.51 g, 3.56 mmol, 2.0 equiv.) at room temperature. After 90 min, the reaction mixture was diluted with diethyl ether (20 mL) and filtered through a short pad of silica gel by using diethyl ether as eluant. The organic layer was subsequently washed with an aqueous saturated solution of Na_2CO_3 and brine (25 mL each), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:1) furnished **15** (425 mg, 86%) as a colorless oil.

Hydroazulenes 4a and 4c: To a stirred suspension of potassium hydroxide powder (1.21 g, 21.6 mmol, 10.0 equiv.) in benzene (400 mL) in a Dean–Stark apparatus was added 18-crown-6 (285 mg, 1.08 mmol, 0.5 equiv.) and oxo aldehyde **15** (600 mg, 2.16 mmol, 1.0 equiv.), and the mixture was stirred at 80 °C for 2 h. The reaction mixture was poured into H_2O (150 mL), and the aqueous layer was extracted with diethyl ether (4 × 100 mL). The combined organic phases were washed with aqueous HCl (1 N) and brine (100 mL each), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) furnished **4a** (194 mg, 35%) and **4c** (112 mg, 20%) as light yellow oils (**4a**/**4c** = 1.7:1). Data for **4a**: R_f = 0.50 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = –18.9 (*c* = 1.05, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2954, 2918, 2859, 1677, 882 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.72–6.70 (m, 1 H), 4.64 (s, 2 H), 2.57–2.51 (m, 1 H), 2.38–2.12 (m, 4 H), 2.07–2.03 (m, 1 H), 2.01–1.92 (m, 2 H), 1.91–1.73 (m, 2 H), 1.71 (s, 3 H), 1.69–1.53 (m, 2 H), 1.38–1.24 (m, 3 H), 1.24–1.13 (m, 1 H), 0.94 (d, *J* = 5.9 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 202.33 (s), 148.99 (s), 146.46 (s), 142.00 (d), 109.54 (t), 56.82

(d), 50.55 (d), 40.26 (t), 40.20 (d), 35.67 (t), 32.93 (d), 31.02 (t), 30.76 (t), 30.66 (t), 27.10 (t), 22.42 (q), 21.28 (q), 17.15 (q) ppm. GC-MS (EI): *m*/*z* (%) = 260 (5) [M$^+$], 164 (100). $C_{18}H_{28}O$ (260.41): calcd. C 83.02, H 10.84; found C 83.15, H 10.68. Data for **4c**: R_f = 0.28 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = +73.8 (*c* = 1.03, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2957, 2919, 2856, 1669, 882 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 6.84–6.83 (m, 1 H), 4.66 (s, 1 H), 4.61 (s, 1 H), 2.65–2.58 (m, 1 H), 2.37–2.15 (m, 4 H), 2.09–2.03 (m, 1 H), 1.99–1.90 (m, 3 H), 1.61 (s, 3 H), 1.69–1.44 (m, 4 H), 1.41–1.26 (m, 2 H), 1.22–1.11 (m, 1 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 204.34 (s), 148.35 (s), 145.63 (s), 144.82 (d), 110.05 (t), 58.80 (d), 50.22 (d), 39.76 (d), 34.60 (t), 33.06 (t), 32.69 (t), 32.13 (t), 30.68 (t), 29.35 (d), 25.77 (t), 22.05 (q), 21.27 (q), 15.70 (q) ppm. GC-MS (EI): *m*/*z* (%) = 260 (6) [M$^+$], 164 (100). $C_{18}H_{28}O$ (260.41): calcd. C 83.02, H 10.84; found C 83.02, H 10.67.

Basic Equilibration of 4c: To a stirred suspension of potassium hydroxide powder (76 mg, 1.35 mmol, 10 equiv.) in benzene (15 mL) was added 18-crown-6 (18 mg, 67.5 μmol, 0.5 equiv.) and hydroazulene **4c** (35 mg, 134.6 μmol, 1.0 equiv.), and the mixture was stirred at 80 °C for 4 h. The reaction mixture was poured into brine (10 mL), and the aqueous layer was extracted with diethyl ether (4 × 15 mL). The combined organic phases were washed with aqueous HCl (1 N) and brine (15 mL each), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) furnished **4a** (16 mg, 46%) and **4c** (12 mg, 34%) as light yellow oils (**4a**/**4c** = 1.3:1).

Diketone 16: To a solution of dioxane **14** (190 mg, 0.502 mmol, 1.0 equiv.) in acetone (5 mL) was added bis(benzonitrile)dichloridopalladium(II) (2 mg, 5.02 μmol, 0.01 equiv.) at room temperature. After 24 h, the solvent was removed under reduced pressure, and the residue was filtered through a short pad of silica gel using diethyl ether as eluant. Evaporation of the solvent and purification of the crude product by flash column chromatography on silica gel (diethyl ether/pentane, 1:2) yielded **16** (107 mg, 73%) as a colorless oil. R_f = 0.25 (diethyl ether/pentane, 1:2). $[\alpha]_D^{25}$ = –114.9 (*c* = 1.01, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2954, 2929, 2872, 1715, 1698, 885 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.67 (s, 1 H), 4.64 (s, 1 H), 2.52–2.46 (m, 2 H), 2.42–2.35 (m, 1 H), 2.13 (s, 3 H), 2.14–2.07 (m, 2 H), 2.06–1.85 (m, 4 H), 1.83–1.78 (m, 1 H), 1.68 (s, 3 H), 1.66–1.54 (m, 2 H), 1.45–1.36 (m, 2 H), 1.34–1.15 (m, 3 H), 1.03–0.95 (m, 1 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 216.59 (s), 208.55 (s), 145.79 (s), 109.96 (t), 58.98 (d), 45.27 (t), 43.96 (d), 40.71 (d), 40.63 (t), 35.78 (d), 35.41 (t), 34.78 (t), 31.32 (t), 30.05 (q), 28.23 (t), 27.11 (t), 22.39 (q), 21.30 (q), 17.34 (q) ppm. GC-MS (EI): *m*/*z* (%) = 292 (0.3) [M$^+$], 43 (100). $C_{19}H_{32}O_2$ (292.46): calcd. C 78.03, H 11.03; found C 78.05, H 11.08.

Hydroazulenes 4b and 4d: To a solution of potassium hydroxide (2.50 g, 44.6 mmol, 40.9 equiv.) in methanol (95 mL) was added diketone **16** (318 mg, 1.09 mmol), and the mixture was stirred at 65 °C for 48 h. The reaction mixture was poured into H_2O (80 mL), and the aqueous layer was extracted with diethyl ether (4 × 80 mL). The combined organic phases were washed with brine (80 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) gave **4b** (156 mg, 52%) and **4d** (126 mg, 42%) as colorless oils (**4b**/**4d** = 1.2:1). Data for **4b**: R_f = 0.66 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = +165.9 (*c* = 1.03, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2954, 2917, 2871, 1672, 881 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.65 (s, 2 H), 2.61–2.60 (m, 1 H), 2.38–2.24 (m, 3 H), 1.98 (s, 3 H), 2.06–1.83 (m, 6 H), 1.71 (s, 3 H), 1.68–1.61 (m, 1 H), 1.48–1.34 (m, 1 H), 1.33–1.17 (m, 4 H), 0.92–0.90 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 205.37 (s), 153.03 (s), 146.51 (s), 141.13 (s), 109.50 (t), 56.94 (d), 52.22 (d), 39.80 (t), 39.42 (d), 37.95 (t), 35.40 (t), 33.14 (d), 31.15 (t), 29.09 (t), 27.72 (t), 22.49 (q), 21.11 (q), 17.58 (q), 16.72 (q) ppm. GC-MS (EI): *m*/*z* (%) = 274 (8) [M$^+$], 178 (100). $C_{19}H_{30}O$ (274.44): calcd. C 83.15, H 11.02; found C 82.81, H 11.12. Data for **4d**: R_f = 0.41 (diethyl ether/pentane, 1:10). $[\alpha]_D^{25}$ = +150.8 (*c* = 1.00, in $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2958, 2917, 2859, 1664, 880 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.65 (s, 1 H), 4.58 (s, 1 H), 2.68–2.63 (m, 1 H), 2.29–2.21 (m, 3 H), 1.97 (s, 3 H), 2.07–1.71 (m, 5 H), 1.59 (s, 3 H), 1.62–1.53 (m, 2 H), 1.46–1.38 (m, 1 H), 1.34–1.23 (m, 3 H), 1.15–1.08 (m, 1 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 207.10 (s), 155.97 (s), 145.53 (s), 140.55 (s), 109.97 (t), 60.27 (d), 52.19 (d), 39.15 (d), 37.89 (t), 34.60 (t), 33.40 (t), 33.10 (t), 30.20 (t), 29.60 (d), 26.39 (t), 21.88 (q), 21.20 (q), 17.04 (q), 15.68 (q) ppm. GC-MS (EI): *m*/*z* (%) = 274 (11) [M$^+$], 178 (100). $C_{19}H_{30}O$ (274.44): calcd. C 83.15, H 11.02; found C 82.93, H 11.14.

Synthesis of the Hydroazulenes 4b and 4d by PPTS-Induced Acetal Cleavage and Aldol Condensation: To a solution of dioxane **14** (590 mg, 1.56 mmol, 1.0 equiv.) in acetone (60 mL) and H_2O (1.2 mL) was added PPTS (392 mg, 1.56 mmol, 1.0 equiv.) at room temperature. After 24 h, the solvent was removed in vacuo, and the residue was taken up in diethyl ether (50 mL). The organic layer was subsequently washed with an aqueous saturated solution of $NaHCO_3$ (25 mL) and brine (25 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. To a solution of potassium hydroxide (3.58 g, 63.8 mmol, 40.9 equiv.) in methanol (136 mL) was added the crude diketone **16** (1.0 equiv.), and the mixture was stirred at 65 °C for 48 h. The reaction mixture was poured into H_2O (110 mL), and the aqueous layer was extracted with diethyl ether (4 × 100 mL). The combined organic phases were washed with brine (100 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) gave **4b** (197 mg, 46%) and **4d** (163 mg, 38%) as colorless oils (**4b**/**4d** = 1.2:1).

Basic Equilibration of 4d: To a solution of potassium hydroxide (1.33 g, 23.7 mmol, 35.1 equiv.) in methanol (50 mL) was added hydroazulene **4d** (180 mg, 0.656 mmol, 1.0 equiv.), and the mixture was stirred at 65 °C for 24 h. The reaction mixture was poured into H_2O (40 mL), and the aqueous layer was extracted with diethyl ether (4 × 40 mL). The combined organic phases were washed with brine (40 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (diethyl ether/pentane, 1:10) gave **4b** (90 mg, 50%) and **4d** (74 mg, 41%) as colorless oils (**4b**/**4d** = 1.2:1).

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