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Stereocontrolled entry to β-*C*-glycosides and bis-*C*,*C*-glycosides from *C*-glycals: preparation of a highly functionalized triene from D-mannose

Ana M. Gómez,* Marta Casillas, Serafín Valverde and J. Cristóbal López*

Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain

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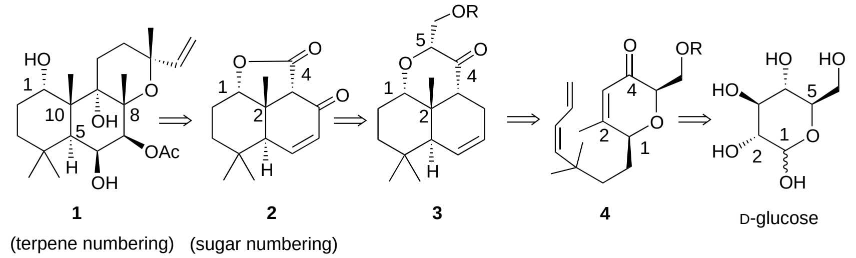
Abstract—The C(3) hydroxyl group of *C*-glycals can be readily converted into mixed halo-acetals of 2-bromo-acetaldehyde. Radical reaction of the latter mediated by tri-*n*-butyltin hydride, with or without a radical acceptor, led diastereoselectively to either β-*C*-glycosides or bis-*C*,*C*-glycosides, respectively. The latter have been transformed into a highly functionalized triene, which is a potential precursor in a proposed synthesis of labdane type diterpenes from D-mannose. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The use of carbohydrates as starting materials in organic synthesis has become a commonly used strategy for more than two decades.[1,2] Extension of the scope of carbohydrates as suitable building blocks, thus, relies on the development of convenient key intermediates, which would comply with a series of requirements such as easy stereocontrolled access, high degree of functionalization and versatility. In this context, two areas of special development in the chemistry of carbohydrates have been the stereocontrolled preparation of branched chain sugars[3] and the synthesis of carbocyclic compounds.[4–6]

In 1992, Tsang and Fraser-Reid[7] reported the synthesis of *trans* decalin **2**,[8] which had been used in Ziegler's total synthesis[9] of *Forskolin* **1**, a labdane-type diterpene endowed with important biological properties,[10] from D-glucose. Tsang and Fraser-Reid's synthesis elegantly combined the stereoselective preparation of a branched chain *C*-glycoside derivative, **4**, with the formation of a carbocyclic decalin derivative, **3**, readily obtained by Diels–Alder cycloaddition of the former. The sequential incorporation of the branches at C(1) and C(2) in compound **4** required, however, multistep sequences. The formation of the β-*C*-glycosidic bond (branch at C(1)) was carried out via nucleophilic addition of an organolithium reagent to a glucose-derived lactone, followed by the stereoselective aldose reduction process introduced independently by Gray[11] and Kishi.[12] The introduction of the methyl group at C(2) also required a multistep sequence (Scheme 1).[7]

Based on this seminal contribution, we decided to explore a novel approach to labdane-type diterpenes



Scheme 1. Tsang and Fraser-Reid's retrosynthesis of Forskolin from D-glucose.

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* Corresponding authors.

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from carbohydrates that would also involve the formation of a branched chain carbohydrate and a Diels–Alder cycloaddition, but in which the number of steps related to the installation of the branches will be minimized. In this paper we disclose a novel, stereocontrolled, access to bis-*C*,*C*-glycosides,[12,13] with an additional branch at C(2), (e.g. **12b**, Scheme 3), from *C*-glycals (e.g. **10**, Scheme 3). The synthetic utility of this protocol has been illustrated with the preparation of a monosaccharide-derived triene **18**, which is a potential intermediate in a proposed synthesis of labdane type diterpenes.

2. Results and discussion

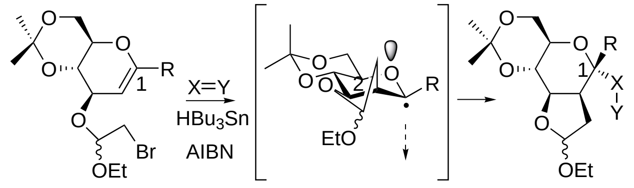
2.1. The approach

Our strategy,[13] outlined in Scheme 2(a), features an intramolecular Diels–Alder (IMDA) reaction[14] of a highly functionalized monosaccharide derivative (e.g. **5**), which is to be prepared from D-mannose. The relative stereochemistry for the branches at C(1) and C(2) in the intermediate **5** was chosen by overlapping with a substituted cyclohexane, **6**, which had previously been reported by Taber and Saleh[15] to undergo a stereoselective Diels–Alder cycloaddition to afford *trans*-decalin **7** (Scheme 2(b)). Shortly after this project was started, a similar approach, outlined in Scheme 2(c), was reported by Hanna et al.[16] In Hanna's approach D-galactal was stereoselectively correlated with the intermediate triene **9** (Scheme 2(c)) by way of consecutive *C*-Ferrier (branch at C(1)) and Claisen-Ireland (branch at C(2)) rearrangements. Our approach differed from that of Hanna's in which provisions for the installation of a quaternary center at C(8) had been made. In fact, the tetrasubstituted carbon atom at C(8) in **1** was retrosynthetically correlated with the C(1) anomeric center of bis-*C*,*C*-glycoside **5**.

2.2. Stereoselective installation of the branches at C(1) and C(2)

In our designed synthesis we considered the rapid assembly of the carbon branches at C(1) and C(2) crucial. We have thus developed a method in which the stereocontrolled construction of the quaternary carbon at C(1) and the branch at C(2) occurs in just one synthetic operation. The method, outlined in Scheme 3, is an extension of previous work carried out by some of us in Fraser-Reid's laboratories.[17] We had already shown how a glycal could be correlated with a *C*-glycoside possessing a branch at C(2) (e.g. **10a→12a**). However, it remained to be established whether a substituent at C(1) would display any effect on such a process.

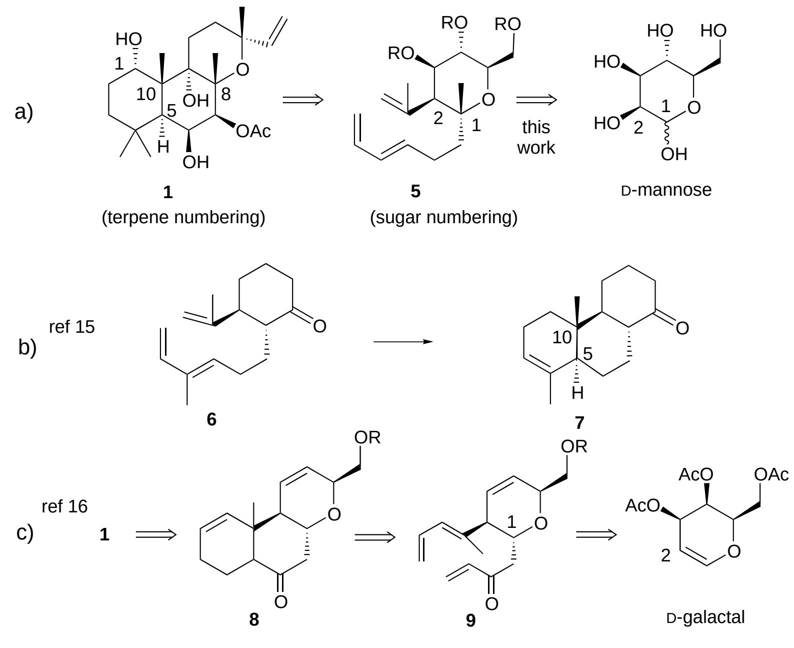
Accordingly, *C*-methyl glycal **14** (Scheme 4), readily prepared from glycosyl chloride **13** by treatment with MeLi,[18] was converted into mixed halo-acetals **15**,[19,20] and treated with HBu_3Sn to afford in a stereoselective manner β-*C*-methyl glycal **16**.[21] The stereochemistry at C(1) in **16** was assigned on the basis of a NOE effect between the C(7)-*endo* proton and the methyl group protons at the anomeric position. Analogously, treat-



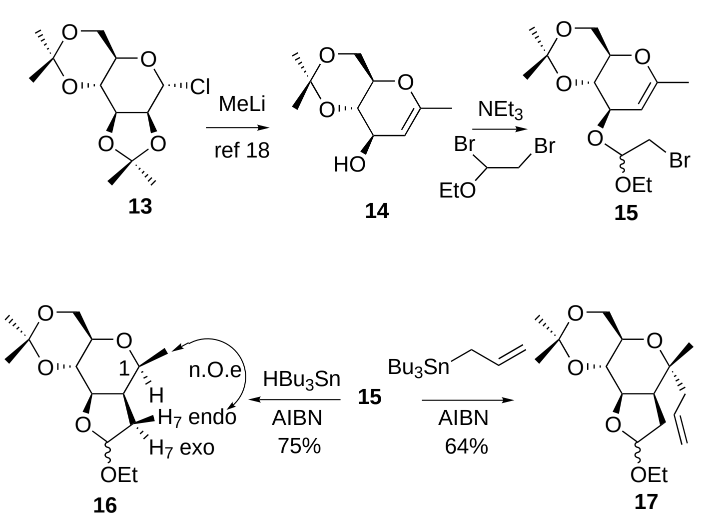
10 **11** **12**

a R= H (ref 17)
b R= Me, this work

Scheme 3.



Scheme 2.



Scheme 4.

ment of **15** under Keck's conditions with allyl tributyltin[22] in the presence of AIBN resulted in the formation of the bis-*C*,*C*-glycoside **17**.[23]

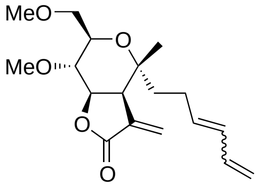
2.3. Elaboration of the triene moiety from 17

In our planned synthesis the diene had to be built on the *C*-glycoside α-chain and the dienophile installed at the C(2) branch. The allyl group, introduced at C(1), was chosen because it provides the required number of carbon atoms as well as the functionality to build the pendant diene moiety by way of hydroboration, followed by Wittig reaction.

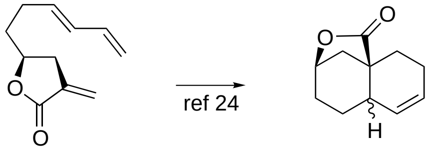
The substituent at C(2) was to be transformed in a substituted dienophile, and we chose the *exo*-methylenic lactone, **18**, as our target since a similar α-methylene lactone had been shown by Maier and Pérez to undergo an efficient intramolecular Diels–Alder reaction (IMDA) (Scheme 5).[24]

Exchange of the acid labile isopropylidene protecting group in **17** by conversion to the more robust methyl ethers led to compound **20** (two steps, 70 and 93% yield) (Scheme 6), which upon Jones oxidation of the ethyl acetal moiety led to lactone **21** (97% yield). Hydroboration of the double bond furnished hydroxy lactone **22** (76% yield), which upon Swern oxidation (70% yield), followed by Wittig reaction with allyltriphenylphosphonium bromide (*n*-BuLi, THF) yielded diene **23** in 20% yield as an (*E*)/(*Z*) mixture (ratio: (*E*)/(*Z*) = 1/1.7).

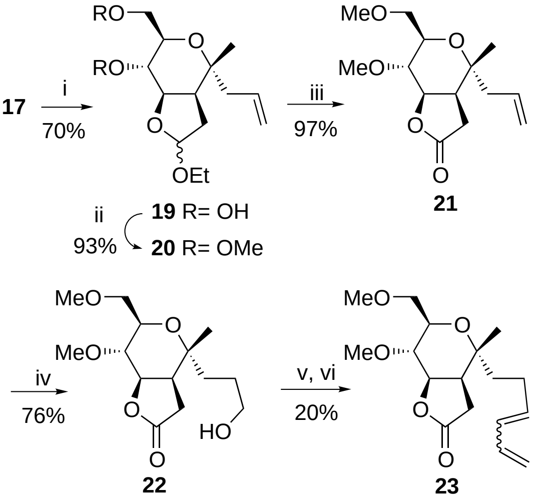
An alternative protocol in which the acetal→lactone oxidation would be carried out after construction of the diene moiety was also considered (Scheme 7). Accordingly, hydroboration of **20** led to hydroxy compound **24** (82% yield), which was uneventfully oxidized to aldehyde **25** with PCC (80% yield). Wittig reaction of **25** with allyltriphenylphosphonium bromide, using *n*-BuLi as a base, afforded diene **26** albeit in low yield (27% yield, the use of different bases such as *tert*-BuOK,



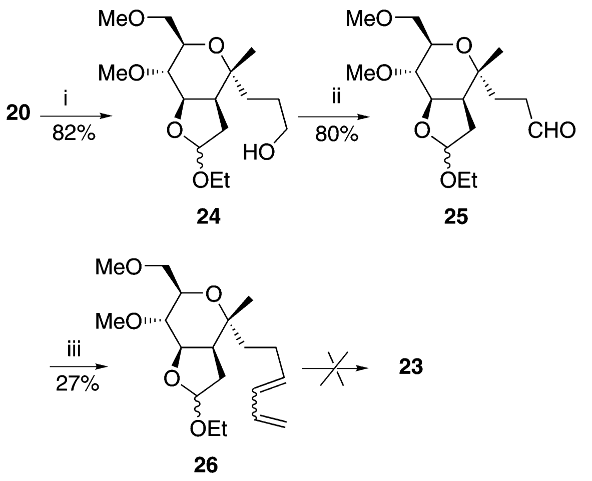
18



Scheme 5.



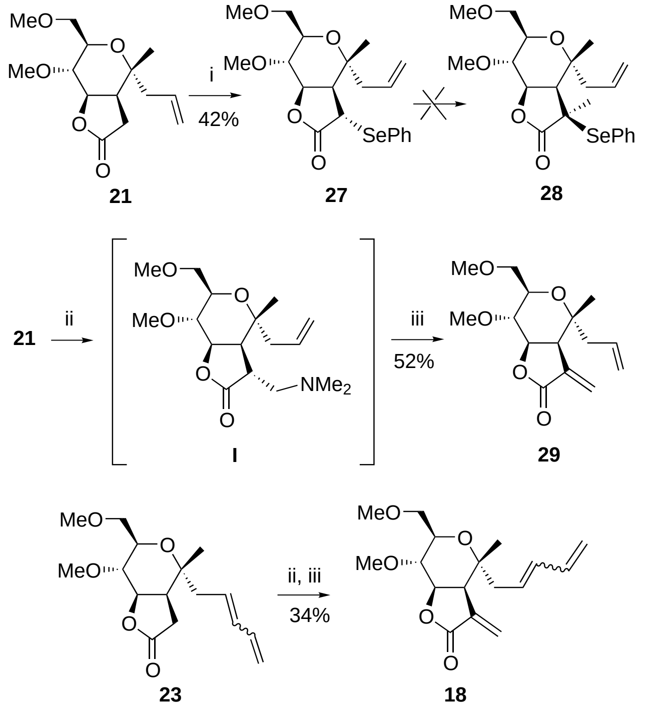
Scheme 6. (i) TsOH, EtOH; (ii) NaH, MeI; (iii) Jones reagent; (iv) borane methyl sulfide, H_2O_2, NaOH; (v) (a) Swern reagent, 70%; (b) $BrPh_3PCH_2CH{=}CH_2$, BuLi, THF, 20%.



Scheme 7. (i) Borane methyl sulfide, H_2O_2, NaOH; (ii) PCC; (iii) $BrPh_3PCH_2CH{=}CH_2$, BuLi, THF.

HMDSLi did not result in improved yields). Jones oxidation of the latter did not lead to **23** and only extensive decomposition was observed.

Installation of the exocyclic methylene moiety was next attempted and model studies were carried out with lactone **21** (Scheme 8). We first explored Grieco's methodology,[25] based on the ready *cis* elimination of selenoxides. According to this approach, the sequential introduction of a phenylselenyl group and a methyl substituent on a γ-butyrolactone, followed by elimination of the corresponding selenoxide would afford the corresponding methylenic lactone. Accordingly, phenylselenylation of lactone **21** was carried out with diphenyldiselenide in the presence of lithium hexamethyldisilazide and afforded selenolactone **27** in 42% yield. However, we were unable to incorporate the methyl group α to the lactone unit even in the presence of different bases (LDA, $(TMS)_2NLi$, $(TMS)_2NNa$).



Scheme 8. (i) $(TMS)_2NLi$, THF then PhSeSePh, HMPA; (ii) LDA, THF, then $Me_2N^+{=}CH_2$ Br^-; (iii) MeI, MeOH then DBU.

As a second alternative for the methylenation step, we chose a method developed by Danishefsky,[26] based on the dimethylaminomethylenation of lactones followed by amine quaternization and subsequent base-induced elimination. Accordingly, lactone **21** was treated with Eschenmoser's salt in the presence of lithium hexamethyldisilazide in THF, followed by treatment with MeI and DBU to afford the methylenic lactone **29** in 52% yield. The same protocol was also employed for the synthesis of **18** when starting from lactone **23**. Initial attempts to effect IMDA on **18** under thermal conditions have not yet succeeded, probably due to the strain associated with the starting lactone; we are currently considering the preparation of novel trienes and our results will be reported in due course.

3. Summary

In summary, we have described a completely stereoselective method for the efficient preparation of β-*C*-glycosides (e.g. **16**) and bis-*C*,*C*-glycosides (e.g. **17**) from readily available *C*-glycals.[18] The stereochemical outcome of the method is dictated by stereoelectronic factors through the well-known preferred axial approach of 1-glycopyranosyl radicals,[27,28] which has been termed *radical anomeric effect*,[29] along with the steric effects inferred from bicyclic nature of radical **11**.[17,19] This method when coupled with our recently described protocol for the preparation of *C*-glycals from glycosyl chlorides[18] would allow the efficient assembly of highly branched monosaccharide derivatives (e.g. compound **17** was prepared from inexpensive D-mannose in five steps).

4. Experimental

4.1. General procedures

All reactions were performed in dry flasks fitted with a glass stopper or rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was conducted in Kiesel gel 60 F_{254} (Merck). Detection was first by UV (254 nm) then charring with a solution of 20% aqueous sulfuric acid (200 mL) in acetic acid (800 mL). Anhydrous $MgSO_4$ or $NaSO_4$ was used to dry the organic solutions during work-ups, and the removal of the solvents was carried out under vacuum with a rotary evaporator. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Solvents were dried and purified using standard methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 400 or 500 and 75 or 50 MHz, respectively. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent. Proton NMR (^{1}H NMR) are presented in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet), coupling constants in hertz, integration and assignment.

4.2. 2,3:4,6-Di-*O*-isopropyliden-α-D-mannopyranoside chloride 13[30]

To a solution of 2,3:4,6-di-*O*-isopropylidene-D-mannopyranoside[31] (3.5 g, 13.5 mmol) and triphenylphosphine (2 equiv.) in dry THF (27 mL) was added CCl_4 (5 equiv.). The reaction was heated under reflux for 2 h, then cooled, filtered through a small pad of Celite and evaporated to give a residue, which was purified by flash chromatography (*n*-hexane/EtOAc, 9:1) to yield **13** (3.57 g, 95%): $[\alpha]_D^{25}=+52.9$ ($c=1.35$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (s, 3H, Me), 1.36 (s, 3H, Me), 1.44 (s, 6H, 2×Me), 3.99 (dd, $J_{5,6}=4.4$ Hz, $J_{6,6'}=8.8$ Hz, 1H, H-6), 4.08 (dd, $J_{5,6'}=5.9$ Hz, $J_{6,6'}=8.8$ Hz, 1H, H-6′), 4.18 (dd, $J_{3,4}=3.5$ Hz, $J_{4,5}=7.8$ Hz, 1H, H-4), 4.41 (ddd, $J_{4,5}=7.8$ Hz, $J_{5,6}=4.4$ Hz, $J_{5,6'}=5.9$ Hz, 1H, H-5), 4.86 (dd, $J_{2,3}=5.8$ Hz, $J_{3,4}=3.5$ Hz, 1H, H-3), 4.93 (d, $J_{2,3}=5.8$ Hz, 1H, H-2), 6.05 (s, 1H, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 113.3, 109.5, 97.7, 89.2, 82.4, 78.6, 72.3, 66.7, 26.9, 25.8, 25.2, 24.7

4.3. 2,6-Anhydro-1,3-dideoxy-5,7-*O*-(1-methylethylidene)-D-arabino-hep-2-enitol 14

To a solution of glycosyl chloride **13** (250 mg, 0.89 mmol) in dry THF (3 mL) at room temperature was added MeLi (1.5 M, 5 equiv.). After the starting material had disappeared (3 h) the reaction mixture was quenched with H_2O. Et_2O was then added and the organic phase was washed with brine and dried (Na_2SO_4). Evaporation of the organic layer followed by flash chromatography (*n*-hexane/EtOAc, 9:1) afforded **14** (95 mg, 53%). $[\alpha]_D^{25}=-4.5$ ($c=0.42$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.28 (s, 3H, Me), 1.41 (s, 3H, Me), 1.53 (s, 3H, Me), 4.05 (m, 2H, 2H-7), 4.14 (dd, $J_{4,5}=6.1$ Hz, $J_{5,6}=7.4$ Hz, 1H, H-5), 4.53 (dt, $J_{5,6=6,7}=7.4$ Hz, $J_{6,7'}=6.0$ Hz, 1H, H-6), 4.68 (m, 1H, H-4), 4.69 (m, 1H, H-3; ^{13}C NMR (50 MHz, C_6D_6) δ 169.0, 105.9, 100.6, 86.3, 74.6, 74.0, 67.5, 27.4, 25.8, 25.3; anal. calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.07; H, 7.82%.

4.4. 2,6-Anhydro-4-*O*-(2-bromo-1-ethoxyethyl)-1,3-dideoxy-5,7-*O*-(1-methylethylidene)-D-arabino-hep-2-enitol 15

A solution of 1,2-dibromoethyl ether was prepared by dropwise addition of bromine (2.17 mL, 8 equiv.) to a stirred solution of ethyl vinyl ether (5.03 mL, 10 equiv.) in dry CH_2Cl_2 (50 mL) maintained at −78°C. The solution was kept at −78°C for 90 min and then was allowed to warm to rt for about 60 min. A solution of *C*-glycal **14** (1.05 g, 5.26 mmol) in triethylamine (10.5 mL) was added and the resulting mixture was stirred at rt overnight. Concentration under reduced pressure and flash chromatography (hexane/ethyl acetate; 95:5) led to diastereomeric acetals **15** as a 1:1 mixture (1.42 g, 77%), 200 MHz; ^{1}H NMR δ ($CDCl_3$) 4.85 (m, 1H), 4.76 (m, 1H), 4.65 (t, $J=5.3$ Hz, H-4, one isomer), 4.49 (m, 2H), 4.30 (t, $J=6.8$ Hz, H-4, other isomer), 3.93 (m, 1H), 4.10 (m, 1H), 3.60 (m, 2H, $C\underline{H}_2Br$, one isomer), 3.31 (m, 2H, $C\underline{H}_2Br$, other isomer), 1.84 (t, 3H, $J=1.0$ Hz, CH_3, one isomer), 1.82 (t, 3H, $J=1.0$ Hz, CH_3, other isomer), 1.42 (s, 3H, CH_3, one isomer), 1.34 (s, 3H, CH_3, other isomer), 1.21 (t, 3H, $J=7.0$ Hz, CH_3, one isomer), 1.20 (t, 3H, $J=7.0$ Hz, CH_3, other isomer); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.1, 160.7, 108.8, 101.6, 99.2, 98.0, 96.7, 84.4, 83.9, 80.6, 77.4, 73.2, 72.6, 66.4, 65.4, 62.0, 61.0, 31.9, 31.5, 26.4, 26.3, 25.0, 15.0, 13.6.

4.5. (4a*R*,6*R*,6a*S*,9a*R*,9b*S*)-6-Allyl-2,2,6-trimethyloctahydrofuro[2′,3′,4,5]pyrano[3,2-*d*][1,3]dioxin-8-yl ethyl ether 17

Bromo acetals **15** (1.42 g, 4.05 mmol), allyltributyltin (3.75 mL, 12.15 mmol, 3 equiv.) and AIBN (0.4 mmol) were heated in degassed toluene (80°C) for 48 h. Concentration in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate; 95:5) to afford **17** as a 1:1 mixture of epimers (808 mg, 64%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75 (m, 1H), 4.96–5.15 (m, 3H), 4.72 (m, 1H), 3.79–4.25 (m, 4H), 3.71 (m, 1H, $C\underline{H}_2CH_3$), 3.40 (m, 1H, $C\underline{H}_2CH_3$), 2.84 (dd, $J=7.6$ Hz, $J=15.4$ Hz, 1H), 2.60 (ddd, $J=4.1$ Hz, $J=7.0$ Hz, $J=15.4$ Hz, 1H), 2.48 (m, 1H), 2.22 (m, 1H), 2.10 (dd, $J=7.0$ Hz, $J=14.5$ Hz, 1H), 1.99 (m, 1H), 1.81 (m, 1H), 1.59 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.15 (t, $J=7.1$ Hz, 3H), 1.13 (t, $J=7.1$ Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.9, 133.5, 117.8, 117.7, 108.7, 108.5, 105.3, 105.3, 86.1, 83.5, 82.4, 80.3, 79.0, 74.0, 73.8, 67.6, 66.7, 63.3, 62.5, 50.2, 44.6, 43.8, 34.9, 34.7, 26.7, 26.6, 25.3, 23.2, 21.5, 17.3, 17.0, 14.9, 14.1. MS *m*/*z* 313.1 (M^++1); anal. calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.07; H, 8.89%.

4.6. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-Allyl-2-ethoxy-7-methoxy-6-(hydroxymethyl)-4-methylhexahydro-4*H*-furo[3,2-*c*]pyran-7-ol 19

To a 0.01 M solution of bis-*C*,*C*-glycoside **17** (550 mg, 1.76 mmol) (1:1 anomeric mixture at the acetal position) in ethanol was added *p*-toluenesulfonic acid (3 equiv., 1.04 g). The resulting solution was stirred at rt for 48 h after which time NEt_3 was added. The resulting solution was concentrated under vacuum and subjected to flash chromatography (*n*-hexane/EtOAc, 1:1) yielding diol **19** as a 10:1 anomeric mixture (335 mg, 70%). ^{1}H NMR, δ (200 MHz, $CDCl_3$): 1.17 (s, 3H, Me), 1.18 (t, $J=7.1$ Hz, CH_3 major), 1.19 (t, $J=7.1$ Hz, minor), 1.87 (m, 2H), 2.16 (m, 1H), 2.29 (m, 1H), 2.97–3.40 (m, 6 H), 4.56–4.89 (m, 1H), 5.03 (m, 1H), 5.12 (m, 1H), 5.21 (dd, $J=1.2$, 4.4 Hz, 1H), 5.68–5.82 (m, 1H). ^{13}C NMR, δ (50 MHz, $CDCl_3$): 15.1, 21.3, 34.6, 43.9, 50.0, 62.9, 64.8, 71.5 (one isomer), 72.8 (other isomer), 78.5 (one isomer), 78.6 (other isomer), 83.0, 84.6, 105.8, 118.2, 133.4. M/e 273.2 (M^++1), 267.3 (M^+–15), 255.3, 249.3, 231.2, 228.2, 227.2, 209.2, 191.2, 185.2, 167.2, 145.3, 105.2, 85.3; anal. calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.57; H, 8.54%.

4.7. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-Allyl-2-ethoxy-7-methoxy-6-(methoxymethyl)-4-methylhexahydro-4*H*-furo[3,2-*c*]pyran 20

To a solution of diol **19** (320 mg, 1.2 mmol) in dry THF (12 mL) at 0°C was added sodium hydride (1.5 equiv. per OH, 3.6 mmol) and the suspension was stirred for 1 h under argon, after which time tetra-*n*-butylammonium iodide (2.4 mmol) and methyl iodide (12 mmol) was added. The resulting mixture was stirred for 3 h and quenched by careful addition of water. The reaction was then extracted with dichloromethane (3× 10 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated. The residue was chromatographed (*n*-hexane/EtOAc, 75:25) to yield compound **20** (336 mg, 93%). ^{1}H NMR, δ (300 MHz, $CDCl_3$) selected signals for the major isomer: 1.18 (t, $J=7.1$ Hz, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.89 (m, 2H), 2.09 (m, 1H), 2.30 (m, 1H), 2.78 (dt, $J=6.8$, 8.5 Hz, 1H), 3.38 (s, 3H, OMe), 3.49 (s, 3H, OMe), 3.38–3.72 (m, 5H), 3.80 (dd, $J=4.1$, 8.3 Hz, 1H), 4.72 (dd, $J=6.7$, 4.2 Hz, 1H), 5.04 (m, 2H), 5.16 (dd, $J=2.3$, 4.5 Hz, 1H), 5.71 (m, 1H). ^{13}C NMR, δ (50 MHz, $CDCl_3$): 15.2, 22.0, 35.0, 44.1, 50.1, 58.6, 59.3, 62.8, 73.1, 77.2, 78.1, 82.6, 83.9, 105.4, 118.0, 133.8.

4.8. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-Allyl-7-methoxy-6-(methoxymethyl)-4-methyltetrahydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one 21

Jones reagent was added dropwise to a solution of acetal **20** (300 mg, 1 mmol) in acetone until the red colour persisted. The reaction crude was treated with isopropanol and triethylamine. Elimination of the solvent and flash chromatography (*n*-hexane/EtOAc, 1:1) yielded lactone **21** (254 mg, 95%). $[\alpha]^{25}_{D}=-29.5$ ($c=0.74$, $CHCl_3$). ^{1}H NMR, δ (300 MHz, $CDCl_3$): 2.03 (s, 3H, CH_3), 2.15 (m, 1H), 2.32 (m, 1H), 2.56 (d, $J=3.4$ Hz, 1H), 2.60 (d, $J=8.6$ Hz, 1H), 2.83 (ddd, $J=3.4$, 6.3, 8.6 Hz, 1H), 3.39 (s, 3H, OMe), 3.40 (m, 1H,), 3.48 (s, 3H, OMe), 3.50 (ddd, $J=1.8$, 8.5, 4.0 Hz, 1H), 3.73 (dd, $J=1.8$, 10.2 Hz, 1H), 4.00 (dd, $J=3.3$, 8.8 Hz, 1H), 5.11 (m, 3H), 5.72 (m, 1H, $C\underline{H}=CH_2$). ^{13}C NMR, δ (50 MHz, $CDCl_3$): 22.6, 31.1, 44.7, 46.1, 58.1, 59.4, 71.2, 77.2, 77.6, 83.4, 85.6, 118.8, 132.9, 176.9; anal. calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.12; H, 7.92%.

4.9. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-(3-Hydroxypropyl)-7-methoxy-6-(methoxymethyl)-4-methylhexahydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one 22

A solution of lactone **21** (254 mg, 0.94 mmol) in dry THF (15 mL) at 0°C was treated with borane methyl sulfide (30 µL, 0.33 equiv., 0.313 mmol) and kept at this temperature for 30 min. The reaction mixture was then allowed to warm to rt and maintained at this temperature for 3 h, after which time the reaction was cooled to 0°C and treated with H_2O_2 (33%, 290 µL, 3 equiv., 2.82 mmol) and 2N NaOH (1 equiv., 0.94 mmol). The reaction was then heated at 60°C for 45 min. Elimination of the solvent and flash chromatography (*n*-hexane/EtOAc, 2:8) led to alcohol **22** (190 mg, 70%). $[\alpha]^{25}_{D}=-47.0$ ($c=0.61$, $CHCl_3$). ^{1}H NMR, δ (300 MHz, $CDCl_3$): 1.20 (s, 3H, CH_3), 1.40–1.80 (m, 4H), 2.04 (m, 1H), 2.62 (d, $J=3.9$ Hz, 1H), 2.65 (d, $J=8.8$ Hz, 1H), 2.79 (ddd, $J=3.4$, 6.2, 8.8 Hz, 1H), 3.41 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.48–3.51 (m, 1H), 3.53–3.74 (m, 4H), 4.00 (dd, $J=3.4$, 9.0 Hz, 1H), 5.11 (dd, $J=3.4$, 6.2 Hz, 1H). ^{13}C NMR, δ (50 MHz, $CDCl_3$): 21.7 (Me), 27.1, 30.9, 35.8 (C-1″, C-1′, C-2′), 47.6 (C-2), 57.8 (OMe), 59.3 (OMe), 62.1, 70.5 (C-6, C-3′), 76.5, 77.4, 85.3 (C-3, C-4, C-5), 83.7 (C-1), 176.4 (C=O); anal. calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.63; H, 8.52%.

4.10. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-[(3*E*/*Z*)-3,5-Hexadienyl)-7-methoxy-6-(methoxymethyl)-4-methylhexahydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one 23

Alcohol **22** (155 mg, 0.54 mmol) was oxidized with PCC (350 mg, 3 equiv., 1.61 mmol) in dry CH_2Cl_2 (10 mL) in the presence of molecular sieves. Filtration of the reaction mixture over a pad of Florisil® yielded the corresponding aldehyde, which was used in the next step without further purification. Data for the aldehyde: ^{1}H NMR, δ (200 MHz, $CDCl_3$): 1.15 (s, 3H, CH_3), 1.30–1.78 (m, 4H), 2.40–2.62 (m, 2H), 2.80 (m, 1H), 3.39 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.40–3.68 (m, 4H), 3.90 (m, 1H), 5.12 (m, 1H), 9.76 (s, 1H, CHO).

A suspension of $Ph_3P^+CH_2CH=CH_2$ Br^- (617 mg, 3 equiv., 1.61 mmol) in dry THF (10 mL) at 0°C under argon, was treated with *n*-BuLi (1.6 M, 1 mL, 3 equiv.). The resulting solution turned red and at this time the above-mentioned aldehyde (0.54 mmol), in dry THF (7 mL), was added. The reaction mixture was allowed to warm to rt and after 4 h was quenched by addition of H_2O, extracted with CH_2Cl_2 and the organic layer dried (Na_2SO_4). Evaporation of the solvent and flash chromatography (*n*-hexane/EtOAc, 7:3) led to diene **23** (33.6 mg, 20%) as a 1:1.7 (*E*):(*Z*) mixture. ^{1}H NMR, δ (300 MHz, $CDCl_3$): 1.17 (s, 3H, CH_3 anomer from *E*), 1.25 (s, 3H, CH_3 anomer from *Z* isomer), 1.40–1.60 (m, 2H), 2.05–2.40 (m, 2H), 2.57–2.65 (m, 2H), 2.75–2.78 (m, 1H), 3.39 (s, 3H, OMe from *Z*), 3.40 (s, 3H, OMe from *E*), 3.43 (d, $J=6.2$ Hz, 1H), 3.48 (s, 3H, OMe from *E*), 3.51 (s, 3H, OMe from *Z*), 3.55–3.58 (m, 1H), 3.73 (d, $J=10.4$ Hz, 1H), 3.92 (dd, $J=3.4$, 9.0 Hz, 1H), 4.97 (d, $J_{5',6'}=10.3$ Hz, 1H minor isomer), 5.07–5.12 (m, 2H), 5.20 (d, $J_{5',6'}=17.1$ Hz, 1H major isomer), 5.37

(ddd, $J=5.6$, 6.5, 11.7 Hz, 1H major isomer), 5.67 (dt, $J_t=7.2$ Hz, $J_d=14.4$ Hz, 1H minor isomer), 5.96–6.09 (m, 1H), 6.28 (dt, $J_t=10.2$ Hz, $J_d=17.0$ Hz, 1H minor isomer), 6.62 (dt, $J_t=10.3$ Hz, $J_d=16.8$ Hz, 1H major isomer). ^{13}C NMR, δ (75 MHz, $CDCl_3$): 22.0, 21.8 (Me), 29.7, 30.1, 30.7, 30.9, 39.4, 39.7, 47.0, 47.3, 58.1, 59.3, 59.5, 70.7, 71.1, 76.6, 77.6, 82.6, 83.2, 83.7, 85.4, 85.6, 115.4, 117.5, 129.7, 130.0, 131.3, 132.1, 134.0, 136.9, 176.6; anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 66.01; H, 8.32%.

4.11. 3-[(3a*S*,4*R*,6*R*,7*S*,7a*R*)-2-Ethoxy-7-methoxy-6-(methoxymethyl)-4-methylhexahydro-4*H*-furo[3,2-*c*]pyran-4-yl]-1-propanol 24

To a solution of bis-*C*,*C*-glycoside **20** (181 mg, 0.6 mmol) in dry THF (15 mL) at 0°C, under argon, was added borane methyl sulfide (80 μL, 1.1 equiv., 0.66 mmol) and the resulting solution stirred for 30 min and then allowed to warm to rt for 2 h. The reaction mixture was then re-cooled to 0°C and treated with H_2O_2 (33%, 100 μL, 3 equiv., 1.8 mmol) and 2N NaOH (1 equiv., 0.6 mmol), the resulting mixture was then heated at 60°C for 1 h. After evaporation of the solvent the residue was chromatographed (*n*-hexane/EtOAc, 7:3) to yield hydroxy compound **24** (170 mg, 89%). Selected data for the major isomer: ^{1}H NMR, δ (200 MHz, $CDCl_3$): 1.15 (s, 3H, CH_3), 1.19 (t, $J=7.1$ Hz, 3H, CH_3), 1.40–1.80 (m, 4H), 1.92 (m, 2H), 2.73 (ddd, $J_{2,1''}=3.4$, 8.7 Hz, $J_{2,3}=6.8$ Hz, 1H), 3.39 (s, 3H, OMe), 3.48 (s, 3H, OMe), 3.43–3.75 (m, 9H), 3.84 (dd, $J_{3,4}=$ 4.1 Hz, $J_{4,5}=8.7$ Hz, 1H), 4.74 (dd, $J_{3,4}=4.1$ Hz, $J_{2,3}=$ 6.8 Hz, 1H), 5.18 (dd, $J=2.0$, 4.6 Hz, 1H). ^{13}C NMR, δ (50 MHz, $CDCl_3$): 15.2, 21.3, 27.4, 35.0, 35.9, 51.6, 58.4, 59.3, 60.3, 62.3 72.6, 76.9, 77.1, 78.1, 83.7, 105.4; anal. calcd for $C_{16}H_{30}O_6$: C, 60.35; H, 9.50. Found: C, 60.07; H, 9.82%.

4.12. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-2-Ethoxy-4(3*Z*/*E*)-3,5-hexadienyl]-7-methoxy-6-(methoxymethyl)-4-methylhexahydro-4*H*-furo[3,2-*c*]pyran 26

Alcohol **24** (170 mg, 0.54 mmol) was oxidized with PCC (348 mg, 3 equiv., 1.61 mmol) in CH_2Cl_2 (15 mL) in the presence of molecular sieves for 2 h. The reaction mixture was then filtered through a pad of Florisil® and the solvent evaporated to yield aldehyde **25**, which was used without further purification in the next step. Data for **25**: ^{1}H NMR, δ (200 MHz, $CDCl_3$): 1.15 (s, 3H, CH_3), 1.21 (t, $J=7.1$ Hz, 3H, CH_3), 1.36–1.78 (m, 4H), 2.22 (m, 2H), 2.80 (m, 1H), 3.38 (s, 3H), 3.47 (s, 3H), 3.36–3.55 (m, 4H), 3.76 (m, 1H), 4.73 (dd, $J_{3,4}=4.1$ Hz, $J_{2,3}=6.7$ Hz, 1H), 5.16 (dd, $J=2.5$, 4.2 Hz, 1H), 9.74 (s, 1H, CHO).

To a suspension of $Ph_3P^+CH_2CH=CH_2$, Br^- (621 mg, 3 equiv., 1.62 mmol) in dry THF (15 mL) at 0°C and under argon, was added *n*-BuLi (1.6 M, 1.1 mL, 3 equiv.). After the solution turned red, aldehyde **25** (0.54 mmol) in THF (10 mL) was added. The reaction was allowed to warm to rt and after 1 h the reaction was quenched with H_2O, extracted with CH_2Cl_2, and dried over Na_2SO_4. Elimination of the solvent and flash chromatography (*n*-hexane/EtOAc, 8:2) led to diene **26** as a 45:55 (*E*):(*Z*) mixture (49.5 mg, 27%). ^{1}H NMR, δ (300 MHz, $CDCl_3$): 1.13 (s, 3H, CH_3 anomeric from *E*), 1.15 (s, 3H, CH_3 anomeric from *Z*), 1.18 (t, $J=7.0$ Hz, 3H, CH_3 from *E*), 1.19 (t, $J=7.0$ Hz, 3H, CH_3 from *Z*), 1.40–1.50 (m, 4H), 1.87–1.93 (m, 4H), 2.07–2.23 (m, 4H), 2.73–2.78 (m, 2H), 3.39 (s, 3H, OMe from *Z*), 3.40 (s, 3H, OMe from *E*), 3.41–3.56 (m, 8H), 3.48 (s, 3H, OMe from *E*), 3.49 (s, 3H, OMe from *Z*), 3.71–3.76 (m, 4H), 4.73 (dd, $J_{3,4}=4.1$ Hz, $J_{2,3}=6.7$ Hz, 2H), 4.97 (d, $J=10.3$ Hz, 1H), 5.07–5.12 (m, 2H), 5.20 (d, $J=17.1$ Hz, 1H), 5.37 (ddd, $J=5.6$, 6.5, 11.7 Hz, 1H), 5.67 (dt, $J_t=7.2$ Hz, $J_d=14.4$ Hz), 5.94–6.08 (m, 1H), 6.28 (dt, $J_t=10.2$ Hz, $J_d=17.0$ Hz, 1H), 6.64 (dt, $J_t=10.3$ Hz, $J_d=16.8$ Hz, 1H). ^{13}C NMR, δ (75 MHz, $CDCl_3$): 14.1, 15.2, 21.4, 22.7, 27.1, 29.4, 29.7, 31.9, 34.1, 35.0, 51.5, 51.9, 58.1, 58.5, 59.3, 59.5, 62.7, 63.5, 72.7, 76.6, 77.6, 78.2, 79.5, 79.9, 83.7, 83.9, 105.0, 105.4, 112.0, 113.5, 128.4, 128.6, 131.9, 132.0, 132.1, 132.2; anal. calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.87.07; H, 9.23%.

4.13. (3*R*,3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-Allyl-7-methoxy-6-(methoxymethyl)-4-methyl-3-(phenylselanyl)tetrahydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one 27

To a solution of lactone **21** (150 mg, 0.55 mmol) in dry THF at −78°C, under argon, was added $(TMS)_2NLi$ (1 M, 1.7 mL, 1.67 mmol), the temperature was allowed to raise to 0°C and the reaction cooled again at −78°C. PhSeSePh (520 mg, 1.67 mmol) and DMPU (210 μL, 1.67 mmol) were then added and the reaction temperature allowed to warm to rt for 5 h. The reaction was quenched by the addition of an aqueous ammonium chloride solution, extracted with CH_2Cl_2, and dried ($MgSO_4$). Elimination of the solvent and flash chromatography (*n*-hexane/EtOAc, 8:2) afforded seleno lactone **27** (80 mg, 42% corrected yield based on recovered lactone (10 mg)). $[\alpha]_D^{25}=-16.1$ ($c=0.46$, $CHCl_3$). ^{1}H NMR, δ (300 MHz, $CDCl_3$): 1.17 (s, 3H, CH_3), 2.11 (dd, $J=8.0$, 13.8 Hz, 1H), 2.25 (dd, $J=6.8$, 13.8 Hz, 1H), 2.79 (dd, $J_{2,1''}=1.5$ Hz, $J_{2,3}=6.0$ Hz, 1H), 3.37 (s, 3H, OMe), 3.33–3.49 (m, 2H), 3.43 (s, 3H, OMe), 3.69 (dd, $J=2.1$, 10.6 Hz, 1H), 3.86 (d, $J=1.5$ Hz, 1H), 3.89 (dd, $J_{3,4}=3.0$ Hz, $J_{4,5}=9.0$ Hz, 1H), 4.74 (dd, $J_{3,4}=3.0$ Hz, $J_{2,3}=6.0$ Hz, 1H), 4.99–5.11 (m, 2H), 5.30–5.64 (m, 1H), 7.30–7.80 (m, 5H). ^{13}C NMR, δ (50 MHz, $CDCl_3$): 22.8, 31.6, 38.5, 45.0, 54.7, 58.1, 59.4, 71.1, 77.2, 83.9, 84.3, 119.1, 126.4, 129.5, 132.6, 136.3, 175.5.

4.14. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-4-Allyl-7-methoxy-6-(methoxymethyl)-4-methyl-3-methylentetrahydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one 29

To a solution of lactone **21** (76 mg, 0.28 mmol) in dry THF (7 mL) at −78°C, under argon, was added $(TMS)_2NLi$ (1 M, 840 μL, 0.84 mmol) and the temperature was raised to −35°C. The reaction mixture was cooled again to −78°C and DMPU (traces) and Eschenmoser's salt (156 mg, 3 equiv., 0.84 mmol) were added. The temperature was allowed to raise to rt and after 5 h no more starting material was observed (TLC). The reaction was then quenched by the addition of H_2O, extracted with CH_2Cl_2, dried (Na_2SO_4) and the solvent evaporated. The resulting crude tertiary amine was dissolved in methanol (1 mL) and MeI (0.5 mL) was added. The resulting solution was kept in the dark at rt for 48 h, after which time a white solid precipitate appeared. Evaporation of the solvent under vacuum yielded a residue which was taken up in 1,3 dioxolane and treated with DBU (125 μL, 3 equiv., 0.84 mmol) at rt for 4 h. Evaporation of the solvent and flash chromatography led to **29** (27.5 mg, 52% corrected yield). $[\alpha]_D^{25}=-67.4$ ($c=0.69$, $CHCl_3$). ^1H NMR, δ (300 MHz, $CDCl_3$): 1.09 (s, 3H, CH_3), 2.22 (dd, $J=8.2$, 13.7 Hz, 1H), 2.42 (dd, $J=6.2$, 13.8 Hz, 1H), 3.34 (ddd, $J=1.7$, 1.8 Hz, $J_{2,3}=6.5$ Hz, 1H), 3.39 (s, 3H, OMe), 3.43 (dd, $J_{5,6}=3.8$ Hz, $J_{6,6}=10.6$ Hz, 1H), 3.50 (s, 3H), 3.55 (ddd, $J_{5,6}=2.1$, 3.8 Hz, $J_{4,5}=9.2$ Hz, 1H), 3.74 (dd, $J_{5,6}=2.1$ Hz, $J_{6,6}=10.6$ Hz, 1H), 4.06 (dd, $J_{3,4}=3.2$ Hz, $J_{4,5}=9.2$ Hz, 1H), 5.07 (dd, $J_{3,4}=3.2$ Hz, $J_{2,3}=6.5$ Hz, 1H), 5.17 (m, 2H), 5.57 (d, $J=1.8$ Hz, 1H), 5.75 (m, 1H), 6.37 (d, $J=1.8$ Hz, 1H). ^{13}C NMR, δ (75 MHz, $CDCl_3$): 23.2, 44.5, 51.6, 58.0, 59.4, 70.9, 77.0, 77.3, 83.1, 84.4, 119.1, 124.7, 132.8, 135.7, 169.9; anal. calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.90; H, 7.62%.

4.15. (3a*S*,4*R*,6*R*,7*S*,7a*R*)-7-Methoxy-6-(methoxymethyl)-4-methyl-3-methylen-4-[2*Z*/*E*-2,4-pentadienyl]tetrahydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one 18

$(TMS)_2NLi$ (1 M, 484 μL, 0.484 mmol) was added to a solution of diene **23** (50 mg, 0.162 mmol) in dry THF (7 mL), under argon, at −78°C and the temperature allowed to raise to −40°C for several minutes and then cooled again at −78°C. DMPU (traces) and Eschenmoser's salt (90 mg, 3 equiv., 0.484 mmol) were then added. The mixture was allowed to warm to rt and stirred for 5 h, after which time H_2O was added and the reaction mixture was extracted (CH_2Cl_2), dried (Na_2SO_4) and the solvent evaporated. The resulting tertiary amine was then dissolved in anhydrous methanol (1 mL) and treated with MeI (0.5 mL) and kept at rt for 48 h. After a white precipitate was observed, Et_2O (2 mL) was added and the solvent was evaporated under vacuum. The quaternary amine was then taken up in 1,3 dioxolane and treated with DBU (73 μL, 3 equiv., 0.486 mmol). After stirring the reaction mixture for 4 h and evaporation of the solvents, the residue was purified by flash chromatography (*n*-hexane/EtOAc, 85:15) to yield triene **18** (10 mg, 34% corrected yield) as a 1:1.7 (*Z*)/(*E*) mixture. ^1H NMR, δ (300 MHz, $CDCl_3$): 1.09 (s, 3H, CH_3 from *Z*), 1.25 (s, 3H, CH_3 from *E*), 1.50–1.80 (m, 2H), 2.05–2.30 (m, 2H), 3.27 (dt, $J_t=1.7$ Hz, $J_d=6.5$ Hz, 1H), 3.40 (s, 3H, OMe from *E*), 3.41 (s, 3H, OMe from *Z*), 3.42–3.49 (m, 1H), 3.51 (s, 3H, OMe from *Z* and *E*), 3.53–3.58 (m, 1H), 3.74 (dd, $J=1.95$, 10.6 Hz, 1H), 3.99 (dd, $J=3.2$, 9.2 Hz, 1H), 4.98 (d, $J=10.1$ Hz, 1H from *E*), 5.06–5.09 (m, 2H, from *E*), 5.12 (d, $J=11.2$ Hz, 1H from *Z*), 5.21 (d, $J=16.8$ Hz, 1H from *Z*), 5.39–5.47 (m, 1H from *Z*), 5.59 (d, $J=1.7$ Hz, 1H), 5.68 (dt, $J_t=7.1$ Hz, $J_d=14.3$ Hz, 1H from *E*), 5.98–6.11 (m, 1H), 6.30 (dt, $J_t=10.3$ Hz, $J_d=17.0$ Hz, 1H from *E*), 6.38 (d, $J=1.9$ Hz, 1H), 6.62 (dddd, $J=1.1$, 10.1, 11.2, 16.8 Hz, 1H from *Z*).

^{13}C NMR, δ (75 MHz, $CDCl_3$): 22.5, 22.7, 26.8, 29.7, 39.7, 42.4, 52.7, 53.0, 58.1, 59.4, 71.0, 71.6, 76.8, 77.2, 82.9, 83.1, 84.3, 84.7, 115.4, 124.5, 124.8, 125.1, 125.7, 131.2, 131.5, 133.9, 136.9, 135.5, 135.8, 170.7, 172.1; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.07; H, 7.62%.

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