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A chiral cyclohex-2-enone carrying a hexofuranosyl substituent which directs highly stereoselective 1,4-conjugate additions

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Abstract

The reaction of (*Z*)-3-deoxy-3-*C*-[(hydroxymethyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose, prepared from D-glucose, with 1,1-dimethoxycyclohexane in the presence of propanoic acid at 135°C, then at 200°C, provided two Claisen rearrangement products, namely (2*R*,3*R*,4*S*,5*S*)-2,3-(isopropylidene)dioxy-5-[(1*R*)-1,2-(isopropylidene)dioxyethyl]-4-[(1*S*)- and (1*R*)-2-oxocyclohexyl]-4-vinyltetrahydrofuran in a ratio of 3.3:1. L-Selectride® reduction of the major product gave the corresponding (*S*)-cyclohexanol exclusively. In contrast, the Claisen rearrangement of the aforementioned allylic alcohol with 3,3-dimethoxycyclohexene proceeded with complete stereoselectivity to provide the corresponding 4-[(1*S*)-2-oxocyclohex-3-enyl]-4-vinyltetrahydrofuran exclusively. The 1,4-conjugate additions to the thus formed cyclohexenone derivative with dimethyl and divinylcuprates proceeded with complete π-facial selection to provide the 3-methylated and 3-vinylated cyclohexanone derivatives, both in high yields.

1. Introduction

The use of carbohydrates as naturally occurring materials for organic synthesis has been expanding.[1] In expectation of the use of carbohydrate derivatives as enantiomerically pure building blocks, we have been concerned with the transformation of D-glucose into a variety of multifunctionalized oxa-, aza- and carbocyclic products. For example, we reported the orthoester (Johnson) Claisen rearrangement[2] of an allylic alcohol **2**,[3] which was prepared from D-glucose via 'diacetone gluc-3-ulose' **1** (Scheme 1). The rearrangement product (**3**), obtained as a single diastereomer in a high yield of 80%, has served as an enantiomerically pure starting material for total synthesis of a variety of natural products.[4,5] This

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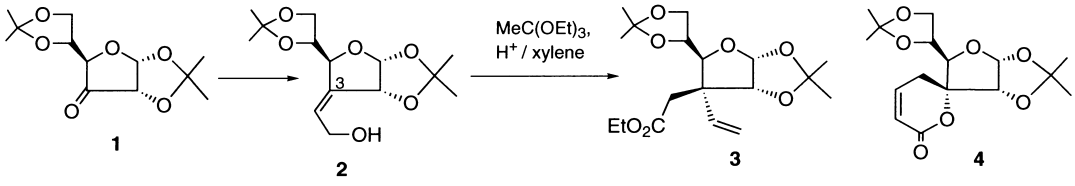
high stereoselectivity observed in the thermal [3,3]-sigmatropic rearrangement of **2** originates in its trioxabicyclo[3.3.0]octane core structure. Thus, the formation of a σ-bond at C-3 of the hexofuranosyl ring in **2** occurred exclusively from the less hindered β-side (the upper side) of the bicyclic ring. We have also investigated orthoester Claisen rearrangement reactions applied to other carbohydrate-derived substrates. Consequently, a number of the rearrangement products were obtained stereoselectively.[6] With regard to the 3-ulose **1**, some previous reports reinforce its usefulness for stereoselective reactions, which rely on the conformationally rigid structure of **1**. For instance, Kakinuma and co-workers have extensively studied the intermolecular epoxidation and dihydroxylation, while the intramolecular Overman and [2,3]-Wittig rearrangements have been realized on a number of C-3 modified templates derived from **1**.[7] One recent disclosure by this group revealed the utility of another chiral template (**4**), which was also prepared from **1**. The alkaline epoxidation of **4** proceeded stereoselectively to provide a single epoxide, which was efficiently converted into (*R*)-mevalonolactone and its deuteriated analog.[7a,c] Encouraged by these informative findings, we have independently explored to seek highly stereoselective reactions using chiral templates derived from **2**. We report herein the stereoselective 1,2-hydride addition to a chiral cyclohexanone **8** and the 1,4-conjugate addition of dimethyl or divinylcuprate to a chiral cyclohex-2-enone **12**. The substrates **8** and **12**, both carrying a 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl group as a sterically demanding substituent, were prepared from the Claisen rearrangement of **2** with 1,1-dimethoxycyclohexane and with 3,3-dimethoxycyclohexene. We expected that this hexofuranosyl substituent would serve as a stereodirecting element.



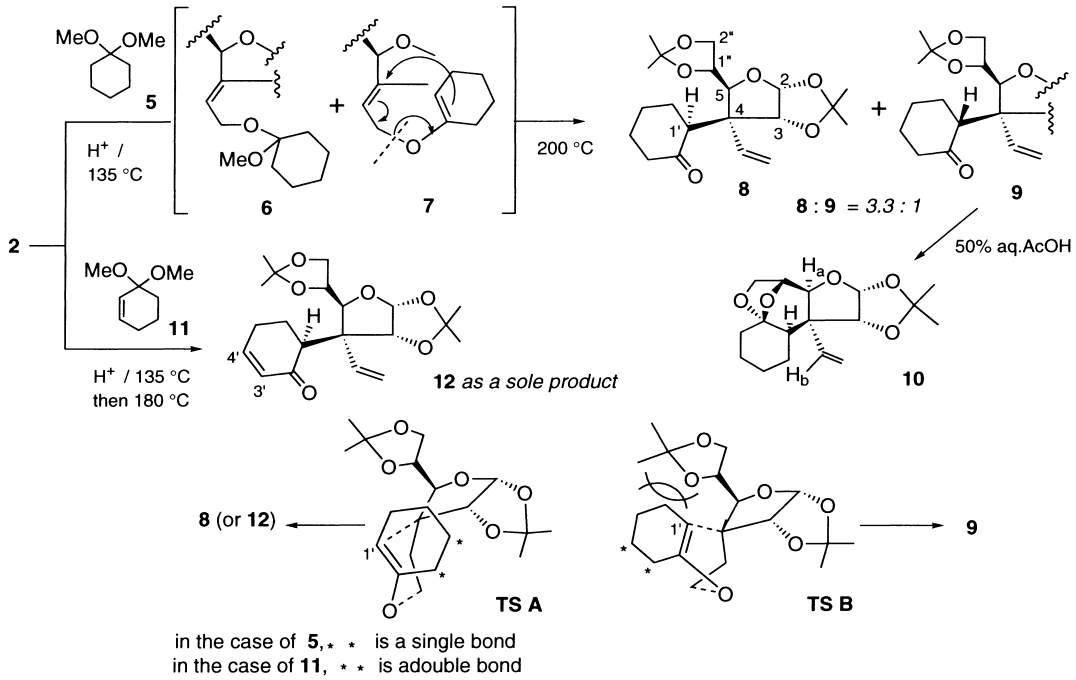
Scheme 1.

2. Results and discussion

*2.1. Claisen rearrangement of **2** with 1,1-dimethoxycyclohexane and 3,3-dimethoxycyclohexene*

We first explored the Claisen rearrangement of **2** with 1,1-dimethoxycyclohexane **5** (Scheme 2). Treatment of **2** with **5** (neat) in the presence of a catalytic amount of propanoic acid at 135°C for 6.5 h provided a mixture of the initially formed ketal **6**, the allyl vinyl ether **7**, and **2** (^{1}H NMR analysis). The mixture was purified roughly by passing through a short column of silica gel. The mixture of **6**, **7** and **2** was dissolved in toluene, and the resulting solution was heated at 200°C (in a sealed tube) for 30 h. As a result, two rearrangement products, **8** and **9**, were isolated in 20% and 6% yields, respectively, after chromatographic separation. Unreacted **2** was also recovered in 50% yield. To improve the yields of **8** and **9**, we screened the reaction temperature and the reaction time. However, both prolonged reaction time and higher reaction temperature resulted in a significant decrease in the yields of **8** and **9** (recovery of **2** was also reduced). We concluded that the conditions described earlier were optimal for obtaining **8** and **9**. The major product **8** was crystallized and a single crystal X-ray structure determination was obtained for **8**.[8] This verified the stereochemistry of the newly introduced two contiguous stereogenic centers (C-4 and C-1′) as depicted. Regarding the crystal structure of **8**, the 2-oxocyclohexyl group exists

approximately perpendicularly (intersectionally) to the carbohydrate moiety. In addition, the carbonyl group turns toward the lower side (the α-side) of the hexofuranosyl ring. The structure of the minor product **9** was determined as depicted on the basis of the following result. Mild acid hydrolysis of **9** gave ketal **10**, in which the carbonyl group in **9** was attacked intramolecularly by the liberated diol to form the ketal. In the NOE difference experiments for **10**, a 6.6% signal enhancement was observed for H_b when H_a was irradiated. Therefore, H_a and the vinyl group align in a *cis* relationship. These facts revealed that the configurations at the quaternary carbon in **8** and **9** are the same, and thus the configuration at C-1′ in **9** was opposite to that in **8**. As anticipated in the light of our previous findings,[3] the σ-bond formation in the Claisen rearrangement proceeded exclusively from the less hindered upper side (β-side) of the trioxabicyclo[3.3.0]octane skeleton in **7**. With regard to the stereochemical outcome for the α-carbon (C-1′) in the 2-oxocyclohexyl moiety, we rationalize the preferential formation of **8** by using transition state (**TS**) models as shown. In **TS A**, the rearrangement proceeds in a chair-like conformation with minimal non-bonded interaction between the cyclohexenyl moiety and both isopropylidene groups. **TS A** leads to **8** as the σ-bond formation occurs from the *re*-face of the vinyl carbon (C-1′). Alternatively, a boat-like transition state **TS B** leading to **9** seems to be less favorable, owing to severe interaction between the cyclohexenyl moiety and the side chain isopropylidene group. However, the formation of **9** in lower quantities implies that **TS A** is preferable but not exclusive.



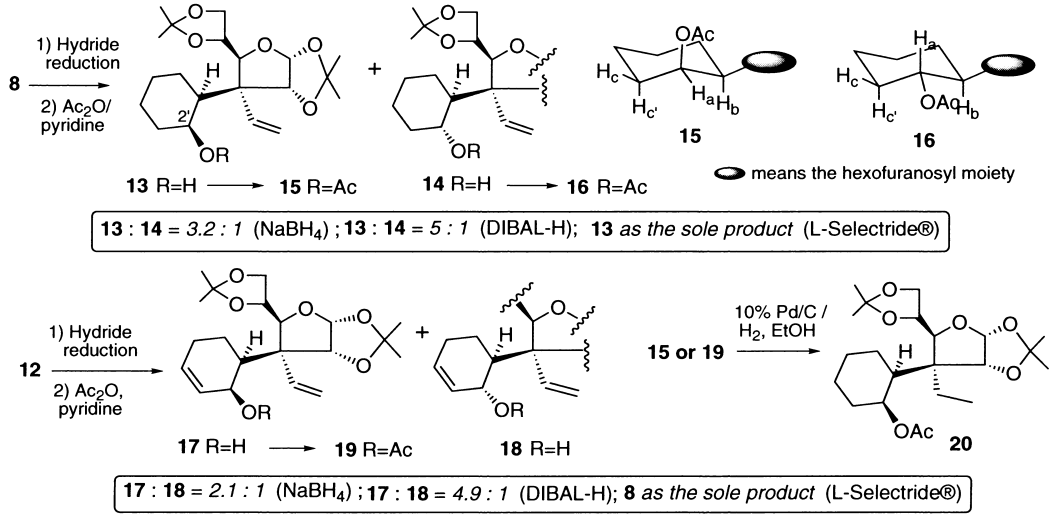
Scheme 2.

The Claisen rearrangement of **2** with 3,3-dimethoxycyclohexene **11** was carried out under analogous conditions to those employed for the case of **2** with **5**. In this case, the rearrangement of the intermediary allyl cyclohexadienyl ether (not shown) was completed at 180°C for 20 h. As a result, a single product **12** was isolated as crystals in 36% yield and 49% of unreacted **2** was recovered. As for the case of **2** with **5**, it was preferable to stop the reaction at about 50% consumption of **2** for optimal yield of **12** and also the optimal recovery of **2**. The structure of **12** was verified by a single crystal X-ray analysis.[8] The exclusive

stereoselectivity observed for the Claisen rearrangement of **2** with **11** was well explained using the same transition state argument developed for that of **2** with **5**. In the transition state for the rearrangement of the intermediary allyl cyclohexadienyl ether, partial conformational change of the carbocyclic moiety (i.e. the cyclohexenyl versus the cyclohexadienyl) may be principally responsible for the stereochemical outcome.

2.2. *Hydride reduction of **8** and **12***

To evaluate the ability of the hexofuranosyl moiety to work as a stereodirecting element, we investigated a hydride reduction of the carbonyl functionality in **8** and **12** (Scheme 3). Sodium borohydride ($NaBH_4$) reduction of **8** in MeOH provided **13** and **14** in yields of 67% and 21%, respectively. The configuration of the newly introduced stereogenic center (C-2′) in **13** and **14** was verified as depicted by ^1H NMR analysis of the corresponding acetates **15** and **16**, prepared from **13** and **14**. In the ^1H NMR of **15**, a signal attributable to H_a appeared at δ 5.32 as a broad singlet. In contrast, that of **16** appeared at δ 4.85 as a triplet of doublets with $J_{a,b}=J_{a,c'}=9.5$ Hz and $J_{a,c}=4.0$ Hz. Diisobutylaluminum hydride (DIBAL-H) reduction of **8** in CH_2Cl_2 at −78°C provided **13** and **14** in yields of 70% and 14%, respectively. Furthermore, lithium tri-*sec*-butylborohydride (L-Selectride®) reduction of **8** provided **13** as the sole product in 89% yield.

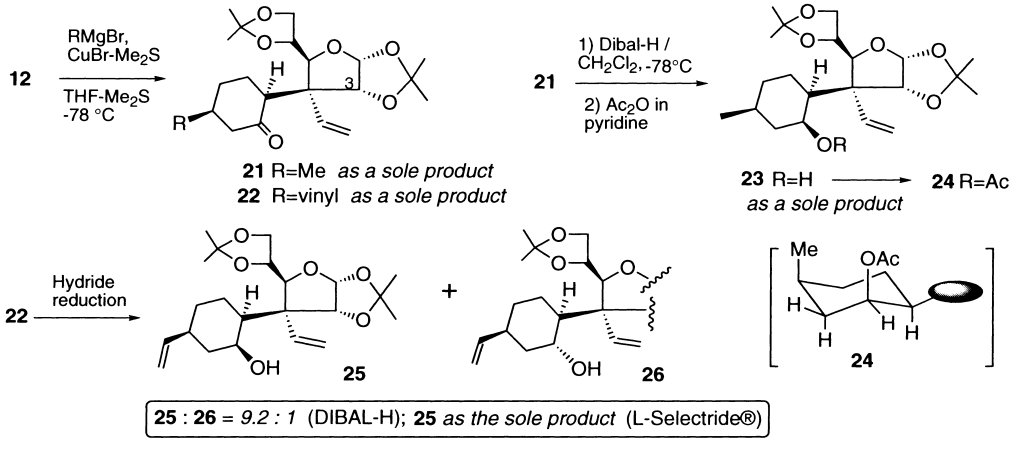


Scheme 3.

$NaBH_4$ reduction of **12** provided the 1,2-adducts **17** and **18** in 62% and 30% yields, respectively. DIBAL-H reduction of **12** provided **17** and **18** in 79% and 16% yields, respectively. Interestingly, L-Selectride® reduction of **12** proceeded in a 1,4-conjugate addition mode to provide the cyclohexanone **8** quantitatively. The stereochemistry of the newly introduced carbinol in the major product **17** was confirmed by the following chemical modifications. The reduction product **17** was acetylated to **19**, and the two vinyl groups in **19** were simultaneously hydrogenated to provide **20**. Independently, the vinyl group in the stereochemically defined acetate **15** was hydrogenated. As the product **20** obtained in the latter reaction was completely identical to the product of the former reaction, the major adduct **17** possesses (*S*)-carbinol carbon.

2.3. 1,4-Conjugate addition of two organocuprates to **12** and DIBAL-H reduction of the products

To evaluate further the role of the hexofuranosyl moiety in **12** for stereoselective organic reactions, we investigated the 1,4-conjugate addition of two organocuprates to the cyclohex-2-enone **12**. We chose dimethyl- and divinylcuprates, prepared by mixing the corresponding Grignard reagents and cuprous bromide in a mixed solution of THF and dimethyl sulfide (Scheme 4). Both conjugate additions of the two cuprate complexes to **12** proceeded smoothly at −78°C to provide the 1,4-adducts **21** and **22** in 95% and 90% yields, respectively. Other isomeric adducts (1,2- or 1,4-) were not detected. The structures of **21** and **22** were determined to be those as depicted on the basis of ^{1}H NMR analysis. With regard to the highly stereoselective 1,4-additions to **12**, it is likely that the organomagnesium species formed in the reaction mixtures may chelate with the oxygen atoms in **12**, although we have no experimental evidence for this assumption. If a chelate forms between the carbonyl in the cyclohexenone and the oxygen of the isopropylidene ketal at C-3, the methyl or vinyl nucleophile readily attacks to the proximal *si*-face of the β-carbon of the enone system leading to **21** or **22**. DIBAL-H reduction of **21** at −78°C provided **23** as a single product in 90% yield. The stereochemistry of the introduced carbinol carbon was determined on the basis of the ^{1}H NMR analysis of the acetate **24** prepared from **23** under rather harsh conditions (Ac_2O:pyridine, 50°C, 84 h). The methine proton bearing the acetoxyl group was assigned to be equatorially oriented (at δ 5.27 as a broad singlet in the ^{1}H NMR analysis). Compared to the reduction of **8**, the stereoselection of the hydride delivery to **21** was complete; thus, it was proposed that installation of a methyl group into the cyclohexyl ring realized a more biased steric environment around the 2-oxocyclohexyl moiety in **21**. DIBAL-H reduction of **22** afforded two carbinols, **25** and **26**, in 83% and 9% yield, respectively. In contrast, L-Selectride® reduction of **22** at 0°C provided **25** as the single product, albeit in a low yield of 42% (14% recovery of **22**).

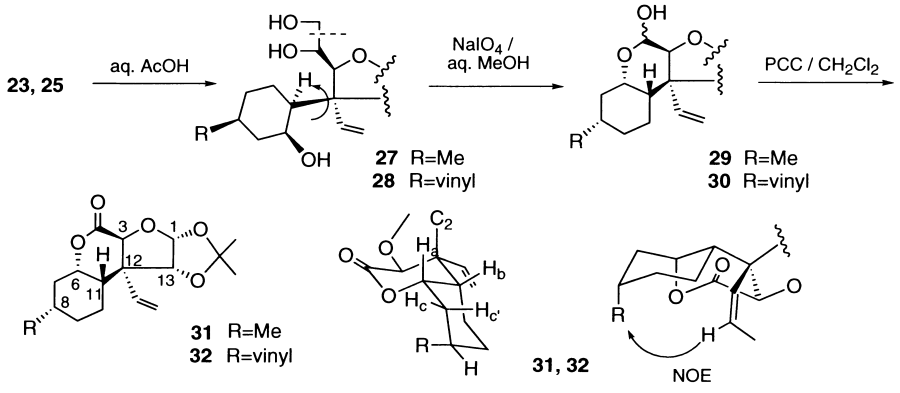


Scheme 4.

2.4. Stereochemical assignment of **23** and **25**

The structural assignments of **23** and **25** were confirmed by transforming them into **31** and **32** (Scheme 5). Mild acid hydrolysis of **23** and **25** provided diols **27** and **28**. By glycol cleavage mediated by $NaIO_4$, **27** and **28** were converted into diastereomeric mixtures of hemiacetals **29** and **30**. Pyridinium chlorochromate (PCC) oxidation of **29** and **30** provided δ-lactones **31** and **32**. The stereochemistry of **31**

and **32**, thence those of **23** and **25**, were confirmed on the basis of ^{1}H NMR analysis. The ring juncture of the cyclohexyl ring and δ-lactone in **31** was in a *cis* relationship, supported by the signal attributable to H_a at δ 4.83 with $J_{H_a,H_b}=J_{H_a,H_c}=J_{H_a,H_c'}=3.9$ Hz. This was also the case for **32**. Signal enhancement was observed for the methyl (5.7%) in **31** or the newly introduced vinyl group (1.0%) in **32**, when the pre-existing vinyl group was irradiated.



Scheme 5.

In conclusion, we have investigated the orthoester (Johnson) Claisen rearrangement of **2**, readily prepared from D-glucose, with 1,1-dimethoxycyclohexane or with 3,3-dimethoxycyclohexene, resulting in the formation of **8** or **12** stereoselectively or exclusively. The 1,2-hydride additions to **8** and **12** proceeded with useful levels of stereoselectivity. Importantly, the 1,4-additions to the enone **12** with two organocuprates proceeded with complete π-facial selection. Consequently, the hexofuranosyl moieties in **8** and **12** served well for directing the hydride delivery and the carbon nucleophiles attack. Further manipulation of **8** and **12** would provide enantiomerically pure multifunctionalized carbon frameworks equipped with a number of stereogenic centers, including an asymmetric quaternary carbon.

3. Experimental

Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^{1}H NMR spectra were recorded by a JEOL JNM-GSX 270 (at 270 MHz) or by a JEOL JNM-LA300 (at 300 MHz) FT NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 67.5 MHz or 75 MHz in $CDCl_3$ solution. High-resolution mass spectra (HRMS) were measured by a JEOL JMS-DX-302 spectrometer (EI, 70 eV). Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 GF_{254} (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel 60 K070 (Katayama Chemicals). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from the reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator with bath at 35–45°C.

3.1. (2R,3R,4S,5S)-2,3-(Isopropylidene)dioxy-5-[(1R)-1,2-(isopropylidene)dioxyethyl]-4-[(1S)- **8** and (1R)-2-oxocyclohexyl]-4-vinyltetrahydrofuran **9**

A solution of **2** (1.02 g, 3.56 mmol) in 1,1-dimethoxycyclohexane **5** (10 ml) was heated at 135°C for 6.5 h in the presence of propanoic acid (0.013 ml, 0.18 mmol). The solution was concentrated in vacuo with the aid of toluene. The residue was transferred to a short silica gel column and the column was eluted with EtOAc:hexane (1:10 then 1:1) providing a mixture consisting of **6**, **7** and unreacted **2** (1.03 g) as an oil, which was used for the next step. The mixture was dissolved in toluene (40 ml) and the resulting solution was divided into 5–10 sealed tubes with a screw stopper. Each sealed tube was heated at 200°C for 30 h. After cooling to ambient temperature, all reaction mixtures were combined and concentrated in vacuo with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:16, 1:12, 1:8, 1:2, and finally 3:4) providing 266 mg of **8** (20%), 78 mg of **9** (6%), and 505 mg of **2** (50%). **8**: colorless needles; mp 123.5–124.5°C; TLC, R_f 0.42 (EtOAc:hexane, 1:3); $[\alpha]_D^{22}$ −24.8 (*c* 0.86, $CHCl_3$); IR (neat) 2985, 2940, 1715, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.33, 1.37, 1.53 (3s, 3H, 6H, 3H, 4×C(CH_3)$_2$), 1.65–1.83, 1.90–1.98 (2m, 4 H, cyclohexyl ring protons), 2.07–2.23 (m, 1 H, cyclohexyl ring proton), 2.45–2.53 (m, 3 H, cyclohexyl ring protons), 3.17 (dd, J=13.4, 3.8 Hz, 1 H, H-1′), 3.95 (dd, J=8.4, 5.9 Hz, 1 H, H-2′′), 4.05 (d, J=8.4 Hz, 1 H, H-2′′), 4.13 (d, J=5.9 Hz, 1 H, H-5), 4.22 (dt, J=8.4, 5.9 Hz, 1 H, H-1′′), 4.88 (d, J=3.7 Hz, 1 H, H-3), 5.10 (d, J=17.7 Hz, 1 H, –CH=CH_2), 5.12 (d, J=11.9 Hz, 1 H, –CH=CH_2), 5.63 (d, J=3.7 Hz, 1 H, H-2), 6.24 (dd, J=17.7, 11.9 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (67.5 MHz) δ 25.7, 26.1, 26.2, 26.6, 26.8, 29.4, 31.8, 44.3, 52.9, 53.7, 68.7, 73.6, 84.0, 84.3, 105.1, 109.8, 111.3, 116.0, 137.1, 211.3. Anal. calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.66; H, 8.49. **9**: colorless oil; TLC, R_f 0.48 (EtOAc:hexane, 1:3); $[\alpha]_D^{21}$ +54.8 (*c* 1.23, $CHCl_3$); IR (neat) 2985, 2930, 1715, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.31, 1.35. 1.42, 1.48 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.55–1.84 (m, 4 H, cyclohexyl ring protons), 2.02–2.19 (m, 1 H, cyclohexyl ring proton), 2.30–2.48 (m, 3 H, cyclohexyl ring protons), 2.78 (dd, J=11.5, 3.9 Hz, 1 H, H-1′), 3.82–3.98 (m, 2 H, 2×H-2′′), 4.15–4.25 (m, 2 H, H-5, H-1′), 4.97 (d, J=3.7 Hz, 1 H, H-3), 5.28 (dd, J=11.4, 1.5 Hz, 1 H, –CH=CH_2), 5.43 (dd, J=18.0, 1.5 Hz, 1 H, CH=CH_2), 5.76 (d, J=3.7 Hz, 1 H, H-2), 6.15 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (67.5 MHz) δ 25.4, 25.7, 26.3, 26.5, 26.8, 29.7, 33.0, 44.3, 52.4, 56.2, 69.7, 73.7, 84.1, 84.3, 104.0, 109.7, 111.4, 117.7, 135.4, 212.6; HRMS calcd for $C_{20}H_{30}O_6$ (M^+) m/z 366.2042, found 366.2037.

3.2. Selective removal of the side chain acetal in **9**. Preparation of **10**

A solution of **9** (16.3 mg, 0.04 mmol) in 50% aqueous AcOH (1 ml) was stirred for 29 h and concentrated in vacuo with the aid of toluene and EtOH. The residue was purified by column chromatography on silica gel (toluene:EtOH, 1:18) providing 9.3 mg (68%) of **10** as a colorless oil: TLC, R_f 0.72 (EtOAc:toluene, 1:1); $[\alpha]_D^{22}$ +97.7 (*c* 0.43, $CHCl_3$); IR (neat) 3090, 2940, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.31, 1.54 (2s, 3 H×2, 2×C(CH_3)$_2$), 1.42–1.88 (m, 8 H, cyclohexyl ring protons), 2.00 (dd, J=12.8, 3.3 Hz, 1 H, H-1′), 3.71 (dd, J=7.3, 5.1 Hz, 1 H, H-2′′), 3.84 (d, J=7.3 Hz, 1 H, H-2′′), 4.06 (d, J=1.8 Hz, 1 H, H-5), 4.45 (d, J=3.7 Hz, 1 H, H-3), 4.68 (dd, J=5.1, 1.8 Hz, 1 H, H-1′′), 5.29 (d, J=11.0 Hz, 1 H, –CH=CH_2), 5.30 (d, J=17.6 Hz, 1 H, –CH=CH_2), 5.80 (d, J=3.7 Hz, 1 H, H-2), 6.02 (dd, J=17.6, 11.0 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (67.5 Hz) δ 23.5, 25.8, 26.1, 26.9, 27.4, 35.8, 45.3, 50.3, 64.4, 74.7, 78.6, 85.7, 105.0, 107.2, 110.9, 115.5, 139.1; HRMS calcd for $C_{17}H_{25}O_5$ [$(M+H)^+$] m/z 309.1702, found 309.1713.

3.3. Claisen rearrangement of **2** with 3,3-dimethoxycyclohexene **11**. (2R,3R,4S,5S)-2,3-(Isopropylidene)dioxy-5-[(1R)-1,2-(isopropylidene)dioxyethyl]-4-[(1S)-2-oxocyclohex-3-enyl]-4-vinyltetrahydrofuran **12**

A solution of **2** (1.05 g, 3.67 mmol) in 3,3-dimethoxycyclohexene **11** (7 ml) was heated at 135°C for 3 h in the presence of propanoic acid (0.014 ml, 0.18 mmol). The solution was concentrated in vacuo with the aid of toluene. The mixture was dissolved in toluene (40 ml) and the resulting solution was divided into 5–10 sealed tubes. Each sealed tube with a screw stopper was heated at 180°C for 20 h. After cooling to room temperature, all reaction solutions were combined and concentrated in vacuo with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:8) providing 482 mg (36%) of **12** and 515 mg of **2** (49%). **12**: colorless needles; mp 140.5–141.5°C; TLC, R_f 0.61 (EtOAc:hexane, 1:1); $[\alpha]_D^{22}$ +31.9 (*c* 1.10, $CHCl_3$); IR (neat) 2985, 2935, 1735, 1690 cm^{-1}; ^1H NMR (270 MHz) δ 1.32, 1.35, 1.38, 1.54 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.60–1.84 (m, 1 H, cyclohexenyl ring proton), 2.40–2.51 (m, 3 H, cyclohexenyl ring protons), 3.16 (dd, J=14.1, 2.8 Hz, 1 H, H-1′), 3.95 (dd, J=8.4, 6.0 Hz, 1 H, H-2″), 4.12 (d, J=8.4 Hz, 1 H, H-2″), 4.15 (d, J=6.0 Hz, 1 H, H-5), 4.29 (td, J=8.4, 6.0 Hz, 1 H, H-1″), 4.61 (d, J=3.7 Hz, 1 H, H-3), 5.16 (dd, J=11.4, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.21 (dd, J=18.0, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.69 (d, J=3.7 Hz, 1 H, H-2), 5.95–6.03 (m, 1 H, H-3′), 6.28 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2), 6.78–6.87 (m, 1 H, H-4′);^{13}C NMR (67.5 MHz) δ 25.7, 26.3, 26.5, 26.8, 27.3, 50.2, 54.0, 68.8, 73.7, 84.4, 84.9, 105.0, 109.8, 111.5, 115.8, 130.9, 137.3, 147.0, 199.4. Anal. calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.64; H, 8.02.

3.4. Hydride reduction of **8**. (2R,3R,4S,5S)-2,3-(Isopropylidene)dioxy-5-[(1R)-1,2-(isopropylidene)-dioxy-ethyl]-4-[(1S,2S)- **13** and (1S,2R)-2-hydroxycyclohexyl]-4-vinyltetrahydrofuran **14**

3.4.1. DIBAL-H reduction

The following reaction was carried out under Ar. To a cooled (−78°C) solution of **8** (14.6 mg, 0.04 mmol) in CH_2Cl_2 (1 ml) was added DIBAL-H (1.0 M solution in toluene, 0.10 ml, 0.1 mmol). After stirring at −78°C, the solution quenched with H_2O and the resulting gels were removed by filtration and washed with EtOAc. The combined filtrate and washing were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:13) providing 10.3 mg of **13** (70%) and 2.1 mg (14%) of **14**. **13**: colorless oil; TLC, R_f 0.78 (EtOAc:hexane, 1:1); $[\alpha]_D^{21}$ +49.2 (*c* 1.04, $CHCl_3$); IR (neat) 3500, 2985, 2935, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.31, 1.37, 1.43, 1.48 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.13–1.84 (m, 9 H, cyclohexyl ring protons), 3.85–3.97 (m, 1 H, H-2′), 4.15–4.22 (m, 3 H, H-1″, H-2″, H-2″), 4.30–4.37 (m, 1 H, H-5), 5.19 (d, J=3.7 Hz, 1 H, H-3), 5.25 (dd, J=11.4, 1.8 Hz, 1 H, –CH=C*H*$_2$), 5.34 (dd, J=18.0, 1.8 Hz, 1 H, –CH=C*H*$_2$), 5.65 (d, J=3.7 Hz, 1 H, H-2), 6.10 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (67.5 MHz) δ 20.0, 22.7, 25.5, 26.4, 26.5, 27.0, 35.0, 44.1, 57.4, 67.9, 69.3, 73.5, 84.7, 84.8, 104.7, 109.6, 110.9, 116.5, 137.6; HRMS calcd for $C_{20}H_{32}O_6$ (M^+) m/z 368.2199, found 368.2207. **14**: colorless oil; TLC, R_f 0.66 (EtOAc:hexane, 1:1); $[\alpha]_D^{20}$ +55.9 (*c* 0.33, $CHCl_3$); IR (neat) 3480, 2985, 2935, 1645 cm^{-1}; ^1H NMR (270 MHz) δ 1.32, 1.39, 1.43, 1.51 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.06–1.78 (m, 7 H, cyclohexyl ring protons), 1.82–2.02 (m, 2 H, cyclohexyl ring protons), 3.14 (br s, 1 H, OH), 3.38–3.52 (m, 1 H, H-2′), 3.90 (dd, J=8.4, 7.3 Hz, 1 H, H-2″), 4.21 (dd, J=8.4, 5.9 Hz, 1 H, H-2″), 4.31 (ddd, J=9.5, 7.3, 5.9 Hz, 1 H, H-1″), 4.42 (d, J=9.5 Hz, 1 H, H-5), 4.76 (d, J=3.7 Hz, 1 H, H-3), 5.35 (dd, J=11.4, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.53 (dd, J=18.0, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.68 (d, J=3.7 Hz, 1 H, H-2), 6.07 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2); HRMS calcd for $C_{20}H_{32}O_6$ (M^+) m/z 368.2199, found 368.2197.

3.4.2. L-Selectride® reduction

The following reaction was carried out under Ar. Compound **8** (17.3 mg) in THF (1 ml) was treated with L-Selectride® (1.01 M solution in THF, 0.19 ml) at room temperature for 30 min, and the solution was quenched with saturated aqueous NH_4Cl. Et_2O extraction and purification by silica gel chromatography provided 15.5 mg (89%) of **13**.

*3.5. Acetylation of **13** and **14***

Compound **13** (10.0 mg, 0.03 mmol) was acetylated with 0.5 ml of Ac_2O in pyridine (0.5 ml) for 60 h. Concentration of the reaction mixture and purification of the residue by column chromatography on silica gel (EtOAc:hexane, 1:12) provided 9.8 mg (88%) of **15**. Analogously, 2.9 mg of **14** was acetylated to provide 3.2 mg (quant.) of **16**. **15**: colorless oil; TLC, R_f 0.56 (EtOAc:hexane, 1:3); IR (neat) 2980, 2935, 1740, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.30, 1.38, 1.42, 1.47 (4s, 3 H×4, 4×C$(CH_3)_2$), 1.15–1.67 (m, 5 H, cyclohexyl ring protons), 1.73–1.90 (m, 3 H, cyclohexyl ring protons), 2.01–2.11 (m, 1 H, cyclohexyl ring proton), 2.08 (s, 3 H, OC(O)CH_3), 3.87–3.95 (m, 1 H, H-2″), 4.08–4.23 (m, 3 H, H-2″, H-1″, H-5), 5.01 (d, J=3.7 Hz, 1 H, H-3), 5.23 (dd, J=11.4, 1.6 Hz, 1 H, –CH=CH_2), 5.32 (br s, 1 H, H-2′), 5.36 (dd, J=18.0, 1.6 Hz, 1 H, –CH=CH_2), 5.67 (d, J=3.7 Hz, 1 H, H-2), 5.88 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2). **16**: colorless oil; TLC, R_f 0.53 (EtOAc:hexane, 1:3); IR (neat) 2980, 2935, 1730, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.31, 1.38, 1.43, 1.48 (4s, 3 H×4, 4×C$(CH_3)_2$), 1.21–1.40, 1.55–1.65, 1.66–1.80 (3m, total 8H, cyclohexyl ring protons), 1.95–2.08 (m, 1 H, cyclohexyl ring proton), 2.01 (s, 3 H, OC(O)CH_3), 3.94 (dd, J=8.4, 6.8 Hz, 1 H, H-2″), 4.15 (dd, J=8.4, 5.9 Hz, 1 H, H-2″), 4.15 (d, J=8.4 Hz, 1 H, H-5), 4.30–4.40 (m, 1 H, H-1″), 4.70 (d, J=3.7 Hz, 1 H, H-3), 4.85 (td, J=9.5, 4.0 Hz, 1 H, H-2′), 5.12 (dd, J=11.7, 1.5 Hz, 1 H, –CH=CH_2), 5.36 (dd, J=18.0, 1.5 Hz, 1 H, –CH=CH_2), 5.63 (d, J=3.7 Hz, 1 H, H-2), 5.88 (dd, J=18.0, 11.7 Hz, 1 H, –C*H*=CH_2).

*3.6. DIBAL-H reduction of **12**. (2*R,*3*R,*4*S,*5*S)-2,3-(Isopropylidene)dioxy-5-[(1*R)-*1,2-(isopropylidene)-dioxyethyl]-4-[(1*S,*2*S) **17** and (1*S,*2*R)-*2-hydroxycyclohex-3-enyl]-4-vinyltetrahydrofuran **18***

The following reaction was carried out under Ar. To a cooled (−78°C) solution of **12** (29.3 mg, 0.08 mmol) in CH_2Cl_2 (1 ml) was added DIBAL-H (1.0 M solution in toluene, 0.24 ml, 0.24 mmol). After stirring at −78°C for 30 min, an additional 0.24 ml of DIBAL-H was added. The mixture was stirred at −78°C for an additional 30 min and quenched with water (0.2 ml). The resulting gels were removed by filtration through a Celite pad, washed with EtOAc and the combined filtrate and washing were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:8) providing 23.2 mg (79%) of **17** and 4.7 mg (16%) of **18**. **17**: colorless oil; TLC, R_f 0.41 (EtOAc:hexane, 1:3); $[\alpha]_D^{22}$ +101.4 (*c* 1.18, $CHCl_3$); IR (neat) 3490, 2985, 2935, 1690, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.32, 1.35, 1.42, 1.49 (4s, 3 H×4, 4×C$(CH_3)_2$), 1.54–2.24 (m, 5 H, cyclohexenyl ring protons), 3.88–3.96 (m, 1 H, H-2″), 4.12–4.25 (m, 3 H, H-2″, H-1″, H-5), 4.36–4.42 (m, 1 H, H-2′), 5.26 (d, J=3.7 Hz, 1 H, H-3), 5.27 (dd, J=11.7, 1.5 Hz, 1 H, –CH=CH_2), 5.49 (dd, J=18.0, 1.5 Hz, 1 H, –CH=CH_2), 5.67 (d, J=3.7 Hz, 1 H, H-2), 5.79–5.94 (m, 2 H, H-3′, H-4′), 6.20 (dd, J=18.0, 11.7 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 19.3, 25.5, 26.4, 26.5, 26.6, 27.1, 41.8, 57.0, 65.5, 69.4, 73.7, 84.7, 85.0, 104.9, 109.7, 111.0, 116.8, 129.0, 130.9, 137.4; HRMS calcd for $C_{20}H_{30}O_6$ (M^+) m/z 366.2042, found 366.2042. **18**: colorless oil; TLC, R_f 0.55 (EtOAc:hexane, 1:2); $[\alpha]_D^{22}$ +47.0 (*c* 0.64, $CHCl_3$); IR (neat) 3490, 2985, 2935, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.33, 1.37, 1.43, 1.50 (4s, 3 H×4, 4×C$(CH_3)_2$), 1.60–1.80, 1.97–2.10 (2m, total 6H, cyclohexenyl ring protons), 3.85–3.94 (m, 1 H,

H-2′′), 4.15–4.31 (m, 3 H, H-2′′, H-1′′, H-5), 4.41–4.48 (m, 1 H, H-2′), 4.75 (d, J=3.7 Hz, 1 H, H-3), 5.33 (dd, J=11.7, 1.5 Hz, 1 H, –CH=C*H*$_2$), 5.54 (dd, J=18.0, 1.5 Hz, 1 H, –CH=C*H*$_2$), 5.57–5.63 (m, 1 H, H-4′), 5.76 (d, J=3.7 Hz, 1 H, H-2), 5.82–5.90 (m, 1 H, H-3′), 6.13 (dd, J=18.0, 11.7 Hz, 1 H, –C*H*=CH$_2$); ^{13}C NMR (75 MHz) δ 24.1, 25.2, 25.5, 26.4, 26.9, 45.4, 57.2, 68.2, 69.6, 73.1, 84.6, 85.4, 104.5, 109.9, 111.6, 117.5, 129.2, 130.4, 138.0; HRMS calcd for $C_{20}H_{30}O_6$ (M^+) m/z 366.2042, found 366.2042.

3.7. *Acetylation of* ***17***

Compound **17** (23.3 mg, 0.06 mmol) was acetylated with 0.5 ml of Ac_2O in pyridine (0.5 ml) for 8 h. Concentration of the reaction mixture and purification of the residue by column chromatography on silica gel (EtOAc:hexane, 1:11) provided 24.8 mg (95%) of **19**. **19**: colorless oil; TLC, R_f 0.43 (EtOAc:hexane, 1:5); $[\alpha]_D^{21}$ +185.1 (*c* 0.95, $CHCl_3$); IR (neat) 2990, 2935, 1740, 1640 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.30, 1.36, 1.42, 1.48 (4s, 3 H×4, 4×C(CH$_3$)$_2$), 1.55–1.75, 1.85–1.95, 2.01–2.25 (3m, total 5 H, cyclohexenyl ring protons), 2.06 (s, 3 H, OC(O)CH$_3$), 3.92 (dd, J=8.1, 6.0 Hz, 1 H, H-2′′), 4.07–4.22 (m, 3 H, H-2′′, H-1′′, H-5), 5.16 (d, J=3.7 Hz, 1 H, H-3), 5.24 (dd, J=11.7, 1.5 Hz, 1 H, –CH=C*H*$_2$), 5.31–5.34 (m, 1 H, H-2′), 5.42 (dd, J=18.0, 1.5 Hz, 1 H, –CH=C*H*$_2$), 5.70 (d, J=3.7 Hz, 1 H, H-2), 5.92–5.97 (m, 2 H, H-3′, H-4′), 5.93 (dd, J=18.0, 11.7 Hz, 1 H, –C*H*=CH$_2$); ^{13}C NMR (75 MHz) δ 20.3, 21.4, 25.6, 26.3, 26.4, 26.6, 27.1, 40.1, 56.7, 69.4, 69.5, 73.7, 84.4, 85.5, 105.2, 110.0, 111.2, 117.8, 125.4, 132.4, 136.3, 170.0. Anal. calcd for $C_{22}H_{32}O_7$: C, 64.69; H, 7.90. Found: C, 64.80; H, 7.96.

3.8. *(2*R*,3*R*,4*S*,5*S*)-4-Ethyl-2,3-(isopropylidene)dioxy-5-[(1*R*)-1,2-(isopropylidene)dioxyethyl]-4-[(1*S*,2*S*)-2-(acetoxy)cyclohexyl]tetrahydrofuran* ***20***

3.8.1. *From* ***19***

A solution of **19** (23.2 mg, 0.057 mmol) in EtOH (1 ml) was stirred under atmospheric hydrogen in the presence of 10% palladium on charcoal (11 mg) for 30 min. The catalyst was removed by filtration through a Celite pad, washed with EtOH and the combined filtrate and washing were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:30) providing 21.3 mg (91%) of **20** as a colorless oil: TLC, R_f 0.52 (EtOAc:hexane, 1:5); $[\alpha]_D^{19}$ +36.6 (*c* 0.53, $CHCl_3$); IR (neat) 2990, 2935, 1730 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.95 (t, J=7.3 Hz, 3 H, CH$_2$C*H*$_3$), 1.28, 1.36, 1.39, 1.50 (4s, 3 H×4, 4×C(CH$_3$)$_2$), 1.45–1.89 (m, 10 H, cyclohexyl ring protons, C*H*$_2$CH$_3$), 1.96–2.05 (m, 1 H, H-1′), 2.04 (s, 3 H, OC(O)CH$_3$), 3.76 (d, J=9.2 Hz, 1 H, H-5), 3.86 (dd, J=8.4, 6.2 Hz, 1 H, H-2′′), 4.10 (dd, J=8.4, 6.2 Hz, 1 H, H-2′′), 4.37 (ddd, J=9.2, 6.2, 6.2 Hz, 1 H, H-1′), 4.59 (d, J=3.7 Hz, 1 H, H-3), 5.12–5.15 (br s, 1 H, H-2′), 5.65 (d, J=3.7 Hz, 1 H, H-2); ^{13}C NMR (75 MHz) δ 9.8, 20.6, 21.5, 23.3, 24.0, 25.6, 26.0, 26.6, 26.7, 26.8, 31.6, 42.8, 53.4, 69.4, 70.6, 73.4, 85.9, 104.4, 109.3, 110.5, 170.2. Anal. calcd for $C_{22}H_{36}O_7$: C, 64.05; H, 8.80. Found: C, 64.33; H, 8.95.

3.8.2. *From* ***15***

Compound **15** (9.5 mg) in EtOH (1 ml) was hydrogenated under atmospheric hydrogen in the presence of 10% palladium on charcoal (10 mg) for 30 min. Purification of the reaction product provided 9.5 mg (quant.) of **20**, which was identical to that obtained above (^{1}H NMR and IR).

3.9. 1,4-Addition of dimethyl and divinylcuprates to the cyclohexenone ***12****. (2*R*,3*R*,4*S*,5*S*)-2,3-(Isopropylidene)dioxy-5-[(1*R*)-1,2-(isopropylidene)dioxyethyl]-4-[(1*S*,4*S*)-4-methyl-* ***21*** *and [(1*S*, 4*S*)-4-vinyl-2-oxocyclohexyl]-4-vinyltetrahydrofuran* ***22***

The following reactions were carried out under Ar. Cuprous bromide–dimethyl sulfide complex (350 mg, 1.70 mmol) was dissolved in THF and dimethyl sulfide (v/v 2:1, 7 ml). To the solution was added methylmagnesium bromide (0.92 M solution in THF, 3.69 ml, 3.39 mmol) at −78°C. After stirring at −78°C for 15 min, a solution of **12** (103 mg, 0.28 mmol) in THF (5 ml) was added dropwise over a period of 30 min. The mixture was stirred at −78°C for 30 min, quenched with saturated aqueous NH_4Cl solution (0.3 ml), and diluted with EtOAc (120 ml). The whole mixture was washed with saturated NH_4Cl (60 ml) and saturated brine (2×60 ml). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:12) providing 102 mg (95%) of **21** as a colorless oil: TLC, R_f 0.49 (EtOAc:hexane, 1:3); $[\alpha]_D^{21}$ +2.9 (*c* 0.99, $CHCl_3$); IR (neat) 2980, 2960, 1715, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 0.97 (d, J=7.3 Hz, 3 H, CH_3 at C-4′), 1.34, 1.37, 1.53 (3s, 3 H, 6 H, 3 H, 4×C(CH_3)$_2$), 1.45–1.70 (m, 2 H, cyclohexyl ring protons), 1.92–2.07 (m, 1 H, cyclohexyl ring proton), 2.15 (dt, J=12.1, 2.2 Hz, 1 H, cyclohexyl ring proton), 2.19–2.30 (m, 1 H, cyclohexyl ring proton), 2.47–2.61 (m, 1 H, cyclohexyl ring proton), 2.69 (dd, J=12.1, 5.9 Hz, 1 H, cyclohexyl ring proton), 3.13 (dd, J=13.2, 4.4 Hz, 1 H, cyclohexyl ring proton), 3.95 (dd, J=8.4, 5.9 Hz, 1 H, H-2′′), 4.05 (d, J=8.4 Hz, 1 H, H-5), 4.14 (dd, J=8.4, 5.9 Hz, 1 H, H-2′′), 4.22 (dt, J=5.9, 8.4 Hz, 1 H, H-1′′), 4.87 (d, J=3.7 Hz, 1 H, H-3), 5.12 (dd, J=11.4, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.12 (dd, J=18.3, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.66 (d, J=3.7 Hz, 1 H, H-2), 6.23 (dd, J=18.3, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 18.6, 25.7, 26.3, 26.6, 26.8, 31.6, 32.9, 50.3, 52.8, 53.7, 68.7, 73.6, 83.9, 84.3, 105.0, 109.8, 111.3, 116.0, 137.0, 210.4; HRMS calcd for $C_{21}H_{32}O_6$ (M^+) m/z 380.2199, found 380.2207.

Analogously, 49.1 mg (0.14 mmol) of **12** was subjected to the 1,4-addition with divinylcuprate, prepared from cuprous bromide–dimethyl sulfide complex (141.5 mg, 0 69 mmol) and vinylmagnesium bromide (0.99 M in THF, 1.36 ml, 1.35 mmol), in a mixture of THF and Me_2S (v/v 2:1, 3 ml) at −78°C for 30 min. Purification of the reaction product by column chromatography on silica gel (EtOAc:hexane, 1:14) provided 47.7 mg (90%) of **22** as a colorless oil: TLC, R_f 0.53 (EtOAc:hexane, 1:3); $[\alpha]_D^{22}$ −10.7 (*c* 0.53, $CHCl_3$); IR (neat) 2980, 2960, 1715, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.33 1.37, 1.52 (3s, 3H, 6 H, 3 H, 4×C(CH_3)$_2$), 1.47–1.71 (m, 1 H, cyclohexyl ring proton), 1.80–1.91 (m, 1 H, cyclohexyl ring proton), 1.96–2.12 (m, 1 H, cyclohexyl ring proton), 2.16–2.37 (m, 1 H, cyclohexyl ring proton), 2.49 (dt, J=12.5, 2.2 Hz, 1 H, cyclohexyl ring proton), 2.62 (dd, J=12.5, 5.9 Hz, 1 H, cyclohexyl ring proton), 3.00–3.06 (m, 1 H, cyclohexyl ring proton), 3.11 (dd, J=13.2, 4.0 Hz, 1 H, cyclohexyl ring proton), 3.94 (dd, J=8.4, 5.9 Hz, 1 H, H-2′′), 4.05 (d, J=8.4 Hz, 1 H, H-5), 4.14 (dd, J=8.4, 5.9 Hz, 1 H, H-2′′), 4.23 (dt, J=5.9, 8.4 Hz, 1 H, H-1′′), 4.76 (d, J=3.7 Hz, 1 H, H-3), 5.12 (dd, J=11.4, 1.1 Hz, 1 H, –CH=*CH*$_2$), 5.13 (dd, J=18.3, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.15 (dd, J=16.0, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.16 (dd, J=5.9, 1.1 Hz, 1 H, –CH=C*H*$_2$), 5.62 (d, J=3.7 Hz, 1 H, H-2), 5.78 (ddd, J=16.0, 10.7, 5.9 Hz, 1 H, –C*H*=CH_2), 6.24 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 25.7, 26.3, 26.6, 26.8, 30.4, 40.7, 47.1, 53.1, 53.8, 68.8, 73.6, 84.0, 84.4, 105.0, 109.8, 111.4, 116.0, 116.1, 137.1, 139.4, 209.3; HRMS calcd for $C_{22}H_{32}O_6$ (M^+) m/z 392.2199, found 392.2216.

3.10. DIBAL-H reduction of ***21****. (2*R*,3*R*,4*S*,5*S*)-2,3-(Isopropylidene)dioxy-5-[(1*R*)-1,2-(isopropylidene)dioxyethyl]-4-[(1*S*,2*S*,4*S*)-4-methyl-2-hydroxycyclohexyl]-4-vinyltetrahydrofuran* ***23***

The following reaction was carried out under Ar. To a cooled (−78°C) solution of **21** (41.7 mg, 0.11 mmol) in CH_2Cl_2 (1 ml) was added DIBAL-H (1.0 M solution in toluene, 0.33 ml, 0.33 mmol). After stirring at −78°C for 30 min, the reaction was quenched with water (0.2 ml). The resulting gels

were removed by filtration through a Celite pad and washed with EtOAc. The combined filtrate and washing were concentrated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:18) providing 37.7 mg (90%) of **23** as a colorless oil: TLC, R_f 0.47 (EtOAc:hexane, 1:4); $[\alpha]_D^{24}$ +52.1 (*c* 1.09, $CHCl_3$); IR (neat) 3500, 2990, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.19 (d, J=7.3 Hz, 3 H, CH_3 at C-4′), 1.32, 1.37, 1.43, 1.48 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.25–1.85 (m, 8 H, cyclohexyl ring protons), 1.86–2.01 (m, 1 H, OH), 3.87–3.96 (m, 1 H, H-2′′), 4.10–4.23 (m, 3 H, H-2′′, H-1′′, H-5), 4.27–4.34 (br s, 1 H, H-2′), 5.20 (d, J=3.7 Hz, 1 H, H-3), 5.23 (dd, J=11.7, 1.5 Hz, 1 H, –CH=CH_2), 5.42 (dd, J=18.0, 1.5 Hz, 1 H, –CH=CH_2), 5.68 (d, J=3.7 Hz, 1 H, H-2), 6.10 (dd, J=18.0, 11.7 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 17.3, 20.9, 25.5, 26.1, 26.4, 26.5, 27.0, 32.2, 40.1, 44.1, 57.4, 69.1, 69.3, 73.6, 84.8, 84.9, 104.8, 109.6, 110.9, 116.3, 137.6; HRMS calcd for $C_{21}H_{34}O_6$ (M^+) m/z 382.2355, found 382.2334.

*3.11. Acetylation of **23***

Compound **23** (37.2 mg, 0.10 mmol) was acetylated with Ac_2O (0.5 ml) in pyridine (0.5 ml) at 50°C for 84 h. Concentration of the reaction mixture and purification of the residue by column chromatography on silica gel (EtOAc:hexane, 1:17) provided 39.1 mg (95%) of **24** as a colorless oil: TLC, R_f 0.49 (EtOAc:hexane, 1:4); $[\alpha]_D^{23}$ +58.4 (*c* 0.30, $CHCl_3$); IR (neat) 2985, 2940, 1740, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.06 (d, J=7.3 Hz, 3 H, CH_3 at C-4′), 1.32, 1.38, 1.42, 1.47 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.35–2.04 (m, 8 H, cyclohexyl ring protons), 2.06 (s, 3 H, OC(O)CH_3), 3.87–3.95 (m, 1 H, H-2′′), 4.08–4.24 (m, 3 H, H-2′′, H-1′′, H-5), 5.04 (d, J=3.7 Hz, 1 H, H-3), 5.22 (d, J=11.4, 1.5 Hz, 1 H, –CH=CH_2), 5.27 (br s, 1 H, H-2′), 5.35 (dd, J=18.0, 1.5 Hz, 1 H, –CH=CH_2), 5.70 (d, J=3.7 Hz, 1 H, H-2), 5.85 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 18.2, 20.0, 21.5, 25.5, 25.7, 26.3, 26.4, 27.0, 31.5, 35.4, 42.6, 57.1, 69.3, 72.8, 73.5, 84.3, 85.1, 105.0, 109.7, 110.9, 117.2, 136.3, 169.8. Anal. calcd for $C_{23}H_{36}O_7$: C, 65.07; H, 8.55. Found: C, 65.34; H, 8.79.

*3.12. DIBAL-H reduction of **22**. (2R,3R,4S,5S)-2,3-(Isopropylidene)dioxy-5-[(1R)-1,2-(isopropylidene)dioxyethyl]-4-[(1S,2S,4S)- **25** and (1S,2R,4S)-2-hydroxy-4-vinylcyclohexyl]-4-vinyltetrahydrofuran **26***

As described for **21**, 47.7 mg (0.12 mmol) of **22** in CH_2Cl_2 (1 ml) was treated with DIBAL-H (0.37 mmol) at −78°C for 60 min. After workup and purification by column chromatography on silica gel (EtOAc:hexane, 1:20), 40.0 mg (83%) of **25** and 4.5 mg (9%) of **26** were obtained. **25**: colorless oil; TLC, R_f 0.40 (EtOAc:hexane, 1:4); $[\alpha]_D^{22}$ +47.6 (*c* 0.86, $CHCl_3$); IR (neat) 3500, 2990, 2920, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.31, 1.38, 1.43, 1.47 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.25–2.00 (m, 8 H, cyclohexyl ring protons), 2.43–2.54 (m, 1 H, OH), 3.85–3.97 (m, 1 H, H-2′′), 4.10–4.24 (m, 3 H, H-2′′, H-1′′, H-5), 4.33–4.38 (br s, 1 H, H-2′), 5.06 (ddd, J=10.6, 1.8, 1.8 Hz, 1 H, –CH=CH_2), 5.13 (ddd, J=17.2, 1.8, 1.8 Hz, 1 H, –CH=CH_2), 5.20 (d, J=3.7 Hz, 1 H, H-3), 5.24 (dd, J=11.4, 1.8 Hz, 1 H, –CH=CH_2), 5.43 (dd, J=18.0, 1.8 Hz, 1 H, –CH=CH_2), 5.65 (d, J=3.7 Hz, 1 H, H-2), 6.09 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2), 6.29 (ddd, J=17.2, 10.6, 6.6 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 18.0, 25.6, 26.4, 26.5, 27.1, 29.9, 34.7, 39.2, 43.8, 57.4, 69.2, 69.4, 73.6, 84.6, 84.8, 104.7, 109.6, 110.9, 113.5, 116.6, 137.4, 143.9; HRMS calcd for $C_{22}H_{34}O_6$ (M^+) m/z 394.2355, found 394.2372. **26**: colorless oil; TLC, R_f 0.42 (EtOAc:hexane, 1:4); $[\alpha]_D^{23}$ +35.0 (*c* 0.20, $CHCl_3$); IR (neat) 3500, 2980, 2925, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.32, 1.37, 1.43, 1.48 (4s, 3 H×4, 4×C(CH_3)$_2$), 1.50–1.90, 1.90–2.10, 2.25–2.50 (3m, total 9H, cyclohexyl ring protons, OH), 3.87–3.96 (m, 1 H, H-2′′), 4.09–4.25 (m, 3 H, H-2′′, H-1′′, H-5), 4.34–4.42 (m, 1 H, H-2′), 4.92 (ddd, J=10.6, 1.5, 1.5 Hz, 1 H, –CH=CH_2), 4.98 (ddd, J=17.2, 1.5,

1.5 Hz, 1 H, –CH=CH_2), 5.17 (d, J=3.7 Hz, 1 H, H-3), 5.26 (dd, J=11.4, 1.5 Hz, 1 H, –CH=CH_2), 5.44 (dd, J=18.3, 1.5 Hz, 1 H, –CH=CH_2), 5.66 (d, J=3.7 Hz, 1 H, H-2), 5.75 (ddd, J=17.2, 10.6, 6.6 Hz, 1 H, –C*H*=CH_2), 6.10 (dd, J=18.3, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 22.2, 25.5, 26.4, 26.4, 27.0, 29.7, 32.4, 35.1, 40.8, 43.7, 57.3, 68.0, 69.4, 73.5, 84.6, 84.9, 104.6, 109.6, 111.0, 112.5, 116.6, 131.5, 137.5, 143.5.

3.13. Hydrolysis of the side chain acetal in ***23*** *and* ***25****. (2*R*,3*R*,4*S*,5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]-2,3-(isopropylidene)dioxy-4-[(1*S*,2*S*,4*S*)-4-methyl-2-hydroxycyclohexyl]-4-vinyltetrahydrofuran* ***27*** *and (2*R*,3*R*,4*S*,5*S*)-5-[(1*R*)-1,2-dihydroxyethyl]-2,3-(isopropylidene)dioxy-4-[(1*S*,2*S*,4*S*)-2-hydroxy-4-vinylcyclohexyl]-4-vinyltetrahydrofuran* ***28***

A solution of **23** (42.7 mg, 0.11 mmol) in 50% aqueous AcOH (1 ml) was stirred for 26 h and concentrated in vacuo with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:11) providing 35.0 mg (92%) of **27** and 3.2 mg (7%) of **23**. **27**: colorless oil; TLC, R_f 0.42 (EtOAc:hexane, 1:2); $[\alpha]_D^{22}$ +49.3 (*c* 1.25, $CHCl_3$); IR (neat) 3500, 2990, 2920, 1640 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.18 (d, J=7.7 Hz, 3 H, CH_3 at C-4′), 1.32, 1.49 (2s, 3 H×2, 2×C(CH_3)$_2$), 1.50–1.65, 1.65–1.85, 1.90–2.14 (3m, total 11H, cyclohexyl ring protons, 3×OH), 3.73 (dd, J=11.4, 5.5 Hz, 1 H, H-2″), 3.89 (dd, J=11.4, 3.3 Hz, 1 H, H-2″), 3.93 (ddd, J=9.2, 5.5, 3.3 Hz, 1 H, H-1″), 4.21 (d, J=9.2 Hz, 1 H, H-5), 4.29–4.34 (br s, 1 H, H-2′), 5.17 (d, J=3.7 Hz, 1 H, H-3), 5.27 (dd, J=11.4, 1.5 Hz, 1 H, –CH=CH_2), 5.38 (dd, J=18.0, 1.5 Hz, 1 H, –CH=CH_2), 5.71 (d, J=3.7 Hz, 1 H, H-2), 6.14 (dd, J=18.0, 11.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 17.5, 21.0, 26.2, 26.4, 26.8, 32.2, 40.1, 43.5, 57.1, 65.4, 69.0, 70.2, 82.6, 84.6, 104.6, 110.9, 116.5, 137.6; HRMS calcd for $C_{18}H_{29}O_6$ [(M−H)$^+$] m/z 325.2015, found 325.1995.

Analogously, 40.8 mg of **25** was hydrolyzed with 50% aqueous AcOH (1 ml) at 35°C for 15 h. Purification of the product by column chromatography on silica gel (EtOAc:hexane, 1:6) provided 30.0 mg (82%) of **28** as a colorless oil: TLC, R_f 0.65 (acetone:hexane, 1:2); $[\alpha]_D^{21}$ +63.8 (*c* 0.61, $CHCl_3$); IR (neat) 3480, 2990, 2920, 1640 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.31, 1.48 (2s, 3 H×2, 2×C(CH_3)$_2$), 1.54–2.16 (m, 7 H, cyclohexyl ring protons), 2.42–2.55 (br s, 1 H, cyclohexyl ring proton), 3.73 (dd, J=11.7, 6.2 Hz, 1 H, H-2″), 3.85–3.95 (m, 2 H, H-2″, H-1″), 4.21 (d, J=8.8 Hz, 1 H, H-5), 4.36–4.39 (br s, 1 H, H-2′), 5.06 (ddd, J=10.3, 1.8, 1.5 Hz, 1 H, –CH=CH_2), 5.12 (ddd, J=17.2, 1.8, 1.5 Hz, 1 H, –CH=CH_2), 5.20 (d, J=3.7 Hz, 1 H, H-3), 5.28 (dd, J=11.4, 1.5 Hz, 1 H, –CH=CH_2), 5.39 (dd, J=18.3, 1.5 Hz, 1 H, –CH=CH_2), 5.68 (d, J=3.7 Hz, 1 H, H-2), 6.13 (dd, J=18.3, 11.4 Hz, 1 H, –C*H*=CH_2), 6.29 (ddd, J=17.2, 10.3, 6.2 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 18.1, 26.4, 26.9, 29.9, 34.7, 39.2, 43.1, 57.1, 65.5, 69.2, 70.2, 82.8, 84.2, 104.6, 110.9, 113.5, 116.7, 137.5, 143.8; HRMS calcd for $C_{19}H_{31}O_6$ [(M+H)$^+$] m/z 355.2120, found 355.2120.

3.14. $NaIO_4$ oxidation of ***27*** *and* ***28*** *and successive PCC oxidation of the resulting hemiacetals* ***29*** *and* ***30****. (1*R*,3*S*,6*S*,8*S*,11*S*,12*R*,13*R*)-8,15,15-Trimethyl-12-vinyl-2,5,14,16-tetraoxatetracyclo-[11.3.0.0^{3,12}.0^{6,11}]hexadecan-4-one* ***31*** *and (1*R*,3*S*,6*S*,8*S*,11*S*,12*R*,13*R*)-15,15-dimethyl-8,12-divinyl-2,5,14,16-tetraoxatetracyclo[11.3.0.0^{3,12}.0^{6,11}]hexadecan-4-one* ***32***

To a cooled (0°C) solution of **27** (34.3 mg, 0.10 mmol) in MeOH (1 ml) was added aqueous $NaIO_4$ (0.40 M aqueous solution, 0.5 ml, 0.20 mmol). After stirring at ambient temperature for 2 h, the solution was diluted with water (5 ml), then extracted with $CHCl_3$ (3×20 ml). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel

(EtOAc:hexane, 1:5) providing 31.0 mg (97%) of hemiacetal **29** as a colorless oil which was oxidized. To a solution of **29** (31.0 mg, 0.09 mmol) in CH_2Cl_2 (1 ml) were added PCC (41.8 mg, 0.19 mmol) and molecular sieves (MS) 4A (20 mg). The mixture was stirred for 5 h while 41.8 mg and 20 mg of PCC and MS were added after 2 and 3 h. The mixture was transferred to a short column packed with silica gel (1 g), and the column was eluted with excess Et_2O. The ethereal elute was concentrated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:10) providing 22.6 mg (75%) of **31** as a colorless oil: TLC, R_f 0.39 (EtOAc:hexane, 1:3); $[\alpha]_D^{20}$ −40.3 (*c* 1.13, $CHCl_3$); IR (neat) 2990, 2920, 1740, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.06 (d, J=6.8 Hz, 3 H, CH_3 at C-8), 1.34, 1.49 (2s, 3 H×2, CH_3 at C-15), 1.45–1.68, 1.70–1.98 (2m, total 8 H, H-7, 7, 8, 9, 9, 10, 10, 11), 4.54 (d, J=3.7 Hz, 1 H, H-13), 4.71 (s, 1 H, H-3), 4.83 (ddd, J=3.9, 3.9, 3.9 Hz, 1 H, H-6), 5.00 (d, J=18.1 Hz, 1 H, –CH=C*H*$_2$), 5.31 (dd, J=11.2, 1.5 Hz, 1 H, –CH=C*H*$_2$), 5.92 (d, J=3.7 Hz, 1 H, H-1), 5.96 (dd, J=18.1, 11.2 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 20.3, 21.4, 26.7, 26.8, 27.0, 30.9, 35.7, 38.7, 56.1, 88.5, 105.6, 113.4, 116.8, 134.7, 167.7. Anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.19; H, 7.93.

Analogously, 17.6 mg (0.05 mmol) of **28** was treated with aqueous $NaIO_4$ (1.2 mol equiv.) to provide 13.3 mg (83%) of **30**. PCC oxidation of **30** (13.3 mg) and purification of the product by column chromatography on silica gel (EtOAc:hexane, 1:10) provided 11.9 mg (91%) of **32** as a colorless oil: TLC, R_f 0.47 (EtOAc:hexane, 1:2); $[\alpha]_D^{18}$ −40.0 (*c* 0.60, $CHCl_3$); IR (neat) 2980, 2920, 1745, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 1.34, 1.49 (2s, 3 H×2, CH_3 at C-15), 1.52–1.88, 2.04–2.17, 2.30–2.42 (3m, 6 H, 1H, 1H, H-7, 7, 8, 9, 9, 10, 10, 11), 4.54 (d, J=3.7 Hz, 1 H, H-13), 4.72 (s, 1 H, H-3), 4.87 (ddd, J=3.9, 3.9, 3.9 Hz, 1 H, H-6), 4.95–5.05 (m, 3 H, 3×–CH=C*H*$_2$), 5.30 (d, J=11.2 Hz, 1 H, –CH=C*H*$_2$), 5.92 (d, J=3.7 Hz, 1 H, H-1), 5.93 (dd, J=17.8, 11.2 Hz, 1 H, –C*H*=CH_2), 6.09 (ddd, J=16.8, 11.0, 8.4 Hz, 1 H, –C*H*=CH_2); ^{13}C NMR (75 MHz) δ 21.7, 26.8, 27.0, 29.5, 34.7, 35.8, 39.0, 56.2, 88.6, 105.7, 113.5, 117.0, 134.5, 141.7, 167.6. Anal. calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.64; H, 7.65.

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8. X-Ray crystallographic analyses were performed with a Rigaku AFC-5 diffractometer. Crystal data for **8** (crystals of **8** were grown from the hexane solution): $C_{20}H_{30}O_6$; *Mr*=366.45; orthorhombic $P2_12_12$; *a*=15.231(2), *b*=18.578(2), *c*=7.072(2) Å; *V*=2001.1(6) Å^3; *Z*=4; *Dx*=1.216 Mg m^{-3}; MoKα radiation λ=0.71073 Å; 2041 independent reflections, *R*=0.059, ω*R*=0.054, *S*=1.28, 1454 reflections, 265 parameters. Crystal data for **12** (crystals of **12** were grown from the hexane solution): $C_{20}H_{28}O_6$; *Mr*=364.44; orthorhombic $P2_12_12$; *a*=15.249(2), *b*=18.004(2), *c*=7.169(1) Å; *V*=1968.2(4) Å^3; *Z*=4; *Dx*=1.230 Mg m^{-3}; MoKα radiation λ=0.71073 Å; 2014 independent reflections, *R*=0.062, ω*R*=0.059, *S*=1.37, 1551 reflections, 263 parameters. The authors will deposit coordinates for structures of **8** and **12** with the Cambridge Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.