Stereoselective Synthesis of C3–C12 Dihydropyran Portion of Antitumor Laulimalide Using Copper-Catalyzed Oxonium Ylide Formation–[2,3] Shift

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Copper-catalyzed oxonium ylide formation–[2,3] shift of (5*S*,7*R*)-5-allyloxy-1-diazo-8-(*p*-methoxybenzyloxy)-7-methyl-2-octanone (3) proceeded in tetrahydrofuran-dichloromethane (4 : 1) under reflux with an excellent stereoselectivity (97 : 3) to give (2*R*,6*S*)-2-allyl-6-[(2*R*)-3-(*p*-methoxybenzyloxy)-2-methylpropyl]-3-dihydropyranone (2) as a major isomer in 82% yield. The resultant pyranone (2) was converted to the key intermediate (1) of the Mulzer's laulimalide synthesis and its derivatives (14, 15).

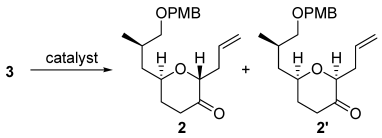
Key words copper catalyst; oxonium ylide; [2,3] shift; 3-pyranone; laulimalide; antitumor

Tetrahydropyran and dihydropyran rings are structural components of a large number of natural products.[1,2] Therefore, considerable attention has recently been directed toward their stereoselective synthesis.[3—8] The microtubule-stabilizing agent (−)-laulimalide,[9—18] also known as fijianolide B, which was isolated from several sponges (*Cacospongia mycofijiensis*,[19] *Hyattella* sp.,[20] *Fasciospongia rimosa*[21]), contains 2,6-*trans* disubstituted 5,6-dihydro-2*H*-pyran as its C5–C9 portion. Stereoselective construction of thermodynamically less stable 2,6-*trans* substituted pyrans is one of most important subjects in synthesis of this attractive antitumor agent and its analogues.

Metal catalyzed carbenoid reactions[22,23] have become a powerful tool for the synthesis of functionalized cyclic compounds including oxacycles. In 1994, Clark and co-workers reported that a copper-catalyzed reaction of 5-allyoxy-1-diazo-2-hexanone predominantly gave 2,6-*trans*-2-allyl-6-methy-3-dihydropyranone in good yield.[24] This result stimulated us to investigate the metal catalyzed stereoselective synthesis of 2,6-*trans* disubstituted 3-pyranone (**2**) from α-diazoketone (**3**) as a feasible method for synthesis of the C5–C9 portion of laulimalide and its analogues because **3** would be converted easily into the key intermediate (**1**) of the Mulzer's laulimalide synthesis,[11,25] as outlined in Chart 1. Herein, we describe the synthesis of **2** in high yield with excellent stereoselectivity by the copper-catalyzed oxonium ylide formation–[2,3] shift of **3** and conversion of **2** into **1** and its derivatives.

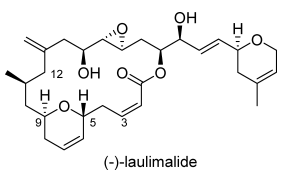
α-Diazoketone (**3**) was prepared readily from the known alcohol (**4**)[11] as shown in Chart 2. Homoallylic alcohol (**4**) was converted to diol by hydroboration–oxidation process with borane–tetrahydrofuran (THF) complex and subsequent treatment with hydrogen peroxide and sodium hydroxide. Then the resulting primary hydroxyl group was protected as a *tert*-butyldimethylsilyl (TBDMS) ether to give the secondary alcohol (**5**) in high yield. *O*-Allylation of **5** was troublesome. Under usual allylation conditions, such as reaction with sodium hydride (NaH) and allyl bromide in THF, no reaction occurred. Several examinations revealed that treatment of **5** with NaH and allyl iodide in the presence of 15-crown-5 in THF at room temperature afforded allyl ether (**6**) in 96% yield. Deprotection of TBDMS group with tetrabutylammonium fluoride (TBAF), followed by two step-oxidation with Dess-Martin periodinane and oxone in dimethylformamide (DMF)[26] gave carboxylic acid (**7**) in 80% overall yield. Conversion of **7** into α-diazoketone (**3**) was achieved by the usual procedure,[27] formation of mixed acid anhydride with ethyl chloroformate and treatment with diazomethane, thereby providing **3** in 85% yield in two steps.

With α-diazoketone (**3**) in hand, we turned our attention to cyclization of **3** by the metal catalyzed reaction (Eq. 1).



(1)

Formation of 2,6-disubstituted 3-pyranone using oxonium ylide formation–[2,3] shift of α-diazoketone has already been examined. Clark and co-workers reported that copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] catalyzed the reaction of 5-allyloxy-1-diazohexan-2-one in dichloromethane to give a 77 : 23 mixture of the corresponding 2,6-*trans*- and 2,6-*cis*-2-allyl-6-methyldihydropyran-3-ones in 68% yield.[24] Very recently, they reinvestigated the catalyst



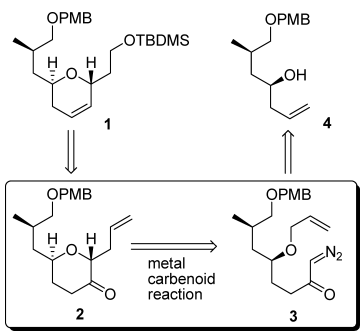


Chart 1

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effect of the same reaction and found that use of copper(II) trifluoroacetylacetonate [Cu(tfacac)$_2$] as a catalyst in CH_2Cl_2 was more effective than that of Cu(hfacac)$_2$ for the diastereoselectivity to give the ratio of *trans* : *cis* = 91 : 9.[28] For that reason, we chose to use mainly Cu(hfacac)$_2$ or Cu(tfacac)$_2$ as the catalyst in the reaction of **3** (Table 1).

When **3** was allowed to react with 0.05 equivalent of Cu(hfacac)$_2$ in CH_2Cl_2 at room temperature for 1.5 h, the oxonium ylide formation–[2,3] shift proceeded smoothly to give the corresponding 3-pyranone in 67% yield as a 80 : 20 mixture of 2,6-*trans* (**2**) and 2,6-*cis* isomers (**2′**) (entry 1). The ratio was determined by the ^{1}H-NMR spectroscopy of the mixture of the diastereomers. Although each pure diastereomer was obtained by careful silica gel column chromatography of the mixture, repeated chromatography was required for complete separation. Stereochemistries of both the diastereomers were confirmed by their NOESY spectra; positive NOE effects were observed between H-6 proton and allylic methylene protons at C-2 position of 2,6-*trans* isomer (**2**) and between H-2 proton and H-6 proton of 2,6-*cis* isomer (**2′**) (Fig. 1). Similar reaction of **3** with Cu(hfacac)$_2$ in THF did not proceed to recover the starting material after 27 h (entry 2).

Reaction with Cu(tfacac)$_2$ gave better result. Thus, **3** was treated with Cu(tfacac)$_2$ in CH_2Cl_2 at room temperature for 7 h to give the 3-pyranone in quantitative yield, but its stereoselectivity was identical to that of the reaction using Cu(hfacac)$_2$ (entry 3). Because of the difficulty of complete separation of two isomers by column chromatography, we further investigated reactions of **3** with Cu(tfacac)$_2$ in several solvents. A similar reaction of **3** in THF at room temperature for 19 h gave **2** as an essentially single product but the yield decreased to 56% (entry 4). Although reflux conditions shortened the reaction time to 3 h, the yield was, unfortunately, not improved (entry 5). Toluene was not suitable for this reaction from the standpoint of either yield or stereoselectivity (entry 6). However, in diethyl ether (Et_2O) the reaction of **3** with Cu(tfacac)$_2$ under reflux gave an almost satisfactory result (72%, **2** : **2′** = >95 : 5) (entry 7). In order to improve both the yield and stereoselectivity, the reactions were examined in combination of two solvents, CH_2Cl_2 giving the highest yield and THF leading the highest stereoselectivity. The results are summarized in Table 1 (entries 8—11). The best result was obtained when **3** and Cu(tfacac)$_2$ was allowed to react in 4 : 1 mixture of THF and CH_2Cl_2 under reflux to afford 80% of **2** and 2% of **2′** after single column chromatography (entry 11).

The other copper(II) catalyst such as copper(II) triflate gave a complex mixture in both CH_2Cl_2 and THF. In the case of the reaction of **3** with dirhodium(II) tetraacetate, the ratio of **2** and **2′** was reversed (entry 14).

One possible rationalization of the observed stereoselectivity in copper-catalyzed reaction of **3** is based on the consideration of the conformation of oxonium ylide (Fig. 2).[28] The conformer (**A**) is favored because both the allyl group and the substituent at C-6 position are accommodated in

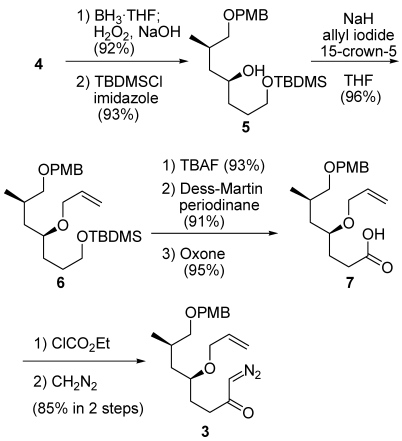

Chart 2

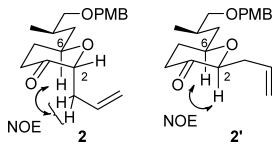

Fig. 1

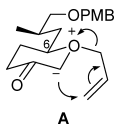

Fig. 2

Table 1. Metal Catalyzed Oxonium Ylide Formation–[2,3] Shift of **3**[a]

Entry	Catalyst	Solvent	Conditions	Yield (%)	*trans* : *cis* (**2** : **2′**)
1	Cu(hfacac)$_2$	CH_2Cl_2	rt, 1.5 h	67	80 : 20[b]
2	Cu(hfacac)$_2$	THF	rt, 27 h	No reaction	
3	Cu(tfacac)$_2$	CH_2Cl_2	rt, 7 h	Quant	80 : 20[b]
4	Cu(tfacac)$_2$	THF	rt, 19 h	56	>99 : 1[b]
5	Cu(tfacac)$_2$	THF	Reflux, 3 h	50	>99 : 1[b]
6	Cu(tfacac)$_2$	Toluene	rt, 1.5 h	57	85 : 15[b]
7	Cu(tfacac)$_2$	Et_2O	rt, 27 h	72	95 : 5[b]
8	Cu(tfacac)$_2$	THF–CH_2Cl_2 (1 : 1)	rt, 7 h	98	86 : 14[b]
9	Cu(tfacac)$_2$	THF–CH_2Cl_2 (10 : 1)	rt, 8 d	59	97 : 3[c]
10	Cu(tfacac)$_2$	THF–CH_2Cl_2 (4 : 1)	rt, 15 h	59	95 : 5[b]
11	Cu(tfacac)$_2$	THF–CH_2Cl_2 (4 : 1)	Reflux, 4 h	82	97 : 3[c]
12	Cu(OTf)$_2$	CH_2Cl_2	rt, 7 h	Complex mixture	
13	Cu(OTf)$_2$	THF	rt, 19 h	Complex mixture	
14	$Rh_2(OAc)_4$	THF–CH_2Cl_2 (4 : 1)	rt, 24 h	11	45 : 55[b]

a) All the reactions were carried out using 0.05 eq of catalyst. *b*) Determined by ^{1}H-NMR. *c*) The ratio was calculated based on the isolated yield of **2** and **2′**.

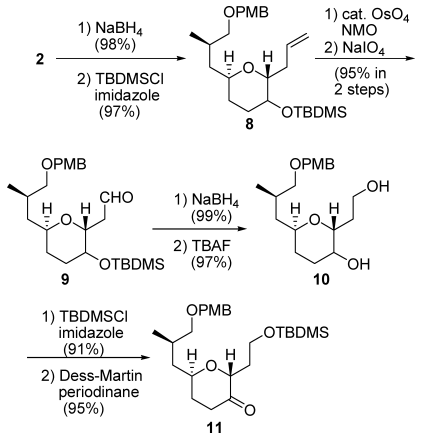

Chart 3

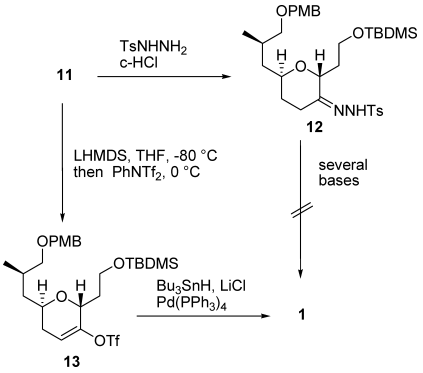

Chart 4

equatorial positions. The subsequent rearrangement proceeds in the same side of the allyl group to give 2,6-*trans* isomer (**2**).

Our next subject was conversion of **2** to Mulzer's laulimalide intermediate (**1**) (Charts 3, 4). The C-3 ketone of **2** was protected as a silyl ether of the corresponding alcohol to avoid isomerization to thermodynamically more stable 2,6-*cis* isomers during the transformation. Reduction of **2** with sodium borohydride in ethanol gave an approximately 5 : 2 mixture of diastereomers of alcohol in 98% yield which was used in the following steps without separation of two diastereomers and was silylated by TBDMS chloride and imidazole in DMF to afford silyl ether **8** in 97% yield. Treatment of **8** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) in THF–water (5 : 1), then sodium periodate gave rise to aldehyde (**9**) in 95% overall yield. The aldehyde (**9**) was reduced by $NaBH_4$ to yield alcohol in 99%, then desilylated with tetrabutylammmonium fluoride (TBAF) in THF to produce **10** (97%). Selective monosilylation of **10** followed by oxidation with Dess-Martin periodinane afforded ketone (**11**) in 86% in two steps.

Application of the Shapiro reaction[29] for construction of a C–C double bond from ketone (**11**) was examined first. Reaction of **11** with *p*-toluenesulfonylhydrazine in ethanol in the presence of concentrated hydrochloric acid gave hydrazone (**12**) in 91% yield. Unfortunately, all attempts of **12** to alkene (**1**) by treatment with several bases, such as *n*-butyl lithium, methyl lithium, *etc.* gave a complex mixture. However, alkene formation of **11** *via* vinyl triflate was successful. Enolization of **11** with lithium hexamethyldisilazide (LHMDS)

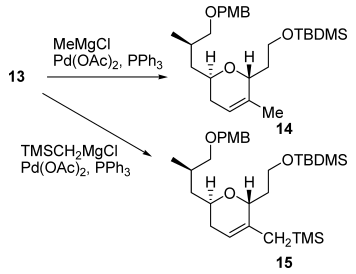

Chart 5

in THF at −80 °C formed less substituted enolate, which was trapped with *N*-phenylbis(trifluoromethanesulfon)imide [$PhNTf_2$][30] to afford vinyl triflate (**13**). Then **13** was reduced with tributyltin hydride and lithium chloride in the presence of tetrakis(triphenylphosphine) palladium[31] to yield Mulzer's laulimalide intermediate (**1**) in 88% from **11**. Spectroscopic data of **1**, including its optical rotation, were identical to those of the reported sample.[11]

The vinyl triflate (**13**) was useful for preparation of the 3-alkyl derivatives of Mulzer's intermediate (Chart 5). Reaction of **13** with methylmagnesium chloride in the presence of palladium(II) acetate and triphenylphosphine provided the corresponding 3-methyl derivative (**14**) in 52% yield from **11**. A similar treatment of **13** with trimethylsilylmethylmagnesium chloride gave rise to **15** in 40% yield from **11**. These derivatives (**14**, **15**) would be used for synthesis of laulimalide analogues, which are expected to show more effective activities than laulimalide itself.

In conclusion, the reaction of α-diazoketone (**3**) and a catalytic amount of $Cu(tfacac)_2$ in THF–CH_2Cl_2 (4 : 1) under reflux gave 2,6-*trans*-3-pyranone (**2**) in 82% yield as a major product (97 : 3). The resulting pyranone (**2**) was converted to Mulzer's key intermediate (**1**) of laulimalide and its derivatives (**14**, **15**).

Experimental

Melting points are uncorrected. IR spectra were recorded using JASCO FT/IR-400 and JASCO FT/IR-460 Plus spectrophotometers. ^{1}H-NMR spectra were determined with Varian Unity plus 500 (500 MHz), Varian Inova Unity XL400 (400 MHz), Varian Gemini 300 (300 MHz), JEOL JNM-AL300 (300 MHz), and JEOL JNM-FX270 (270 MHz) spectrometers, tetramethylsilane as an internal standard. ^{13}C-NMR spectra were determined with Varian Unity plus 500 (125 MHz), Varian Inova Unity XL400 (100 MHz), Varian Gemini 300 (75 MHz), JEOL JNM-AL300 (75 MHz), and JEOL JNM-FX270 (68 MHz) spectrometers. All ^{13}C-NMR spectra were determined with complete proton decoupling. High resolution MS were determined with JEOL JMS-GCmate, JEOL JMS-SX102AQQ, and JEOL JMS-AX505HAD instruments. Optical rotations were measured with JASCO DIP-360 and JASO DIP-1000 polarimeters. Column chromatography was performed on Silica gel 60 (0.063—0.200 mm) (MERCK) and Silica Gel 60 PF_{254} (Nacalai Tesque).

(4*S*,6*R*)-7-(*p*-Methoxybenzyloxy)-6-methyl-1,4-heptanediol A solution of borane–THF complex in THF (1.02 M, 17.5 ml, 17.8 mmol) was added to a solution of (4*S*,6*R*)-1-(*p*-methoxybenzyloxy)-2-methyl-6-hepten-4-ol[11] (3.63 g, 13.7 mmol) in THF (110 ml) at room temperature and the mixture was stirred at the same temperature overnight. The mixture was cooled to 0 °C, 3 M NaOH solution (14 ml) and 30% H_2O_2 solution (14 ml) were added to the mixture. The reaction was stirred at the same temperature for 10 min and then stirred at room temperature overnight. The mixture was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give (4*S*,6*R*)-7-(*p*-methoxybenzyloxy)-6-methyl-1,4-heptanediol (3.57 g, 92%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (3H, d, J=7.0 Hz), 1.44—1.74 (6H, m), 1.88—2.01 (1H, m), 3.10 (2H, br s), 3.23 (1H, t,

J=8.8 Hz), 3.39 (1H, dd, J=9.2, 4.4 Hz), 3.60—3.73 (3H, m), 3.80 (3H, s), 4.46 (2H, s), 6.88 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 18.7, 29.5, 32.6, 35.7, 44.6, 55.4, 63.3, 70.9, 73.1, 76.6, 114.0 (2), 129.6 (2), 129.8, 159.5. IR (neat) cm^{-1}: 3600—3100, 1613, 1586, 1514, 1463. Exact MS m/z: 282.1824 (Calcd for $C_{16}H_{26}O_4$: 282.1831). $[\alpha]_D^{25}$ +9.9° (c=1.00, $CHCl_3$).

(2*R*,4*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-(*p*-methoxybenzyloxy)-2-methyl-4-heptanol (5) A mixture of (4*S*,6*R*)-7-(*p*-methoxybenzyloxy)-6-methyl-1,4-heptanediol (3.57 g, 12.6 mmol), TBDMSCl (2.28 g, 17.7 mmol), and imidazole (1.55 g, 22.7 mmol) in DMF (70 ml) was stirred at room temperature overnight. The mixture was poured into H_2O and the mixture was extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **5** (4.66 g, 93%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 0.93 (3H, d, J=7.0 Hz), 1.34 (1H, ddd, J=13.9, 6.8, 2.9 Hz), 1.41—1.68 (6H, m), 1.89—2.05 (1H, m), 3.27 (1H, dd, J=9.2, 7.3 Hz), 3.33 (1H, dd, J=9.2, 5.5 Hz), 3.62—3.70 (1H, m), 3.64 (2H, t, J=6.0 Hz), 3.80 (3H, s), 4.45 (2H, s), 6.87 (2H, d, J=8.8 Hz), 7.25 (2H, d, J=8.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: −5.2 (2), 18.1, 18.5, 26.1 (3), 29.3, 31.7, 35.3, 43.4, 55.4, 63.6, 70.1, 72.9, 76.5, 113.9 (2), 129.4 (2), 130.4, 159.3. IR (neat) cm^{-1}: 3600—3100, 1613, 1586, 1513, 1463. Exact MS m/z: 396.2698 (Calcd for $C_{22}H_{40}O_4Si$: 396.2696). $[\alpha]_D^{27}$ +5.4° (c=0.63, $CHCl_3$).

(2*R*,4*S*)-4-Allyloxy-7-(*tert*-butyldimethylsilyloxy)-1-(*p*-methoxybenzyloxy)-2-methylheptane (6) After a mixture of **5** (4.66 g, 11.7 mmol), 60% NaH (939 mg, 23.5 mmol) and 15-crown-5 (2.58 g, 11.7 mmol) in THF (45 ml) was stirred at 0 °C for 30 min under nitrogen atmosphere, ally iodide (3.95 g, 23.5 mmol) was added to the mixture at the same temperature. Then the reaction mixture was stirred at room temperature overnight. The mixture was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **6** (4.92 mg, 96%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 0.95 (3H, d, J=6.6 Hz), 1.12—1.31 (1H, m), 1.49—1.67 (4H, m), 1.91—2.04 (1H, m), 3.20 (1H, dd, J=9.2, 7.0 Hz), 3.32 (1H, dd, J=9.2, 5.5 Hz), 3.39—3.44 (1H, m), 3.58—3.63 (2H, m), 3.80 (3H, s), 3.90 (1H, ddt, J=12.5, 5.9, 1.5 Hz), 4.00 (1H, ddt, J=12.5, 5.5, 1.5 Hz), 4.42 (2H, s), 5.12 (1H, dq, J=10.3, 1.3 Hz), 5.23 (1H, dq, J=17.3, 1.7 Hz), 5.89 (1H, ddt, J=17.3, 10.3, 5.7 Hz), 6.87 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: −5.1 (2), 17.5, 18.5, 26.1 (3), 28.6, 30.2, 30.6, 38.7, 55.4, 63.4, 69.8, 72.7, 76.1, 76.7, 113.8 (2), 116.5, 129.2 (2), 131.0, 135.7, 159.2. IR (neat) cm^{-1}: 1613, 1586, 1514, 1463. Exact FAB-MS m/z: 437.3094 (Calcd for $C_{25}H_{45}O_4Si$: 437.3087). $[\alpha]_D^{21}$ +6.5° (c=1.00, $CHCl_3$).

(4*S*,6*R*)-4-Allyloxy-7-(*p*-methoxybenzyloxy)-6-methyl-1-heptanol A solution of TBAF in THF (1.0 M, 5.2 ml, 5.2 mmol) was added to a solution of **6** (1.90 g, 4.33 mmol) in THF (30 ml) at room temperature and the mixture was stirred at the same temperature overnight. The mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (30% EtOAc in hexane) to give (4*S*,6*R*)-4-allyloxy-7-(*p*-methoxybenzyloxy)-6-methyl-1-heptanol (1.31 g, 93%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (3H, d, J=6.8 Hz), 1.15—1.29 (1H, m), 1.53—1.72 (5H, m), 1.88—2.04 (1H, m), 1.95 (1H, br s), 3.22 (1H, dd, J=9.1, 6.5 Hz), 3.31 (1H, dd, J=9.1, 5.8 Hz), 3.42—3.51 (1H, m), 3.62 (2H, td, J=5.7, 1.5 Hz), 3.80 (3H, s), 3.94 (1H, dddd, J=12.5, 5.7, 1.7, 1.3 Hz), 4.00 (1H, dddd, J=12.5, 5.7, 1.7, 1.3 Hz), 4.42 (2H, s), 5.14 (1H, ddt, J=10.3, 1.5, 1.3 Hz), 5.24 (1H, dtd, J=17.3, 1.7, 1.5 Hz), 5.89 (1H, ddt, J=17.3, 10.3, 5.7 Hz), 6.87 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 17.7, 28.5, 30.3, 30.8, 38.4, 55.4, 63.2, 69.9, 72.7, 75.9, 76.8, 113.9 (2), 116.9, 129.3 (2), 130.9, 135.3, 159.2. IR (neat) cm^{-1}: 3600—3100, 1613, 1586, 1514, 1462. Exact MS m/z: 322.2140 (Calcd for $C_{19}H_{30}O_4$: 322.2144). $[\alpha]_D^{22}$ +1.2° (c=1.00, $CHCl_3$).

(4*S*,6*R*)-4-Allyloxy-7-(*p*-methoxybenzyloxy)-6-methylheptanal A mixture of (4*S*,6*R*)-4-allyloxy-7-(*p*-methoxybenzyloxy)-6-methyl-1-heptanol (2.70 g, 8.37 mmol) and Dess-Martin periodinane (4.26 g, 10.0 mmol) in CH_2Cl_2 (60 ml) was stirred at room temperature for 1 h. The mixture was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give (4*S*,6*R*)-4-allyloxy-7-(*p*-methoxybenzyloxy)-6-methylheptanal (2.44 g, 91%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.95 (3H, d, J=6.6 Hz), 1.17 (1H, ddd, J=13.9, 8.2, 5.0 Hz), 1.68 (1H, ddd, J=13.9, 7.6, 5.3 Hz), 1.72—1.83 (1H, m), 1.84—1.99 (2H, m), 2.48 (2H, td, J=7.3, 1.7 Hz), 3.23 (1H, dd, J=9.0, 6.3 Hz), 3.30 (1H, dd, J=9.0, 5.9 Hz), 3.41—3.50 (1H, m), 3.80 (3H, s), 3.93 (2H, dt, J=5.6, 1.4 Hz), 4.42 (2H, s), 5.13 (1H, ddt, J=10.3, 1.7, 1.4 Hz), 5.23 (1H, ddt, J=17.2, 1.7, 1.4 Hz), 5.86 (1H, ddt, J=17.2, 10.3, 5.6 Hz), 6.87 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz), 9.76 (1H, t, J=1.7 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 17.5, 26.6, 30.1, 38.4, 39.7, 55.2, 69.8, 72.6, 75.6, 75.8, 113.7 (2), 116.7, 129.1 (2), 130.7, 135.0, 159.1, 202.4. IR (neat) cm^{-1}: 1724, 1612, 1586, 1513, 1463. Exact MS m/z: 320.1992 (Calcd for $C_{19}H_{28}O_4$: 320.1987). $[\alpha]_D^{26}$ −5.4° (c=1.00, $CHCl_3$).

(4*S*,6*R*)-4-Allyloxy-7-(*p*-methoxybenzyloxy)-6-methylheptanoic Acid (7) Oxone (6.09 g, 9.9 mmol) was added to a solution of (4*S*,6*R*)-4-allyloxy-7-(*p*-methoxybenzyloxy)-6-methylheptanal (2.44 g, 7.62 mmol) in DMF (50 ml) at 0 °C under nitrogen atmosphere and the mixture was stirred at the same temperature overnight. The mixture was quenched with pH 4.1 buffer, and extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give **7** (2.43 g, 95%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (3H, d, J=6.6 Hz), 1.18 (1H, ddd, J=13.9, 8.3, 5.2 Hz), 1.68 (1H, ddd, J=13.9, 8.1, 5.5 Hz), 1.83—2.00 (3H, m), 2.43 (2H, t, J=7.7 Hz), 3.23 (1H, dd, J=9.2, 6.6 Hz), 3.30 (1H, dd, J=9.2, 5.9 Hz), 3.44—3.53 (1H, m), 3.80 (3H, s), 3.96 (2H, d, J=5.5 Hz), 4.42 (2H, s), 5.13 (1H, dd, J=10.3, 1.1 Hz), 5.24 (1H, ddd, J=17.3, 3.3, 1.5 Hz), 5.88 (1H, ddt, J=17.3, 10.3, 5.5 Hz), 6.87 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 17.6, 29.1, 30.2 (2), 38.3, 55.3, 69.9, 72.6, 75.6, 75.8, 113.7 (2), 116.7, 129.0 (2), 130.7, 134.9, 135.0, 158.9. IR (neat) cm^{-1}: 3100—2800, 1709, 1647, 1612, 1585, 1514, 1463. Exact MS m/z: 336.1928 (Calcd for $C_{19}H_{28}O_5$: 336.1937). $[\alpha]_D^{26}$ −1.1° (c=1.00, $CHCl_3$).

(5*S*,7*R*)-5-Allyloxy-1-diazo-8-(*p*-methoxybenzyloxy)-7-methyl-2-octanone (3) According to the reported procedure,[27] a mixture of **7** (403 mg, 1.20 mmol) in THF (10 ml) and Et_3N (145 mg, 1.44 mmol) was stirred at 0 °C. After 20 min $ClCO_2Et$ (143 mg, 1.32 mmol) was added and the mixture stirred for further 30 min at the same temperature. Then a solution of CH_2N_2 in Et_2O was added at the same temperature until a strong yellow color persisted. The mixture was allowed to warm to room temperature and stirred overnight. The excess of CH_2N_2 was destroyed by the addition of few drops of AcOH. The mixture was diluted with H_2O, and extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl solution and brine, and dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (30% EtOAc in hexane) to give **3** (365 mg, 85% in 2 steps) as a colorless oil. ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.98 (3H, d, J=7.0 Hz), 1.10 (1H, ddd, J=13.9, 8.0, 4.8 Hz), 1.60—2.12 (6H, m), 3.21 (2H, dd, J=5.9, 2.9 Hz), 3.27—3.52 (1H, m), 3.32 (3H, s), 3.78 (1H, ddt, J=12.8, 5.5, 1.5 Hz), 3.85 (1H, ddt, J=12.8, 5.1, 1.5 Hz), 4.18 (1H, s), 4.35 (2H, s), 5.03 (1H, ddt, J=10.3, 1.8, 1.5 Hz), 5.24 (1H, ddt, J=16.9, 1.8, 1.5 Hz), 5.85 (1H, dddd, J=16.9, 10.3, 5.5, 5.1 Hz), 6.82 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). ^{13}C-NMR (68 MHz, C_6D_6) δ: 17.9, 29.3, 30.7, 38.7 (2), 54.9, 69.6, 73.0, 75.9, 76.0, 114.1 (2), 115.6, 129.4 (2), 131.4, 136.0, 159.6, 181.3, 193.4. IR (neat) cm^{-1}: 2103, 1734, 1644, 1365. Exact FAB-MS m/z: 361.2110 (Calcd for $C_{20}H_{29}N_2O_4$: 361.2127). $[\alpha]_D^{25}$ −2.6° (c=1.00, $CHCl_3$).

Copper-Catalyzed Oxonium Ylide Formation–[2,3] shift of 3 A solution of **3** (45 mg, 0.125 mmol) and $Cu(tfacac)_2$ (2.3 mg, 0.0063 mmol) in THF and CH_2Cl_2 (4 : 1, 2 ml) was refluxed for 4 h. The mixture was quenched with sat. EDTA solution, and extracted with Et_2O. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane). The first fraction gave (2*S*,6*S*)-2-allyl-6-[(2*R*)-3-{*p*-methoxybenzyloxy}-2-methylpropyl]tetrahydropyran-3-one (**2′**) (1 mg, 2%) as a colorless oil. ^{1}H-NMR (400 MHz, C_6D_6) δ: 0.98 (3H, d, J=6.8 Hz), 1.07 (1H, ddd, J=13.9, 9.0, 3.7 Hz), 1.31—1.47 (2H, m), 1.65 (1H, ddd, J=13.9, 9.3, 4.9 Hz), 1.83—1.93 (1H, m), 2.06—2.15 (1H, m), 2.21 (1H, ddd, J=15.7, 5.4, 3.8 Hz), 2.41—2.49 (1H, m), 2.69—2.76 (1H, m), 3.16 (1H, dd, J=8.8, 6.2 Hz), 3.25 (1H, dd, J=8.8, 5.9 Hz), 3.30—3.37 (1H, m), 3.31 (3H, d, J=0.9 Hz), 3.44 (1H, dd, J=8.2, 4.0 Hz), 4.36 (2H, s), 5.05 (1H, ddt, J=10.3, 2.1, 1.1 Hz), 5.12 (1H, ddt, J=17.1, 2.1, 1.5 Hz), 5.97 (1H, ddt, J=17.1, 10.3, 6.9 Hz), 6.82 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz). ^{13}C-NMR (100 MHz, C_6D_6) δ: 17.2, 30.6, 32.7, 34.5, 37.6, 39.9, 54.7, 72.8, 74.1, 75.8, 82.5, 114.0 (2), 117.0, 129.3 (2), 131.3, 134.9, 159.7, 206.6. IR (neat) cm^{-1}: 1740, 1612, 1586, 1514, 1462. Exact MS m/z: 332.1993 (Calcd for $C_{20}H_{28}O_4$: 332.1987). $[\alpha]_D^{27}$ +17.3° (c=0.33, $CHCl_3$). The second fraction gave (2*R*,6*S*)-2-allyl-6-[(2*R*)-3-{*p*-methoxybenzyloxy}-2-methylpropyl]tetrahydropyran-3-one (**2**) (33 mg, 80%) as a colorless oil. ^{1}H-NMR

(500 MHz, C_6D_6) δ: 0.90—1.00 (1H, m), 0.98 (3H, d, J=6.8 Hz), 1.18—1.28 (1H, m), 1.38—1.47 (1H, m), 1.68 (1H, ddd, J=14.1, 9.8, 4.3 Hz), 2.00—2.23 (3H, m), 2.35—2.43 (2H, m), 3.17 (1H, dd, J=9.0, 6.4 Hz), 3.23 (1H, dd, J=9.0. 6.0 Hz), 3.30 (3H, s), 3.66 (1H, tt, J=9.8, 3.8 Hz), 3.93 (1H, dd, J=9.0, 4.7 Hz), 4.35 (2H, s), 5.03—5.07 (2H, m), 5.81 (1H, ddt, J=17.0, 10.3, 6.9 Hz), 6.81 (2H, d, J=8.7 Hz), 7.23 (2H, d, J=8.7 Hz). ^{13}C-NMR (125 MHz, C_6D_6) δ: 17.3, 30.4, 30.6, 34.8, 35.9, 39.1, 55.0, 68.1, 73.0, 76.1, 78.8, 114.1 (2), 117.3, 129.4 (2), 131.4, 134.6, 159.7, 208.8. IR (neat) cm^{-1}: 1724, 1612, 1586, 1512. Exact MS m/z: 332.1981 (Calcd for $C_{20}H_{28}O_4$: 332.1988). $[\alpha]_D^{28}$ +97.2° (c=1.00, $CHCl_3$).

Reduction of 2 A mixture of **2** (200 mg, 0.602 mmol) and $NaBH_4$ (27 mg, 0.722 mmol) in EtOH (6 ml) was stirred at room temperature overnight. The mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give a mixture of (2*R*,3*R*,6*S*)- and (2*R*,3*S*,6*S*)-2-allyl-6-[(2*R*)-3-(*p*-methoxybenzyloxy)-2-methylpropyl]tetrahydropyran-3-ol (197 mg, 98%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.93 (6/7H, d, J=6.6 Hz), 0.94 (15/7H, d, J=6.6 Hz), 0.98—1.09 (1H, m), 1.23—1.33 (1H, m), 1.53—2.01 (5H, m), 2.22—2.44 (2H, m), 3.19—3.33 (2H, m), 3.68—3.78 (2H, m), 3.80 (3H, s), 3.82—4.04 (1H, m), 4.43 (2H, s), 5.01—5.16 (2H, m), 5.82 (1H, ddt, J=17.1, 10.1, 7.0 Hz), 6.87 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ for the major isomer: 16.7, 26.7 (2), 29.8, 33.6, 35.7, 55.3, 67.1, 68.4, 72.49, 72.51, 75.9, 113.7 (2), 116.8, 129.0 (2), 130.9, 135.1, 159.0. IR (neat) cm^{-1}: 3700—3100, 1613, 1586, 1514, 1462. Exact MS m/z: 334.2165 (Calcd for $C_{20}H_{30}O_4$: 334.2144).

Conversion into 8 A mixture of the alcohol (195 mg, 0.583 mmol), TBDMSCl (149 mg, 0.991 mmol), and imidazole (119 mg, 1.75 mmol) in DMF (5.5 ml) was stirred at room temperature overnight. The mixture was poured into H_2O and the mixture was extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **8** (254 mg, 97%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.04 (3H, s), 0.05 (3H, s), 0.88 (45/7H, s), 0.89 (18/7H, s), 0.92 (15/7H, d, J=6.6 Hz), 0.95 (6/7H, d, J=6.6 Hz), 1.07 (1H, d, J=13.9, 9.5, 3.3 Hz), 1.22—1.34 (1H, m), 1.52—1.78 (4H, m), 1.91—2.03 (1H, m), 2.25—2.33 (1H, m), 2.45—2.54 (1H, m), 3.17—3.36 (4/7H, m), 3.19 (5/7H, dd, J=9.2, 6.8 Hz), 3.30 (5/7H, dd, J=9.2, 5.9 Hz), 3.61—3.68 (2/7H, m), 3.65 (5/7H, tt, J=9.7, 2.9 Hz), 3.75—3.98 (2H, m), 3.80 (3H, s), 4.43 (10/7H, s), 4.44 (4/7H, s), 5.03 (1H, ddt, J=10.3, 2.1, 1.2 Hz), 5.09 (1H, ddt, J=17.2, 2.1, 1.6 Hz), 5.85 (1H, ddt, J=17.2, 10.3, 6.9 Hz), 6.87 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ for the major isomer: −4.8, −4.7, 16.9, 25.80 (3), 25.85, 27.8, 29.8, 29.9, 30.3, 39.1, 55.2, 65.9, 68.8, 72.5, 75.8, 76.0, 113.7 (2), 116.0, 129.1 (2), 135.7, 136.1, 159.0. IR (neat) cm^{-1}: 1613, 1586, 1514, 1463. Exact MS m/z: 448.3032 (Calcd for $C_{26}H_{44}O_4Si$: 448.3009).

Oxidative Cleavage of the Terminal Alkene of 8 An aqueous solution of OsO_4 (4%, 0.36 ml, 0.0562 mmol) and NMO (132 mg, 1.12 mmol) were added to a solution of **8** (252 mg, 0.562 mmol) in THF–H_2O (5 : 1, 6 ml) at 0 °C, then the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc and washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give the crude diol. A mixture of the crude diol and $NaIO_4$ (141 mg, 0.659 mmol) in THF–H_2O (5 : 1, 6 ml) was stirred at room temperature overnight. The mixture was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **9** (240 mg, 95%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 0.89 (3H, d, J=7.3 Hz), 1.10 (1H, ddd, J=13.9, 9.5, 3.3 Hz), 1.23—1.38 (1H, m), 1.50—1.95 (5H, m), 2.69 (2H, dd, J=7.3, 2.6 Hz), 3.17—3.39 (2H, m), 3.55—3.65 (1H, m), 3.80 (3H, s), 3.80—3.95 (2H, m), 4.41 (2H, s), 6.87 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz), 9.70—9.73 (2/7H, m), 9.74 (5/7H, t, J=2.6 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ for the major isomer: −4.9, −4.7, 16.7, 18.0, 25.8 (3), 27.8, 29.8, 30.0, 38.9, 41.2, 55.2, 66.8, 68.2, 71.7, 72.5, 75.8, 113.7 (2), 129.1 (2), 130.1, 159.0, 201.4. IR (neat) cm^{-1}: 1728, 1613, 1586, 1514, 1463. Exact MS m/z: 450.2823 (Calcd for $C_{25}H_{42}O_5Si$: 450.2802).

Reduction of Aldehyde 9 A mixture of **9** (239 mg, 0.53 mmol) and $NaBH_4$ (24 mg, 0.636 mmol) in EtOH (6 ml) was stirred at room temperature overnight. The mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (30% EtOAc in hexane) to give a mixture of the diastereomers of the primary alcohol (237 mg, 99%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.056 (3H, s), 0.061 (3H. s), 0.89 (9H, s), 0.92 (15/7H, d, J=7.0 Hz), 0.93 (6/7H, d, J=6.6 Hz), 0.94—1.01 (1H, m), 1.20—1.32 (1H, m), 1.55—2.30 (7H, m), 2.60—2.66 (5/7H, m), 2.99—3.04 (2/7H, m), 3.19—3.38 (2H, m), 3.73—3.96 (5H, m), 3.80 (3H, s), 4.43 (10/7H, s), 4.45 (4/7H, s), 6.87 (2H, d, J=8.5 Hz), 7.25 (2H, d, J=8.5 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ for the major isomer: −4.9, −4.7, 16.8, 18.1, 25.8 (3), 27.6, 28.6, 29.9, 30.1, 37.8, 55.3, 61.0, 67.2, 68.9, 72.6, 73.8, 75.7, 113.7 (2), 129.2 (2), 130.7, 159.1. IR (neat) cm^{-1}: 3700—3100, 1613, 1586, 1514, 1463. Exact MS m/z: 452.2950 (Calcd for $C_{25}H_{44}O_5Si$: 452.2958).

Diol 10 A solution of TBAF in THF (1.0 M, 0.63 ml, 0.63 mmol) was added to a solution of the alcohol (237 mg, 0.524 mmol) in THF (5 ml) at room temperature and the mixture was stirred at the same temperature overnight. The mixture was quenched with sat. NH_4Cl solution, and extracted with EtOAc. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give **10** (172 mg, 97%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.85—2.30 (9H, m), 0.92 (15/7H, d, J=7.0 Hz), 0.93 (6/7H, d, J=7.0 Hz), 2.29 (2H, br s), 3.15—3.33 (2H, m), 3.56—3.98 (5H, m), 3.81 (3H, s), 4.45 (2H, s), 6.88 (2H, d, J=8.8 Hz), 7.25 (2H, d, J=8.8 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ for the major isomer: 16.6, 26.7 (2), 29.9, 33.0, 34.9, 55.3, 60.0, 67.6, 69.1, 70.3, 72.7, 75.6, 113.7 (2), 129.3 (2), 130.4, 171.4. IR (neat) cm^{-1}: 3700—3100, 1613, 1586, 1514, 1462. Exact MS m/z: 338.2083 (Calcd for $C_{19}H_{30}O_5$: 338.2093).

Monosilylation of 10 A mixture of **10** (95 mg, 0.281 mmol), TBDMSCl (51 mg, 0.337 mmol), and imidazole (38 mg, 0.561 mmol) in DMF (3 ml) was stirred at room temperature for 10 min. The mixture was poured into H_2O and the mixture was extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give the silyl ether (116 mg, 91%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.07 (6H, s), 0.89 (9H, s), 0.93 (6/7H, d, J=7.3 Hz), 0.94 (15/7H, d, J=6.6 Hz), 1.06 (1H, ddd, J=13.9, 9.5, 4.4 Hz), 1.25—2.00 (8H, m), 2.84 (1H, br s), 3.23 (1H, dd, J=9.2, 6.2 Hz), 3.30 (1H, dd, J=9.2, 5.9 Hz), 3.62—3.86 (5H, m), 3.80 (3H, s), 4.42 (2H, s), 6.87 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ for the major isomer: −5.5 (2), 16.7, 18.2, 25.8 (3), 26.8, 27.0, 29.9, 32.2, 36.5, 55.2, 60.2, 67.1, 68.0, 71.4, 72.5, 75.9, 113.6 (2), 128.98 (2), 129.04, 159.0. IR (neat) cm^{-1}: 3600—3100, 1613, 1586, 1514, 1462. Exact FAB-MS m/z: 453.3040 (Calcd for $C_{25}H_{45}O_5Si$: 453.3036).

(2*R*,6*S*)-2-[2-(*tert*-Butyldimethylsilyloxyethyl)-6-[(2*R*)-3-(*p*-methoxybenzyloxy)-2-methylpropyl]tetrahydropyran-3-one (11) A mixture of the silyl ether (196 mg, 0.433 mmol) and Dess-Martin periodinane (220 mg, 0.52 mmol) in CH_2Cl_2 (60 ml) was stirred at room temperature overnight. The mixture was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to **11** (185 mg, 95%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 0.98 (3H, d, J=6.6 Hz), 1.19—1.30 (1H, m), 1.71—2.13 (5H, m), 1.77 (1H, ddd, J=13.9, 9.6, 4.3 Hz), 2.40—2.60 (2H, m), 3.26 (1H, dd, J=9.0, 6.1 Hz), 3.32 (1H, dd, J=9.0, 6.1 Hz), 3.68—3.73 (2H, m), 3.81 (3H, s), 3.95—4.06 (1H, m), 4.17 (1H, dd, J=8.7, 4.8 Hz), 4.43 (2H, s), 6.87 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: −5.4 (2), 16.8, 18.3, 25.9 (3), 30.0 (2), 33.0, 35.7, 38.8, 55.3, 58.9, 67.9, 72.6, 75.7, 75.8, 113.7 (2), 129.1 (2), 130.8, 159.1, 211.9. IR (neat) cm^{-1}: 1725, 1613, 1586, 1514, 1464. Exact MS m/z: 450.2788 (Calcd for $C_{25}H_{42}O_5Si$: 450.2802). $[\alpha]_D^{27}$ +62.9° (c=1.00, $CHCl_3$).

(2*R*,6*S*)-6-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[(2*R*)-3-(*p*-methoxybenzyloxy)-2-methylpropyl]-5,6-dihydro-2*H*-pyran (1) According to the reported procedure,[30] a solution of LHMDS in THF (1.0 M, 0.72 ml, 0.72 mmol) was added to a solution of **11** (54 mg, 0.12 mmol) in THF (1 ml) at −80 °C under nitrogen atmosphere and the mixture was stirred at the same temperature for 1.5 h. After a solution of $PhNTf_2$ (129 mg, 0.361 mmol) in THF (1.5 ml) was added to the cold mixture, the resultant mixture was allowed to warm up to 0 °C and then stirred at 0 °C for 28 h. The mixture was quenched with sat. NH_4Cl solution, and extracted with Et_2O. The extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give **13** which was used in the next step without purification. According to the reported procedure,[31] the crude **13** was diluted THF (1 ml) and this mixture was added to a solution of $Pd(PPh_3)_4$ (2.7 mg, 0.00234 mmol) and LiCl (41 mg, 0.967 mmol) in THF (0.5 ml) at room temperature under nitrogen atmosphere. Then Bu_3SnH (38 mg, 0.132 mmol) was added to the resultant mixture at the same temperature. After stirred for 1.5 h, the mixture was diluted with Et_2O and washed with H_2O and brine,

dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (2.5% EtOAc in hexane) to give **1**[11] (46 mg, 88%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.89 (9H, s), 0.95 (3H, d, J=6.9 Hz), 1.10—1.38 (1H, m), 1.57—1.74 (2H, m), 1.76—1.89 (1H, m), 1.90—1.97 (2H, m), 1.99—2.14 (1H, m), 3.23 (1H, dd, J=9.1, 6.8 Hz), 3.34 (1H, dd, J=9.1, 5.8 Hz), 3.66—3.81 (3H, m), 3.80 (3H, s), 4.30—4.37 (1H, m), 4.43 (2H, s), 5.65—5.72 (1H, m), 5.75—5.84 (1H, m), 6.87 (2H, d, J=8.7 Hz), 7.25 (2H, d, J=8.7 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: −5.33, −5.30, 16.9, 18.3, 26.0 (3), 29.6, 31.5, 36.9, 39.6, 55.3, 59.9, 64.9, 69.4, 72.5, 76.0, 113.7 (2), 124.0, 129.0 (2), 130.0, 131.0, 159.0. IR (neat) cm^{-1}: 2955, 2927, 2855, 1613, 1586, 1514, 1464, 1249, 1181, 1039. Exact MS m/z: 434.2878 (Calcd for $C_{25}H_{42}O_4Si$: 434.2852). $[\alpha]_D^{26}$ −28.0° (c=0.50, $CHCl_3$) {lit.[11] $[\alpha]_D^{20}$ −28.9° (c=1.27, $CHCl_3$)}.

(2*R*,6*S*)-6-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[(2*R*)-3-(*p*-methoxybenzyloxy)-2-methylpropyl]-5-methyl-5,6-dihydro-2*H*-pyran (14) A solution of **13**, which was prepared from **11** (29 mg, 0.00643 mmol), LHMDS (1 M in THF, 0.4 ml, 0.40 mmol) and $PhNTf_2$ (69 mg, 0.193 mmol) according to the procedure described in the preparation of **1**, in THF (0.5 ml) was added to a solution of $Pd(OAc)_2$ (1.5 mg, 0.00666 mmol) and PPh_3 (5.2 mg, 0.02 mmol) in THF (0.5 ml) at room temperature under nitrogen atmosphere. After subsequent addition of MeMgCl in THF (3 M, 0.06 ml, 0.18 mmol), the mixture was stirred for 30 min. The mixture was quenched with sat. NH_4Cl solution, and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (2.5% EtOAc in hexane) to give **14** (15 mg, 52%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.90 (9H, s), 0.95 (3H, d, J=6.6 Hz), 1.00—1.62 (2H, m), 1.62 (3H, s), 1.73—1.81 (2H, m), 1.88—1.91 (2H, m), 1.97—2.13 (1H, m), 3.23 (1H, dd, J=9.1, 6.8 Hz), 3.34 (1H, dd, J=9.1, 5.8 Hz), 3.65—3.81 (3H, m), 3.80 (3H, s), 4.06—4.14 (1H, m), 4.43 (2H, s), 5.45—5.49 (1H, m), 6.87 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: −5.3 (2), 14.1, 16.9, 19.8, 26.0 (3), 29.7, 32.0, 34.5, 39.8, 55.3, 60.1, 64.2, 72.5, 73.0, 76.0, 113.7 (2), 119.4, 129.0 (2), 130.9, 135.7, 159.0. IR (neat) cm^{-1}: 1613, 1587, 1514, 1463. Exact MS m/z: 448.3042 (Calcd for $C_{26}H_{44}O_4Si$: 448.3009). $[\alpha]_D^{22}$ −7.4° (c=0.40, $CHCl_3$).

(2*R*,6*S*)-6-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[(2*R*)-3-(*p*-methoxybenzyloxy)-2-methylpropyl]-5-(trimethylsilylmethyl)-5,6-dihydro-2*H*-pyran (15) According to a procedure similar to that described for the preparation of **14**, treatment of **13**, prepared from **11** (30 mg, 0.00666 mmol) with LHMDS (1 M in THF, 0.4 ml, 0.40 mmol), $PhNTf_2$ (57 mg, 0.16 mmol), with $Pd(OAc)_2$ (1.5 mg, 0.00666 mmol), PPh_3 (5.2 mg, 0.02 mmol), and $TMSCH_2MgCl$ (1 M in THF, 0.2 ml, 0.20 mmol) gave **15** (14 mg, 40%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.02 (9H, s), 0.06 (6H, s), 0.90 (9H, s), 0.94 (3H, d, J=6.9 Hz), 1.11—1.71 (4H, m), 1.73—1.83 (2H, m), 1.89—1.94 (2H, m), 1.99—2.10 (1H, m), 3.22 (1H, dd, J=9.2, 6.9 Hz), 3.33 (1H, dd, J=9.2, 5.6 Hz), 3.66—3.81 (3H, m), 3.80 (3H, s), 4.05—4.11 (1H, m), 4.43 (2H, s), 5.28—5.31 (1H, m), 6.87 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: −5.3, −5.2, −1.1 (3), 16.9, 18.4, 22.7, 26.0 (3), 29.7, 32.0, 34.4, 39.8, 55.3, 60.2, 63.9, 72.5, 72.7, 76.0, 113.7 (2), 116.9, 129.0 (2), 129.6, 137.5, 159.0. IR (neat) cm^{-1}: 1614, 1587, 1514, 1464. Exact MS m/z: 520.3394 (Calcd for $C_{29}H_{52}O_4Si_2$: 520.3404). $[\alpha]_D^{21}$ −5.9° (c=0.27, $CHCl_3$).

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