Synthesis of Highly Substituted Methylenecyclohexenes Using New Domino Reactions with Sultones

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*Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday*

New methods for the synthetic elaboration of sultones with concomitant desulfurization have been developed. Alkylation of sultones with (iodomethyl)trimethylsilane followed by treatment of the resultant silyl compound with tetrabutylammonium fluoride gave rise to sulfur-free methylenecyclohexenes. In a more straightforward fashion, highly substituted compounds of the latter type were readily accessible by alkylation of α-metallated allylic sultones prepared either by deprotonation, radical cyclization/transmetallation, or conjugate 1,6-addition with (iodomethyl)magnesium chloride in a one-pot transformation. An advanced intermediate for the synthesis of several 1,10-*seco*-eudesmanolides was rapidly constructed using such a protocol.

Introduction

Over the past several years, sultones have emerged as valuable heterocyclic intermediates that offer novel options for stereoselective synthesis.[1] Using the temporary sulfur connection[2] depicted in Scheme 1, hydroxyalkyl-substituted dienes **C** can for example be converted into their formal [4+2] cycloadducts with ketene (**D**)[3] with complete regio- and high stereocontrol. This is achieved by esterification of **C** with vinylsulfonyl chloride to give a vinylsulfonate **A**, intramolecular Diels−Alder reaction (IMDA) of **A** to generate sultone **B**, and subsequent oxidative desulfurization of **B** to yield hydroxy ketone **D**.

We envisaged that, similar to the depicted decomposition of the α-oxygenated intermediates **F** involved in the oxidative cleavage, the carbanions **G**[4] would break down to give the exocyclic olefins **E** by β-elimination (Figure 1). The utilization of this process would be preferable to an alternative carbonyl methylenation of **D** to **E** since, next to streamlining the route to **E**, it would even be applicable if a prior oxidative sultone cleavage would lead to a base-sensitive ketone, which might undergo side reactions such as epimerization during the olefination process. Indeed, a desulfurization of sultones **B** with simultaneous methylenation to give the formal [4+2] cycloadducts **E** (from the reaction of dienols **C** with ketene) is readily accomplished via intermediate **G**. We first reported a two-step sequence for this trans-
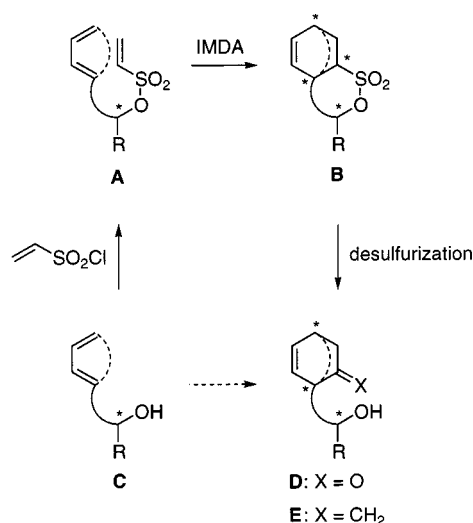
Scheme 1. Temporary sulfur connection for intramolecular Diels−Alder (IMDA) reactions

formation,[5] and later disclosed an alternative one-pot procedure.[6] Here we give a full account of our studies in this area, which eventually provided a rapid access to highly substituted methylenecyclohexenes.
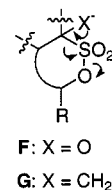

Figure 1. Sultone cleavage by β-elimination

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Results and Discussion

Two-Step Sequence

A two-step desulfurization of sultones (−)-**1**,[3] **4**,[3,7] and **7**[8] to give the hydroxy dienes (−)-**3**, **6**, and **9**, respectively, was achieved in good yields by alkylation with (iodomethyl)-trimethylsilane[9] followed by fluoride-induced β-elimination[10] of the resultant silyl compound with tetrabutylammonium fluoride (Scheme 2). With lithiated sultone **4** as a model substrate, (chloromethyl)trimethylsilane proved to be too unreactive for the alkylation step.[5] Since the methylenecyclohexenes (−)-**3** and **6** can be viewed as [4+2] adducts of allene with the (hydroxyalkyl)dienes from which the sultones (−)-**1** and **4** were prepared,[3] vinylsulfonyl chloride[11] serves as a regio- and stereoselectively reacting allene equivalent for the intramolecular Diels−Alder reaction in these cases. As we already noted during our synthesis of the 1,10-*seco*-eudesmanolide ivangulin (**13**) by methylation of **7** as a 1:1:1:1 diastereomeric mixture,[8] the use of methyllithium was essential for complete lithiation of this substrate. While alkylation of lithiated **7** could be performed in the absence of HMPA by addition of (iodomethyl)trimethylsilane at room temperature and subsequent warming to 40 °C for 30 min (71% of **8**), a superior yield of **8** (1:4:5 diastereomeric mixture) was obtained in the presence of this co-solvent already at room temperature.
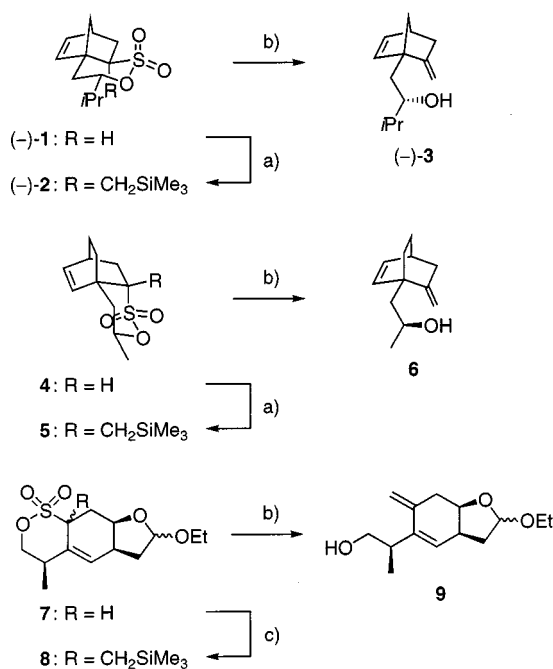
Scheme 2. Two-step desulfurization of sultones with simultaneous methylenation: a) (i) BuLi, THF, −78 °C, (ii) ICH₂SiMe₃, 0 °C to room temp., 78% (−)-**2**, 65% **5**; b) Bu₄NF, THF, reflux, 53% (−)-**3**, 70% **6**, 65% **9**; c) (i) MeLi, THF, −78 °C to room temp., (ii) ICH₂SiMe₃, HMPA, −78 °C to room temp., 84%

1,3-Diene **9** isolated as an acid-sensitive 1:1 mixture of two acetal epimers is a promising general intermediate for

the total synthesis of the highly oxygenated, cytotoxic 1,10-*seco*-eudesmanolides eriolanin (**10**),[12,13] eriolangin (**11**),[12,13a] and 1,6-*O*,*O*-diacetylbritannilactone (**12**)[14] (Figure 2). Due to the 1,3-diene unit in **9**, this compound is activated for an oxygenation to the enediol fragment of **10** and **11**, as well as to the cyclohexene moiety of **12**. Thus, a synthetic approach towards these targets by a route similar to the one that led to ivangulin[8] seems reasonable.
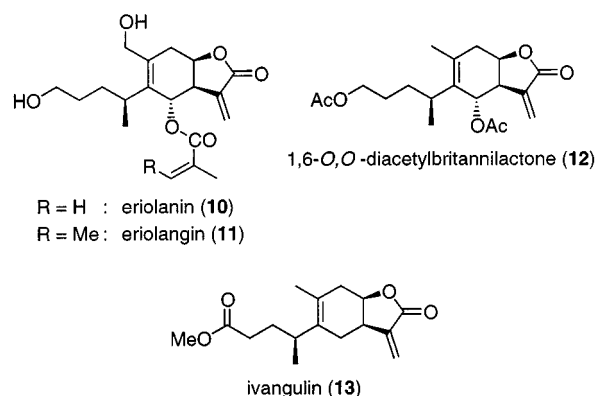

Figure 2. 1,10-*seco*-Eudesmanolides

Domino Processes for the Desulfurization to Diene 9

While the two-step desulfurization of sultones with simultaneous methylenation described above nicely complements our procedures for oxidative[3,15] and reductive[16] sultone cleavage, we were interested in finding a more straightforward access to the semicyclic diene **9**[6] through the application of sequential transformations.[17] To this end, we first attempted to alkylate lithiated sultone **7** with the carbenoid reagent chloromethylmagnesium chloride.[18] However, these experiments met with failure. In contrast, (iodomethyl)magnesium chloride[19] reacted smoothly in the presence of HMPA. The use of potentially alternative co-solvents such as DMPU, ethylenediamine, or TMEDA was unsuccessful (Scheme 3). As anticipated, the intermediate Grignard species **14** spontaneously undergoes β-elimination with rupture of the δ-sultone to deliver the desired 1,3-diene **9** (1:1 diastereomeric mixture) in good yield.
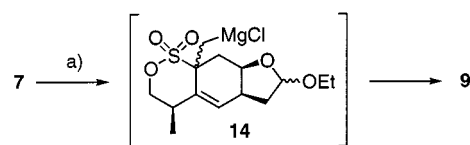
Scheme 3. One-pot desulfurization of sultone **7** to diene **9**: a) (i) MeLi, THF, −78 °C to room temp., (ii) ICH₂MgCl, HMPA, −78 °C to room temp., 69%

In order to further shorten the synthesis of diene **9**, we investigated a nickel-catalyzed ring closure of bromo acetal **15**, our direct precursor of sultone **7**,[8] with diethylzinc ac-

cording to a protocol published by Knochel,[20] which was slightly modified in our case (Scheme 4). To our delight, this alternative to our original chromium(II)-mediated cyclization[8,21] of **15** to **7** eventually allowed the conversion of **15** to **9** to be carried out as a one-pot transformation.
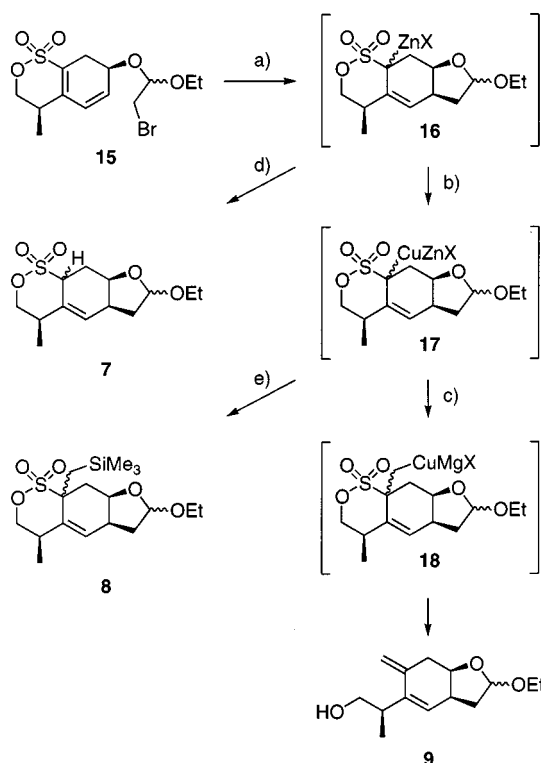
Scheme 4. One-pot conversion of bromo acetal **15** to diene **9**: a) Et$_2$Zn, cat. Ni(acac)$_2$, cat. Bu$_4$NI, THF, −78 °C to 40 °C; b) CuBr·Me$_2$S, −78 °C to 0 °C; c) ICH$_2$MgCl, HMPA, −78 °C to room temp., 68% **9** from **15**; d) aq. NH$_4$Cl, room temp., 68% **7** from **15**; e) ICH$_2$SiMe$_3$, −78 °C to room temp., 64% **8** from **15**

After hydrolysis of the cyclized intermediate **16**, sultone **7** was obtained as a 1:1:1:1 diastereomeric mixture in 68% yield. Furthermore, transmetallation of **16** using CuBr·Me$_2$S and subsequent trapping of the resultant allyl-cuprate **17** with (iodomethyl)trimethylsilane efficiently provided silyl compound **8** as a 1:4:5 mixture of diastereomers. The transmetallation step was essential for the alkylation event. Several attempts to trap the organozinc species **16** with electrophiles failed completely. Moreover, the use of CuBr·Me$_2$S turned out to be important. Indeed, the other copper salts we tried (CuCN, CuI, CuBr) did not effect C−C coupling. Gratifyingly, alkylation of **17** with (iodomethyl)magnesium chloride at −78 °C followed by warming to ambient temperature directly delivered the desired diene **9** in 68% yield. Presumably, intermediate **18** or a related metal species is formed and finally suffers a β-elimination with sultone cleavage to give **9**.

The clean production of **9** from both **7** (cf. Scheme 3) and **15** (cf. Scheme 4) implies a regioselective alkylation of the allylmetal species involved with the carbenoid reagent α to sulfur atom, which has precedent in corresponding sultone

alkylations with methyl iodide[8,16b] or (iodomethyl)trimethylsilane (cf. Scheme 2). Moreover, since no protonation of **14** or **18** to give the methylated derivative[8] of **7** was observed after aqueous workup, the endocyclic carbon−sulfur bond in these intermediates is easily cleaved at room temperature.

Domino Elimination/1,6-Addition/Alkylation/Desulfurization

Encouraged by these findings, we investigated if the domino alkylation/desulfurization described above could be coupled to the generation of lithiated sultones by domino elimination/alkoxide-directed 1,6-addition[16b] with furan-derived substrates **19a**[8] and **19b**.[22] The latter process has already served as a key step in the syntheses of nonactic acid[4] and both hydroxy acid fragments of the macrodiolide antibiotic pamamycin-607.[22,23] Indeed, upon treatment of sultones **19** with 2 equiv. of an organolithium reagent, and subsequent alkylation of the resultant allyllithium intermediates **21** with (iodomethyl)magnesium chloride, the 1,3-dienes **23** were obtained directly in good yields as single diastereomers (Scheme 5, Table 1).[6]
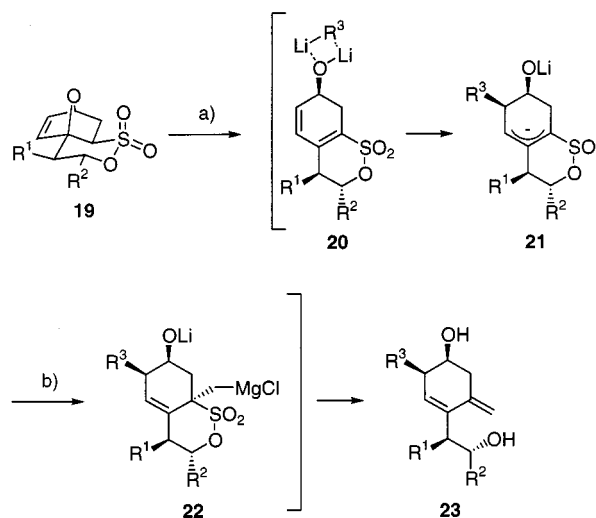
Scheme 5. One-pot conversion of sultones **19** to methylenecyclohexenes **23**: a) 2 equiv. R^{3}Li, THF, −78 °C to 0 °C (MeLi) or −78 °C (BuLi); b) ICH$_2$MgCl, −78 °C to room temp.

Table 1. One-pot conversion of sultones **19** to dienols **23**

Substrate	R^1	R^2	R^3	Product	Yield 23 [%][a]
19a	Me	H	Me	**23a**	62
19a	Me	H	Bu	**23b**	66
19b	H	Pr	Me	**23c**	61
19b	H	Pr	Bu	**23d**	70

[a] Isolated yield after purification by flash chromatography.

Interestingly, the use of HMPA as a co-solvent was not required for the C−C bond formation event **21 → 22**. Conjugate addition of R^{3}Li *syn* to the lithium alkoxide moiety has been rigorously established before, and axial attack of

the electrophilic carbenoid on **21** has precedent in corresponding methylations.[16b] Upon hydrolysis of the organomagnesium intermediate **22a** at low temperature, the known methyl-substituted sultone **24**[24] was isolated as a single diastereomer (Scheme 6). Clearly, the endocyclic carbon−sulfur bond in **22a** is only cleaved at higher temperatures and thus these Grignard species might well be utilized even for extended domino processes prior to aqueous workup.
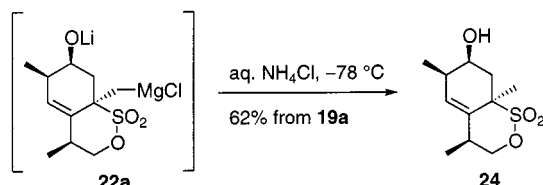
Scheme 6. Trapping of intermediate **22a** by protonation

Conclusion

In summary, novel methods for the rapid synthetic elaboration of sultones with concomitant desulfurization to give stereodefined, highly substituted methylenecyclohexenes have been developed. Application of these processes toward the total synthesis of several cytotoxic 1,10-*seco*-eudesmanolides is currently under investigation in our laboratories.

Experimental Section

General Remarks: All reactions requiring exclusion of moisture were run under argon using flame-dried glassware. − Solvents were dried by distillation from potassium (THF) or CaH$_2$. − Flash chromatography was performed on Merck silica gel 60 (40−63 μm). − Capillary GC analyses were performed with a Shimadzu GC-14A or GC-14B, a Shimadzu C-R6A integrator, and an HP 5 column (25 m length, 0.25 mm i.d., 0.25 μm film). − Melting points were determined with a Kofler microscope desk. − Optical rotations were measured with a Perkin−Elmer 241 polarimeter. − FT-IR spectra were obtained with a Nicolet 205 and a Bruker IFS 28; w = weak, s = strong, m = medium, br = broad. − ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker WM 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) and a Bruker DRX-500 (^{1}H: 500 MHz, ^{13}C: 126 MHz); m$_c$ = multiplet centered at, br = broad; ^{13}C multiplicities were determined using DEPT pulse sequences. − Mass spectra (GC/MS, 70 eV) were recorded with a Hewlett Packard 5972 detector coupled with a Hewlett Packard 5890 GC and a Varian MAT CH-7A coupled with a Varian 1400 GC. High resolution mass spectra (HR-EI, 70 eV) were obtained with a Finnigan MAT 95 and a Varian MAT CH-7A + data system Varian SS 200. − Microanalyses were performed by the analytical laboratory of the Institut für Organische Chemie, Technische Universität Dresden, and the analytical laboratory of the Organisch-Chemisches Institut, Universität Münster. − Methyllithium was purchased from Acros.

Preparation of the Silyl Compounds (−)-2 and 5 (General Procedure): To a solution of sultone (−)-**1**[3] or **4**[3] (1.3 mmol) in dry THF (20 mL) cooled to −78 °C was added BuLi (1.4 equiv., 1.6 M in hexane), and stirring was continued for 1.5 h at −78 °C. The mixture was allowed to warm to 0 °C, and (iodomethyl)trimethylsilane (5 equiv.) was added. After slowly warming to room temperature, the mixture was stirred for an additional 3 h. Sat. aqueous NH$_4$Cl (20 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 20 mL). Drying the combined organic layers with MgSO$_4$, concentration in vacuo, and purification of the residue by flash chromatography [petroleum ether/diethyl ether (7:1) for (−)-**2**, petroleum ether/ether (3:1) for **5**] gave the silyl compounds (−)-**2** and **5**, respectively.

(−)-2: Yield: 78%, white needles, m.p. 110 °C, R_f = 0.47 (petroleum ether/diethyl ether, 7:1). − [α]$_D^{20}$ = −59.1 (c = 1.24 in THF). − IR (neat): ṽ = 2961 (s), 2876 (w), 1467 (w), 1334 (s, SO$_2$OR), 1245 (w), 1167 (s, SO$_2$OR), 975 (m), 893 (s), 843 (s) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.03 (s, 9 H), 0.76 (d, J = 15.3 Hz, 1 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.7 Hz, 3 H), 1.24 (m$_c$, 1 H), 1.34 (dd, J = 2.6, 12.9 Hz, 1 H), 1.39 (d, J = 15.3 Hz, 1 H), 1.85 (dd, J = 2.0, 14.5 Hz, 1 H), 1.91 (m$_c$, 1 H), 2.17 (dd, J = 12.4, 14.8 Hz, 1 H), 2.64 (dd, J = 4.0, 12.6 Hz, 1 H), 2.66 (d, J = 9.3 Hz, 1 H; a significant NOE was observed upon irradiation at δ = 4.38), 2.94 (br. s, 1 H), 4.38 (ddd, J = 1.9, 6.1, 12.3 Hz, 1 H), 5.83 (d, J = 5.5 Hz, 1 H), 6.34 (dd, J = 3.2, 5.6 Hz, 1 H). − ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 1.0 (q), 17.8 (q), 18.1 (q), 23.2 (t), 28.2 (t), 32.4 (d), 36.7 (t), 42.6 (d), 49.2 (t), 60.9 (s), 67.9 (s), 86.5 (d), 139.2 (d), 140.5 (d). − MS (GC/MS, 70 eV): m/z (%) = 329 (0.5) [M$^+$ + 1], 313 (0.5) [M$^+$ − CH$_3$], 175 (6), 134 (100) [M$^+$ − CH$_2$C(CH$_2$SiMe$_3$)SO$_3$H], 119 (78) [M$^+$ − CH$_2$C(CH$_2$SiMe$_3$)SO$_3$H − CH$_3$], 91 (54), 79 (54), 73 (44) [SiMe$_3^+$], 69 (18), 41 (24). − C$_{16}$H$_{28}$O$_3$SSi (328.54): calcd. C 58.49, H 8.59; found C 58.49, H 8.49.

5: Yield: 65%, white needles, m.p. 123 °C, R_f = 0. 39 (petroleum ether/diethyl ether, 3:1). − IR (neat): ṽ = 3345 (w, br), 3047 (w), 2950 (s), 2897 (w), 2873 (w), 1445 (m), 1346 (s), 1331 (s, SO$_2$OR), 1246 (s, SO$_2$OR), 1170 (s), 853 (s), 797 (m), 706 (s), 656 (s) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.11 (s, 9 H), 0.89 (d, J = 14.4 Hz, 1 H), 0.91−0.97 (m, 1 H), 1.21−1.27 (m, 1 H), 1.29 (d, J = 6.6 Hz, 3 H), 1.31 (d, J = 14.8 Hz, 1 H), 1.39−1.45 (m, 1 H), 1.48 (dd, J = 2.1, 14.4 Hz, 1 H), 1.50 (dd, J = 3.0, 13.5 Hz, 1 H), 1.78 (m$_c$, 1 H), 1.79 (dd, J = 12.1, 14.8 Hz, 1 H), 1.95 (dd, J = 2.1, 13.5 Hz, 1 H), 2.55 (m$_c$, 1 H), 4.81 (ddq, J$_d$ = 2.3, 12.5 Hz, J$_q$ = 6.5 Hz, 1 H), 6.04−6.13 (m, 2 H; a significant NOE was observed upon irradiation at δ = 4.81). − ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 1.2 (q), 21.0 (q), 22.9 (t), 24.5 (t), 30.6 (d), 31.0 (t), 37.2 (t), 37.6 (t), 42.3 (s), 64.1 (s), 78.3 (d), 131.0 (d), 136.1 (d). − MS (GC/MS, 70 eV): m/z (%) = 299 (6) [M$^+$ − CH$_3$], 255 (10), 250 (8), 235 (24), 191 (64), 177 (34), 163 (35), 117 (50), 105 (40), 91 (76), 73 (100) [SiMe$_3^+$], 59 (18), 45 (30). − C$_{15}$H$_{26}$O$_3$SSi (314.52): calcd. C 57.28, H 8.34; found C 57.51, H 8.33.

Preparation of Silyl Compound 8 from Sultone 7: To a solution of the diastereomeric mixture of sultones **7**[8] (1 g, 3.5 mmol) in dry THF (10 mL) cooled to −78 °C was added MeLi (2.4 mL, 3.8 mmol, 1.6 M in ether). The mixture was allowed to warm to room temperature within 15 min, stirred for additional 30 min at this temperature, and then cooled again to −78 °C. Dry HMPA (1.3 mL, 7.0 mmol) was added to the orange solution and after obtaining a homogeneous mixture, (iodomethyl)trimethylsilane (2.6 mL, 17.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 12 h with exclusion of light. After addition of sat. aqueous NH$_4$Cl (2 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed

with 0.1 N HCl (10 mL), sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (diethyl ether/ethyl acetate/pentane, 1:2:2) gave the silyl compound **8** (1.1 g, 84%) as an oily mixture of three diastereomers (ratio 1:4:5 by GC) that slowly solidified in a refrigerator. By careful crystallization, the proportion of the major isomer was sufficiently enhanced to allow its spectroscopic characterization by NMR. Assignment of the relative configuration was possible by protodesilylation without concomitant desulfurization using Bu_4NF in THF/H_2O (95:5) at reflux, and comparison of the spectroscopic data of the resultant methylated sultone[8] with reference values.[24] Major isomer: R_f = 0.31 (ether/ethyl acetate/pentane, 1:2:2). − ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.04 (s, 9 H), 0.82 (d, J = 6.7 Hz, 3 H), 1.14 (t, J = 7.2 Hz, 3 H), 1.50 (d, J = 5.0 Hz, 2 H), 1.79 (ddd, J = 4.8, 12.4, 12.4 Hz, 1 H), 2.14 (m_c, 2 H), 2.81 (m_c, 1 H), 2.99 (m_c, 1 H), 3.38 (dd, J = 7.2, 9.5 Hz, 1 H), 3.67 (dd, J = 7.2, 9.5 Hz, 1 H), 4.01 (dd, J = 10.7, 11.9 Hz, 1 H), 4.21 (dd, J = 5.7, 10.7 Hz, 1 H), 4.32 (m_c, 1 H), 5.08 (d, J = 5.0 Hz, 1 H), 5.69 (dd, J = 1.8, 5.1 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 0.0 (q), 12.0 (q), 14.9 (q), 24.4 (t), 30.4 (d), 32.2 (t), 36.1 (d), 38.1 (t), 62.6 (t), 67.4 (s), 71.9 (d), 75.8 (t), 103.0 (d), 125.5 (d), 136.2 (s). − MS (GC/MS, 70 eV): m/z (%) = 265 (16) $[M^+ - SO_3 - C_2H_5]$, 223 (62) $[M^+ - CH_2SiMe_3 - SO_2]$, 209 (15), 196 (36), 177 (57) $[M^+ - HOCH_2CH_3 - CH_2SiMe_3 - SO_2]$, 149 (32) $[177 - C_2H_4]$, 131 (20), 130 (18), 119 (15), 103 (19), 73 (100) $[SiMe_3^+]$, 55 (21), 45 (35).

Preparation of Dienes (−)-3 and 6 (General Procedure): To a solution of (−)-**2** or **5** (0.3 mmol) in dry THF (6 mL) was added Bu_4NF (3 equiv., 1.0 M in THF). The mixture was heated to reflux for 4 h, cooled to room temperature, and treated with sat. aqueous $NaHCO_3$ (5 mL). After separation of the layers, the aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$. Concentration in vacuo and purification of the residue by flash chromatography [petroleum ether/ether (7:1) for (−)-**3**, petroleum ether/diethyl ether (3:1) for **6**] gave the dienes (−)-**3** and **6**, respectively.

Diene (−)-3: Yield: 53%, R_f = 0.25 (petroleum ether/diethyl ether, 7:1), $[\alpha]_D^{20}$ = −120 (c = 1.14 in THF). − IR (neat): $\tilde{\nu}$ = 3390 (m, br, OH), 3057 (w), 2958 (s), 2872 (m), 1652 (m), 1466 (m), 1384 (w), 1367 (w), 1333 (w), 1038 (m), 991 (m), 872 (m), 725 (m) cm^{-1}. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (d, J = 5.0 Hz, 3 H), 0.96 (d, J = 5.0 Hz, 3 H), 1.39 (d, J = 8.3 Hz, 1 H), 1.40−1.58 (m, 1 H), 1.67−1.81 (m, 3 H), 1.89 (m_c, 1 H), 1.98 (dd, J = 2.4, 14.8 Hz, 1 H), 2.38 (m_c, 1 H), 2.92 (m_c, 1 H), 3.57 (ddd, J = 2.5, 4.5, 9.4, 1 H), 4.80 (m_c, 1 H), 4.89 (m_c, 1 H), 5.72 (d, J = 5.5 Hz, 1 H), 6.09 (dd, J = 3.1, 5.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.9 (q), 18.7 (q), 33.4 (t), 34.4 (d), 35.9 (t), 40.7 (d), 53.1 (t), 57.1 (s), 75.1 (d), 102.3 (t), 137.1 (d) 137.4 (d), 155.0 (s). − MS (GC/MS, 70 eV): m/z (%) = 192 (4) $[M^+]$, 174 (3) $[M^+ - H_2O]$, 159 (8) $[M^+ - H_2O - CH_3]$, 131 (27), 118 (56), 105 (60), 92 (37), 80 (100), 73 (30), 71 (20), 55 (19), 43 (25). − MS (HR-EI): 192.1501 ($C_{13}H_{20}O$, M^+: calcd. 192.1514).

Diene 6: Yield: 70%, R_f = 0.32 (petroleum ether/diethyl ether, 3:1). − IR (neat): $\tilde{\nu}$ = 3364 (s, br, OH), 3042 (w), 2934 (s), 2862 (m), 1637 (m), 1459 (w), 1429 (w), 1372 (w), 1117 (m), 1003 (m), 949 (m), 872 (s), 697 (s) cm^{-1}. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (d, J = 6.0, 3 H), 1.35−1.46 (m, 3 H), 1.56−1.62 (m, 1 H), 1.72 (dd, J = 3.1, 14.6 Hz, 1 H), 1.90 (dd, J = 8.3, 14.5, 1 H), 2.10 (m_c, 1 H), 2.25 (m_c, 1 H), 2.63 (m_c, 1 H), 4.13 (m_c, 1 H), 4.67 (m_c, 1 H), 4.71 (m_c, 1 H), 6.28 (m_c, 2 H). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 25.8 (q), 26.3 (t), 31.1 (d), 31.5 (t), 36.5 (t), 42.3 (s), 43.3 (t), 65.8 (d), 102.9 (t), 134.4 (d), 135.2 (d), 153.2 (s). − MS

(GC/MS, 70 eV): m/z (%) = 178 (2) $[M^+]$, 160 (6) $[M^+ - H_2O]$, 145 (8) $[M^+ - CH_3 - H_2O]$, 131 (13), 117 (46), 106 (24), 91 (100) $[C_7H_7^+]$, 77 (28), 65 (13), 58 (12), 51 (11), 45 (33). − MS (HR-EI): 178.1344 ($C_{12}H_{18}O$, M^+: calcd. 178.1358).

Preparation of Diene 9 from Sultone 8: To a solution of the diastereomeric mixture of sultones **8** (3 g, 8.02 mmol) in dry THF (20 mL) was added Bu_4NF (50.4 mL, 50.4 mmol, 1.0 M in THF) with vigorous stirring. The resultant orange mixture was heated to reflux for 30 min, cooled to room temperature, and treated with sat. aqueous $NaHCO_3$ (10 mL). After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried with $MgSO_4$. Concentration in vacuo and purification of the residue by flash chromatography (diethyl ether/pentane, 1:1) gave the readily separated diene diastereomers **9a** and **9b** (combined yield 1.24 g, 65%, **9a/9b** = 1:1).

Diene 9a: R_f = 0.63 (diethyl ether/pentane, 1:1). − IR (neat): $\tilde{\nu}$ = 3412 (s, br, OH), 2970 (s), 2932 (s), 2870 (m), 1642 (w), 1608 (w), 1449 (m), 1342 (s), 1059 (m), 1015 (s) cm^{-1}. − ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (d, J = 7.0 Hz, 3 H), 1.08 (t, J = 7.3 Hz, 3 H), 1.91 (d, J = 13.3 Hz, 1 H), 2.26 (ddd, J = 5.8, 8.1, 13.3 Hz, 1 H), 2.50 (dd, J = 2.3, 15.1 Hz, 1 H), 2.73 (dd, J = 3.4, 15.1 Hz, 1 H), 2.80 (m_c, 1 H), 2.88 (m_c, 1 H), 3.35 (m_c, 1 H), 3.48 (dd, J = 6.0, 10.0 Hz, 1 H), 3.57 (m_c, 1 H), 3.72 (dd, J = 7.0, 10.0 Hz, 1 H), 4.35 (m_c, 1 H), 4.88 (s, 1 H), 5.04 (d, J = 5.8 Hz, 1 H), 5.08 (s, 1 H), 5.47 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.8 (q), 16.5 (q), 36.2 (d), 36.5 (t), 37.4 (d), 40.2 (t), 64.2 (t), 65.9 (t), 77.7 (d), 104.1 (d), 110.1 (t), 127.3 (d), 137.5 (s), 139.2 (s). − MS (GC/MS, 70 eV): m/z (%) = 238 (5) $[M^+]$, 220 (6) $[M^+ - H_2O]$, 208 (8) $[M^+ - CH_2O]$, 207 (16), 193 (24) $[M^+ - C_2H_5]$, 192 (41) $[M^+ - C_2H_5OH]$, 179 (10), 174 (5) $[M^+ - H_2O - C_2H_5OH]$, 91 (100) $[C_7H_7^+]$. − $C_{14}H_{22}O_3$ (238.16): calcd. C 70.56, H 9.30; found C 70.31, H 9.36.

Diene 9b: R_f = 0.28 (diethyl ether/pentane, 1:1). − IR (neat): $\tilde{\nu}$ = 3425 (s, br, OH), 2973 (s), 2930 (s), 2874 (m), 1638 (w), 1605 (w), 1451 (m), 1348 (s), 1091 (m), 1061 (m), 1017 (s) cm^{-1}. − ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (d, J = 6.9 Hz, 3 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.62 (br s, 1 H), 1.84 (ddd, J = 5.6, 13.2, 13.2 Hz, 1 H), 2.14 (ddd, J = 2.4, 8.3, 13.2 Hz, 1 H), 2.51 (m_c, 2 H), 2.74 (m_c, 1 H), 2.95 (m_c, 1 H), 3.40 (m_c, 1 H), 3.46 (dd, J = 6.4, 10.5 Hz, 1 H), 3.60 (dd, J = 5.8, 10.5 Hz, 1 H), 3.72 (m_c, 1 H), 4.32 (dd, J = 5.2, 10.5 Hz, 1 H), 4.92 (s, 1 H), 5.06 (dd, J = 2.4, 5.8 Hz, 1 H), 5.11 (s, 1 H), 5.41 (d, J = 3.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 15.2 (q), 16.9 (q), 36.2 (d), 36.7 (t), 37.5 (d), 39.9 (t), 62.9 (t), 67.1 (t), 74.6 (d), 103.1 (d), 110.9 (t), 126.3 (d), 137.9 (s), 139.4 (s). − MS (GC/MS, 70 eV): m/z (%) = 238 (2) $[M^+]$, 220 (2) $[M^+ - H_2O]$, 208 (12) $[M^+ - CH_2O]$, 207 (16), 193 (28) $[M^+ - C_2H_5O]$, 192 (40) $[M^+ - C_2H_5OH]$, 179 (10), 174 (5) $[M^+ - H_2O - C_2H_5OH]$, 91 (100) $[C_7H_7^+]$. − $C_{14}H_{22}O_3$ (238.16): calcd. C 70.56, H 9.30; found C 70.67, H 9.38.

(Iodomethyl)magnesium Chloride: A solution of isopropylmagnesium chloride (5 mL, 10 mmol, 2 M in diethyl ether) was diluted with dry THF (15 mL). After cooling to −78 °C, diiodomethane (0.8 mL, 10 mmol) was added within 5 min with vigorous stirring, and the resultant yellowish suspension was vigorously stirred for 1 h at −78 °C to give the carbenoid reagent.

Preparation of Diene 9 from Sultone 7: To a solution of sultone **7**[8] (500 mg, 1.74 mmol) in dry THF (10 mL) cooled to −78 °C was slowly added MeLi (1.2 mL, 1.89 mmol, 1.6 M in ether). The mixture was allowed to warm to room temperature within 20 min, stirred until GC (trapping of the allyllithium species with methyl iodide) indicated complete metallation (ca. 30 min) and then cooled

to −78 °C. Dry HMPA (0.7 mL, 3.8 mmol) was added dropwise and after a homogeneous mixture was obtained, the solution was added dropwise via syringe to a suspension of (iodomethyl)magnesium chloride cooled to −78 °C prepared as described above from isopropylmagnesium chloride (10.0 mmol) and diiodomethane (10.0 mmol). The resulting mixture was allowed to warm to room temperature overnight with vigorous stirring. Sat. aqueous NH$_4$Cl (10 mL) was added carefully, and stirring was continued for additional 20 min. Water was added until a clear solution was obtained, the layers were separated and the aqueous layer was adjusted to pH = 7 with 2 N HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with 0.1 N HCl (10 mL), sat. aqueous NaHCO$_3$ (10 mL) and brine (10 mL). After drying with MgSO$_4$, the suspension was filtered through a pad of silica gel and the solvents were evaporated at a maximum bath temperature of 40 °C. The crude product was purified by flash chromatography (diethyl ether/pentane, 1:1) to give the separated diene diastereomers **9a** and **9b** (combined yield 285 mg, 69%, **9a/9b** = 1:1).

Preparation of Silyl Compound 8 from Bromo Acetal 15: To a solution of bromoacetal **15**[8] (500 mg, 1.36 mmol) in dry THF (3 mL) was added dry Ni(acac)$_2$ (16 mg, 0.068 mmol, 5 mol%) and dry Bu$_4$NI (126 mg, 0.34 mmol, 25 mol%). The resultant suspension was cooled to −78 °C, and Et$_2$Zn (0.27 mL, 2.72 mmol) was added dropwise. After warming to room temperature during 1 h, the black suspension was stirred at 40 °C for 2 d and then cooled to −78 °C. A suspension of CuBr·Me$_2$S (839 mg, 4.08 mmol) in dry THF (4 mL) was added dropwise and stirring was continued for 30 min at −78 °C. The resulting mixture was allowed to warm to 0 °C and stirred for additional 3 h at this temperature. After cooling to −78 °C, (iodomethyl)trimethylsilane (0.26 mL, 1.75 mmol) was added, and the mixture was allowed to warm to room temperature overnight with exclusion of light. Sat. aqueous NH$_4$Cl (2 mL) was added carefully, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 0.1 N HCl (10 mL), sat. aqueous NaHCO$_3$ (10 mL) and brine (10 mL), dried with MgSO$_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (diethyl ether/ethyl acetate/pentane, 1:2:2) gave the silyl compound **8** (326 mg, 64%) as a mixture of three diastereomers (ratio 1:4:5 by GC).

Preparation of Diene 9 from Bromo Acetal 15: Bromo acetal **15**[8] (500 mg, 1.36 mmol) was converted into the organocopper intermediate **17** as described above. After addition of CuBr·Me$_2$S, the mixture was stirred for 30 min at −78 °C, 1 h at 0 °C and 1 h at room temperature and then cooled to −78 °C. Dry HMPA (0.5 mL, 2.72 mmol) was added dropwise and after a homogeneous mixture was obtained, the solution was added dropwise via syringe to a suspension of (iodomethyl)magnesium chloride cooled to −78 °C prepared as described above from isopropylmagnesium chloride (10.0 mmol) and diiodomethane (10.0 mmol). The resulting mixture was allowed to warm to room temperature overnight with vigorous stirring. Sat. aqueous NH$_4$Cl (4 mL) was added carefully, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with 0.1 N HCl (10 mL), sat. aqueous NaHCO$_3$ (10 mL) and brine (10 mL). After drying with MgSO$_4$ and concentration in vacuo, the crude product was purified by flash chromatography (diethyl ether/pentane, 1:1) to give the separated diene diastereomers **9a** and **9b** (combined yield 220 mg, 68%, **9a/9b** = 1:1).

Preparation of Dienes 23 (General Procedure): For the preparation of **23a** and **23c**, a solution of the sultone **19**[8,22] (2.05 mmol) in dry THF (20 mL) cooled to −78 °C was treated with MeLi (1.3 mL,

2.05 mmol, 1.6 M in diethyl ether). After TLC showed complete elimination (ca. 15 min), a second equivalent of MeLi (1.3 mL, 2.05 mmol) was added. The temperature was increased to 0 °C, and stirring was continued for additional 45 min at this temperature followed by cooling to −78 °C. For preparation of **23b** and **23d**, a solution of the sultone **19** (2.05 mmol) in dry THF (20 mL) cooled to −78 °C was treated with BuLi (2.6 mL, 4.10 mmol, 1.6 M in hexane), and stirring was continued at −78 °C for additional 45 min. The resultant solution cooled to −78 °C was added dropwise by syringe to a suspension of (iodomethyl)magnesium chloride cooled to −78 °C prepared as described above from isopropylmagnesium chloride (12.3 mmol) and diiodomethane (12.3 mmol). The resulting mixture was allowed to warm to room temperature overnight, treated with sat. aqueous NH$_4$Cl (10 mL), and vigorously stirred for 20 min. Water was added until a clear solution was obtained. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo at 40 °C bath temperature. Purification of the residue by flash chromatography (ethyl acetate/pentane, 2:1) afforded the dienes **23** as colorless sticky oils.

Diene 23a: Yield: 62%, R_f = 0.12 (ethyl acetate/pentane, 2:1). − IR (neat): $\tilde{\nu}$ = 3434−3380 (s, br, OH), 2961 (s), 2932 (s), 2874 (s), 1464 (m), 1458 (m), 1338 (s), 1180 (m), 1123 (m), 1108 (m), 1061 (m), 1037 (m), 1027 (m), 885 (s) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 1.08 (d, J = 7.3 Hz, 3 H), 1.12 (d, J = 6.9 Hz, 3 H), 2.45−2.53 (m$_c$, 2 H), 2.59 (dd, J = 5.6, 14.3 Hz, 1 H), 2.83 (m$_c$, 1 H), 3.51 (dd, J = 6.1, 10.6 Hz, 1 H), 3.63 (dd, J = 5.6, 10.6 Hz, 1 H), 3.91 (m$_c$, 1 H), 4.94 (s, 1 H), 5.18 (s, 1 H), 5.37 (s, 1 H). − ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 16.2 (q), 16.8 (q), 36.0 (d), 36.4 (d), 40.1 (t), 66.9 (t), 68.9 (d), 111.7 (t), 129.0 (d), 137.3 (s), 139.0 (s). − MS (GC/MS, 70 eV): m/z (%) = 182 (6) [M$^+$], 164 (26) [M$^+$ − H$_2$O], 151 (25) [M$^+$ − CH$_2$OH], 149 (24) [M$^+$ − H$_2$O − CH$_3$], 138 (42), 135 (60), 134 (35), 123 (63) [M$^+$ − C$_3$H$_7$O], 122 (14), 121 (35), 119 (41), 109 (38), 107 (78), 105 (66), 95 (49), 94 (12), 93 (55), 91 (100) [C$_7$H$_7^+$], 81 (55), 79 (77), 77 (67), 67 (43), 65 (31), 55 (40), 53 (36), 43 (86), 41 (71). − MS (HR-EI): 182.128 (C$_{11}$H$_{18}$O$_2$, M$^+$: calcd. 182.131).

Diene 23b: Yield: 66%, R_f = 0.28 (ethyl acetate/pentane, 2:1). − IR (neat): $\tilde{\nu}$ = 3434−3371 (s, br, OH), 2961 (s), 2932 (s), 2874 (s), 1460 (m), 1338 (s), 1181 (m), 1122 (m), 1107 (m), 1060 (m), 1035 (m), 1024 (m), 885 (s) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 1.04 (m$_c$, 6 H), 1.32−1.49 (m, 6 H), 2.48 (m$_c$, 1 H), 2.51 (s, 1 H), 2.57 (dd, J = 5.4, 11.8 Hz, 1 H), 2.78 (m$_c$, 1 H), 3.55 (m$_c$, 2 H), 3.88 (m$_c$, 1 H), 4.88 (s, 1 H), 5.13 (s, 1 H), 5.34 (s, 1 H). − ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 16.4 (q), 17.0 (q), 22.8 (t), 29.2 (t), 31.1 (t), 35.8 (d), 36.3 (d), 40.0 (t), 66.7 (t), 68.8 (d), 111.8 (t), 128.7 (d), 137.4 (s), 139.5 (s). − MS (GC/MS, 70 eV): m/z (%) = 224 (3) [M$^+$], 209 (4) [M$^+$ − CH$_3$], 206 (15) [M$^+$ − H$_2$O], 193 (8) [M$^+$ − CH$_2$OH], 180 (21), 176 (27), 121 (23), 119 (27), 109 (29), 105 (27), 95 (19), 93 (26), 92 (9), 91 (60) [C$_7$H$_7^+$], 79 (31), 55 (28), 43 (30), 41 (48), 32 (100). − MS (HR-EI): 224.168 (C$_{14}$H$_{24}$O$_2$, M$^+$: calcd. 224.168).

Diene 23c: Yield: 61%, R_f = 0.18 (ethyl acetate/pentane, 2:1). − IR (neat): $\tilde{\nu}$ = 3482−3338 (s, br, OH), 2961 (s), 2934 (s), 2875 (s), 1464 (m), 1459 (m), 1378 (m), 1338 (s), 1181 (m), 1123 (m), 1107 (m), 1060 (m), 1035 (m), 1025 (m), 908 (m), 885 (s) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 0.89 (t, J = 6.6 Hz, 3 H), 1.04 (d, J = 7.2 Hz, 3 H), 1.41 (m$_c$, 4 H), 1.55 (m$_c$, 1 H), 1.67 (m$_c$, 1 H), 2.94 (m$_c$, 3 H), 3.91 (m$_c$, 2 H), 4.89 (s, 1 H), 5.04 (s, 1 H), 5.40 (s, 1 H). − ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 13.4 (q), 14.0 (q), 17.8 (t), 18.8 (t), 33.1 (t), 36.3 (t), 40.8 (d), 68.9 (t), 69.5 (d), 112.0 (t), 132.9

(d), 133.8 (s), 139.3 (s). − MS (GC/MS, 70 eV): m/z (%) = 210 (0.9) [M$^+$], 195 (7) [M$^+$ − CH$_3$], 192 (7) [M$^+$ − H$_2$O], 166 (8), 138 (13), 123 (21), 121 (21), 120 (55), 119 (11) [M$^+$ − H$_2$O − C$_4$H$_9$O], 105 (56), 91 (34), 55 (32), 43 (43), 41 (31), 32 (100). − MS (HR-EI): 210.152 (C$_{13}$H$_{22}$O$_2$, M$^+$: calcd. 210.152).

Diene 23d: Yield: 70%, R_f = 0.32 (ethyl acetate/pentane, 2:1). − IR (neat): ṽ = 3427−3232 (s, br, OH), 2962 (s), 2929 (s), 2874 (s), 1464 (m), 1340 (s), 1267 (m), 1180 (m), 1160 (m), 1124 (m), 1107 (m), 1058 (m), 1036 (m), 1031 (m), 1027 (m), 885 (s), 738 (m) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 0.82−1.08 (m, 10 H), 1.18−1.54 (m, 6 H), 1.87−1.91 (m$_c$, 2 H), 2.53 (m$_c$, 1 H), 2.52−2.56 (m$_c$, 2 H), 4.01 (m$_c$, 1 H), 4.29 (m$_c$, 1 H), 4.96 (s, 1 H), 5.10 (s, 1 H), 5.46 (s, 1 H). − ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 14.0 (q), 14.1 (q), 18.9 (t), 19.0 (t), 22.7 (t), 29.3 (t), 29.7 (t), 30.8 (t), 39.5 (t), 41.9 (d), 67.6 (t), 69.3 (d), 112.6 (t), 131.8 (d), 137.1 (s), 138.9 (s). − MS (GC/MS, 70 eV): m/z (%) = 253 (0.4) [M$^+$ + 1], 252 (0.4) [M$^+$], 234 (10) [M$^+$ − H$_2$O], 208 (11), 180 (13), 177 (10) [M$^+$ − H$_2$O − C$_4$H$_9$], 162 (49), 120 (24), 107 (26), 106 (23), 105 (53), 95 (22), 93 (28), 91 (43) [C$_7$H$_7^+$], 79 (24), 77 (21), 55 (51), 43 (49), 41 (46), 32 (100). − MS (HR-EI): 252.203 (C$_{16}$H$_{28}$O$_2$, M$^+$: calcd. 252.209).

Preparation of Sultone 24: Iodomethylmagnesium chloride was prepared as described above from isopropylmagnesium chloride (12.3 mmol) and diiodomethane (12.3 mmol). In a separate flask, sultone **19a**[8] (443 mg, 2.05 mmol) was treated with MeLi (two 2.05 mmol portions) as described above to give the allyllithium intermediate **21a**. After cooling the latter solution to −78 °C, it was transferred via cannula to the carbenoid reagent cooled to −78 °C, and the resulting mixture was stirred at −78 °C for 1 h. Sat. aqueous NH$_4$Cl (10 mL) was added, and the mixture was allowed to warm to room temperature within 20 min with vigorous stirring. Water was added until a clear solution was obtained, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo at 40 °C bath temperature. After purification of the yellowish residue by flash chromatography (ether/ethyl acetate/pentane, 1:2:2), sultone **24**[24] (312 mg, 62%) was obtained as a colorless oil, R_f = 0.39 (ether/ethyl acetate/pentane, 1:2:2). − IR (neat): ṽ = 3384 (m, br, OH), 2965 (m), 2880 (m), 1467 (m), 1384 (m), 1342 (s, SO$_2$OR), 1180 (s, SO$_2$OR), 1108 (m), 1056 (m), 966 (s), 871 (m), 848 (m), 804 (s), 758 (m), 660 (s), 581 (m), 551 (m), 521 (m) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 1.00 (d, J = 6.7 Hz, 3 H), 1.08 (d, J = 7.2 Hz, 3 H), 1.68 (s, 3 H), 1.85 (ddd, J = 0.7, 3.7, 13.8 Hz, 1 H), 2.40 (m$_c$, 1 H), 2.59 (m$_c$, 1 H), 2.88 (m$_c$, 1 H), 3.90 (ddd, J = 3.7, 4.8, 9.0 Hz, 1 H), 4.07 (dd, J = 10.7, 11.9 Hz, 1 H), 4.25 (dd, J = 5.5, 10.7 Hz, 1 H), 5.59 (m$_c$, 1 H). − ^{13}C NMR (CDCl$_3$, 126 MHz): δ = 12.3 (q), 14.6 (q), 24.6 (q), 31.8 (d), 34.5 (t), 35.0 (d), 63.4 (s), 65.8 (d), 77.6 (t), 130.8 (d), 134.4 (s). − MS (GC/MS, 70 eV): m/z (%) = 247 (14) [M$^+$ + 1], 228 (5) [M$^+$ − H$_2$O], 183 (12), 167 (64), 149 (20), 138 (100), 123 (66), 109 (46), 95 (39), 79 (25), 67 (20), 55 (13), 39 (48).

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