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SYNTHESIS OF A-RING SYNTHON OF 2α-SUBSTITUTED VITAMIN D_3 ANALOGUES UTILIZING GRIGNARD REACTION TOWARDS METHYL 2,3-ANHYDRO-4,6-*O*-BENZYLIDENE-α-D-MANNO-PYRANOSIDE

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Abstract – A concise route to the Trost A-ring precursor enyne for synthesizing 2α-substituted 1α,25-dihydroxyvitamin D_3 (**1**) is described, in which the 2α-substituents could be introduced *via* addition reaction of Grignard reagent towards the sugar epoxide, easily obtained from D-glucose. In the reaction, the solvent effect was remarkable and the use of toluene gave higher chemical yield and chemical reactivity as compared with ethereal solvents.

INTRODUCTION

1α,25-Dihydroxyvitamin D_3 (**1**), the hormonally active form of vitamin D_3, mediates intestinal calcium absorption, and bone resorption and mineralization. In addition, **1** has been found to exhibit a variety of biological activities in many tissues and cells since the discovery of the fact that **1** induces cell differentiation and proliferation.[1] This renewed interest has prompted numerous efforts to synthesize a huge number of vitamin D analogues in order to investigate biological roles of this hormone and to develop potential therapeutic agents.[2,3]

Previously, we synthesized A-ring modified analogues (**2a-d** and **3a-d**), in which the 2α-alkyl or the 2α-hydroxyalkyl group was introduced to **1**, to study the A-ring conformation- and structure-activity relationships (Figure 1).[4-6] The resulting analogues exhibited interesting biological activities, in particular, 2α-methyl and 2α-(3-hydroxypropyl) analogues (**2a** and **3c**) showed much higher potency than **1** in terms of binding affinity for bovine thymus vitamin D receptor (VDR), elevation of rat serum calcium concentration, and induction of HL-60 cell differentiation.[4,5] For example,

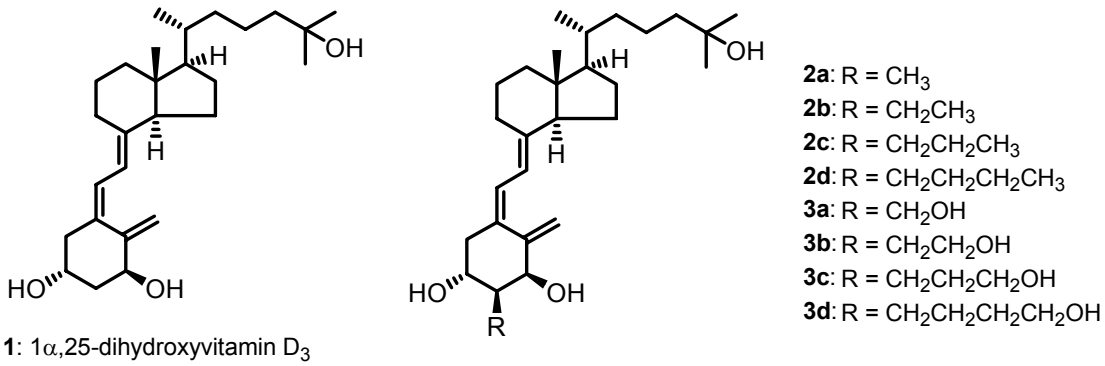
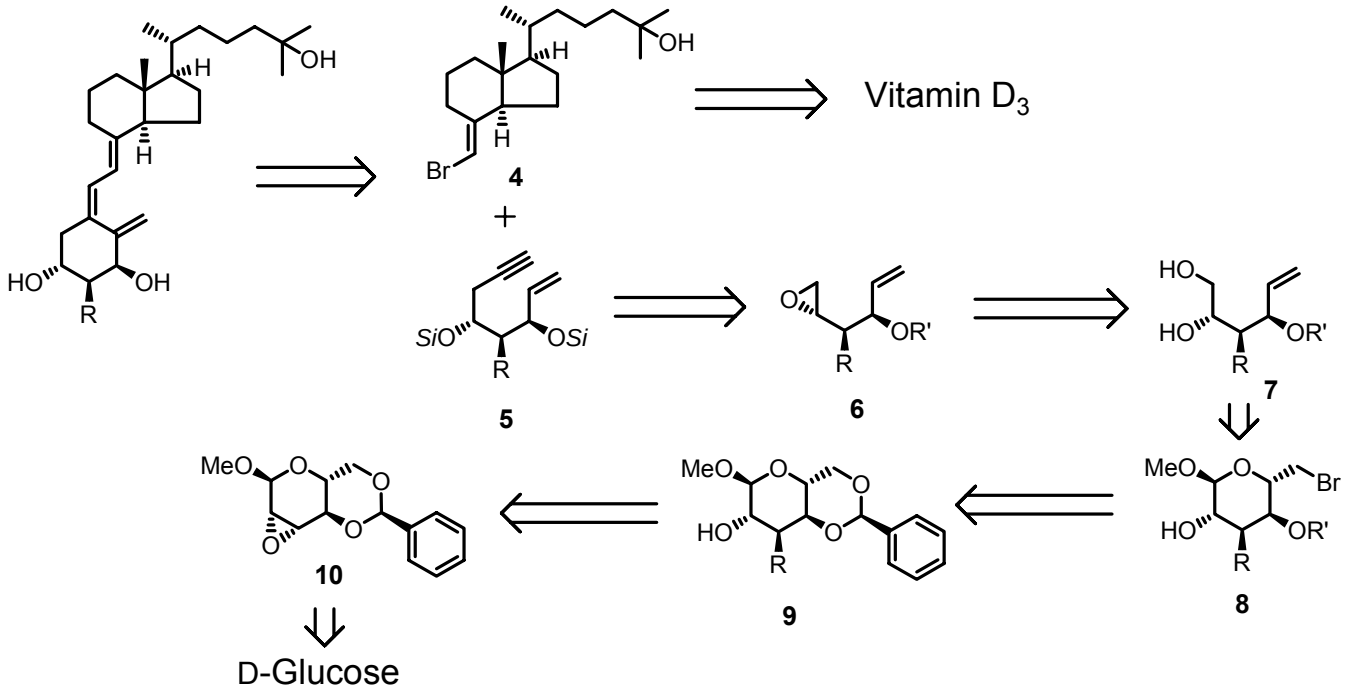


Figure 1. Structures of 1α,25-dihydroxyvitamin D_3 (**1**) and its 2α-alkylated analogues

2α-(3-hydroxypropyl) analogue (**3c**) exhibited 3-fold higher VDR binding affinity, approximately 500 times higher potency for elevation of rat serum calcium concentration than those of **1**.[4b] These remarkably high activities are unique among vitamin D analogues reported to date. On the other hand, structural modifications of the CD-ring side chain have been intensively studied in the past.[7] We report here an improved synthesis of the A-ring precursor enynes from D-glucose, utilizing Grignard reaction as a key reaction. In this step, the use of toluene as a reaction medium was much important for the efficient introduction of the 2α-substituents.

RESULTS AND DISCUSSION

Retrosynthetic analysis of the target analogues is shown in Scheme 1. The analogues were synthesized by employing the convergent method of Trost and co-workers using palladium-catalyzed coupling



Scheme 1. Retrosynthetic analysis of 2α-substituted vitamin D_3 analogues.

reaction of the A-ring synthon, enyne, with the CD-ring portion.[8] The key step of the A-ring synthesis is the introduction of the 2α-substituents by the reaction of epoxide (**10**),[9] which is readily available from methyl α-D-glucoside, with Grignard reagent. So far, only limited compounds (**9**) were synthesized as chiral templates through C(3) alkylation with epoxy ring opening reaction of **10**.[10]

9a: R = CH_3
9b: R = CH_2CH_3
9c: R = $CH_2CH_2CH_3$
9d: R = $CH_2CH_2CH_2CH_3$
9e: R = $CH(CH_3)_2$
9f: R = $CH{=}CH_2$
9g: R = $CH_2CH{=}CH_2$
9h: R = $CH_2CH_2CH{=}CH_2$
9i: R = Ph
9j: R = $C{\equiv}CSi(CH_3)_3$
9k: R = Bn
9l: R = CH_2CH_2Ph

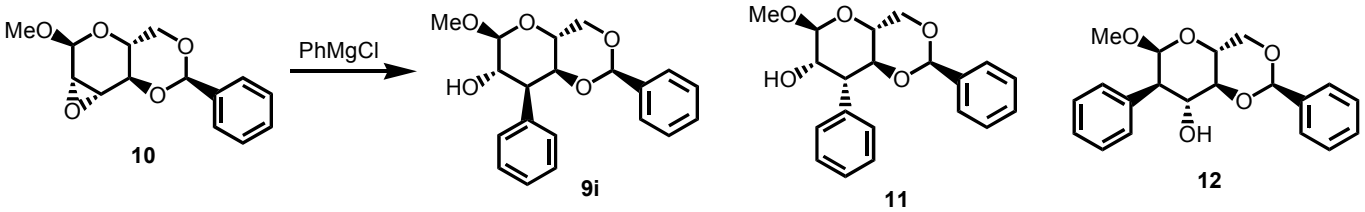
Table 1. Grignard reaction towards epoxide (**10**).

Run	R	Equiv. of RMgCl	Solvent	Temp.	Time (h)	Yield (%)
1	Me	10 + 6	Et_2O - THF	reflux	336	99
2	Me	10	toluene	110 °C	1	73
3	Bn	6	THF	reflux	14	91
4	Bn	10	toluene	110 °C	1	83
5	allyl	3	THF	reflux	2	86
6	*n*-Bu	10	THF	reflux	15	24
7	*n*-Bu	10	toluene	110 °C	1	83
8	Et	10	toluene	110 °C	1	74
9	*n*-Pr	10	toluene	110 °C	1	53
10	vinyl	10	toluene	50 °C	3.5	64
11	$CH_2CH_2CH{=}CH_2$	10	toluene	110 °C	1	49
12	*i*-Pr	10	toluene	110 °C	1	12
13	Ph	15	toluene	80 °C	1.5	73
14	CH_2CH_2Ph	10	toluene	110 °C	1	58
15	$-{\equiv}-SiMe_3$	10	toluene	50 ~ 80 °C	2	19

The results of Grignard reaction for **10** are shown in Table 1. In this study, Grignard reagents having chloride counter anion were used to avoid halohydrin formation, frequently observed when RMgX (X = Br or I) was used in the earlier works.[10a] When reactive Grignard reagents such as MeMgCl, BnMgCl, and allylMgCl were employed in conventional ethereal solvents such as ether or THF, this methodology worked well and gave epoxy ring opened products (**9a**, **9g**, **9k**) in high yield,[10] although the reaction time was relatively long (1 day to 2 weeks) except for allylMgCl (2 h) (Table 1, Runs 1, 3 and 5). However,

in the cases of Grignard reagents having longer alkyl groups or phenyl group, the Grignard reaction gave poor results, the desired products were obtained in low yields (10~20%) such as shown in Table 1, Run 6, and decomposition of starting material (**10**) was often observed. The addition of Cu(I) salt, known as an additive for this type of reaction,[11] gave no improvement in our experiments (data not shown). We found that the use of toluene as a reaction medium was highly effective for the Grignard reaction of epoxide (**10**). For example, epoxide (**10**) was treated with excess *n*-BuMgCl in toluene containing THF (almost 1 equiv. to Mg) for 1 h at 110 °C gave desired product (**9d**) in 83% yield (Table 1, Run 7). As stated above, the same reaction using THF as the solvent gave product (**9d**) only in 24% yield (15 h) (Table 1, Run 6). This solvent effect was also observed when reactive Grignard reagents such as MeMgCl (Table 1, Runs 1 and 2) and BnMgCl (Table 1, Runs 3 and 4) were used. Toluene solution of Grignard reagent was prepared in two ways and gave similar results (data not shown); (1) Grignard reagent was prepared as toluene solution (containing 1 equiv. of THF to stabilize organomagnesium compound in toluene) according to the procedure reported by Tuulmets.[12] (2) The solvent of the THF solution of Grignard reagent from commercial source was removed *in vacuo*, and the residue was diluted with toluene so that the concentration is adjusted to 1 M.

A wide variety of substituents were able to be introduced when Grignard reagent in toluene was used (Table 1); alkyl groups such as methyl (**9a**), ethyl (**9b**), *n*-propyl (**9c**), *n*-butyl (**9d**), 3-butenyl (**9h**) and 2-phenylethyl (**9l**) groups, and unsaturated substituents such as vinyl (**9f**) and phenyl (**9i**) groups. 2α-Hydroxyalkylvitamin D_3 analogues[4] would be synthesized *via* hydroboration of alkenes (**9f-h**). This series of analogues have been synthesized *via* stepwise elongation of 2α-side chain.[4] Utilizing this method, 2α-hydroxyalkyl series of analogues would be synthesized more efficiently in shorter steps. Although the introduction of bulky groups such as isopropyl group (**9e**) and trimethylsilylethynyl group (**9j**) gave poor results, this methodology should be convenient in synthesizing a variety of 2α-substituted



10 **9i** **11** **12**

Table 2. The reaction of PhMgCl toward epoxide (**10**).

Run	Equiv. of PhMgCl	Solvent	Additive (eq.)	Temp.	Time (h)	Yield (%)		
						9i	**11**	**12**
1	6	THF	none	reflux	17	-	-	20
2	10	toluene	none	80 °C	1.5	73	-	-
3	5	Et_2O - THF	CuI (0.3)	reflux	7.5	-	41	-

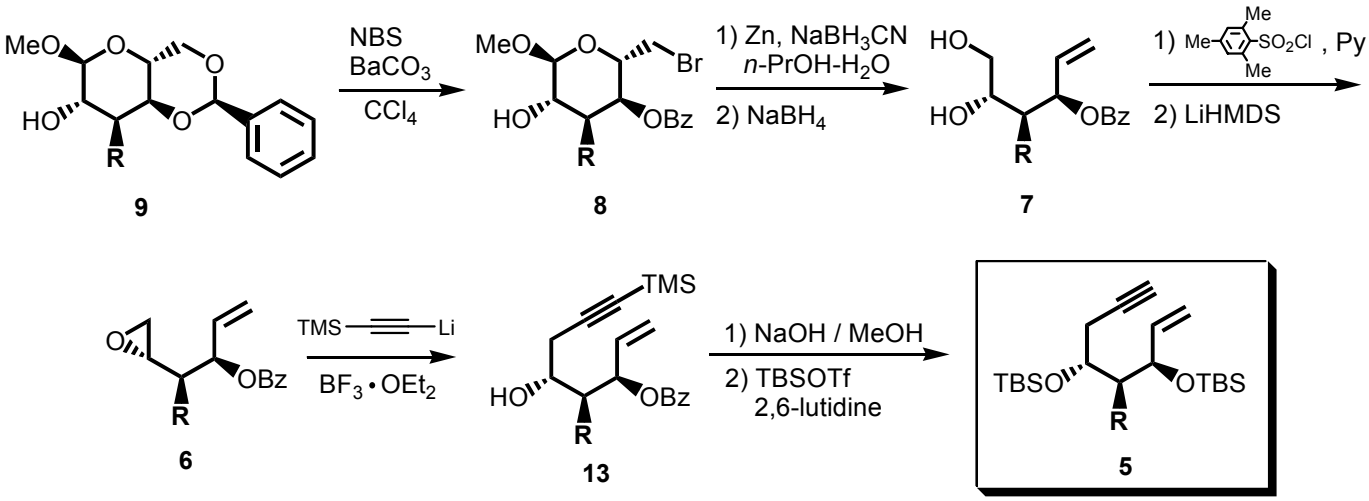
vitamin D_3 analogues.

This solvent effect is remarkable when PhMgCl was examined (Table 2). When PhMgCl was employed in THF, no desired product (**9i**) was obtained, and only isolable material was the regioisomer (**12**) in 20% yield (Table 2, Run 1). When this reaction was carried out in toluene at 80 °C, the desired product (**9i**) was obtained in 73% yield (Table 2, Run 2). Interestingly, when the reaction was carried out in ether in the presence of 0.3 equiv. of CuI at reflux, 3-epimer (**11**) was obtained in 41% yield (Table 2, Run 3). This product distribution was observed only in this PhMgCl case. The reason why this epimer (**11**) was formed in the presence of CuI is not clear, but the reaction would proceed *via* one-electron transfer, forming an intermediate having a radical center on C(3) of the sugar moiety.

In this epoxide ring opening reaction, the activation of epoxide through coordination of Lewis acidic metal ion should be required. In ethereal solvent, magnesium atom in Grignard reagent is believed to be complexed with solvent molecules having a donor atom.[13] In other word, coordination site(s) of magnesium ion would be occupied by the solvent molecule(s), which would prevent the magnesium ion from coordinating to the epoxide molecule, and it would lead to side reactions such as electron-transfer reaction. In contrast, in the less polar solvent such as toluene, there would be vacant coordination site(s) on the magnesium ion, and the magnesium ion would be more Lewis acidic and form a complex with the epoxide more easily. The preparations of organomagnesium compounds in hydrocarbon solvent have long been known,[14] the use in organic syntheses is, to the best of our knowledge, only limited. Canonne *et al*. reported that the reaction of Grignard reagents, prepared in benzene or toluene in the presence of 1 equiv. of ether or THF, with bulky ketones such as diisopropylketone was shown to increase the addition products against the reduction products.[15] Similar studies have been further investigated quite recently by Tuulmets *et al*.[12,16] Alexakis *et al*. reported that the Grignard reagents in toluene showed a strongly increased reactivity in the diastereoselective addition reaction of the hydrazone functionality.[17] We believe that the toluene solution of Grignard reagents is quite useful in organic synthesis in view of different, often higher reactivity in comparison with that of the ethereal solutions.

The epoxy ring opened compounds were able to lead to A-ring synthon enynes (**5**) through several steps as shown in Scheme 2, some of which were already reported.[4,5] Shortly, (**9**) was subjected to NBS in the presence of $BaCO_3$[18] to give bromide (**8**), which upon reductive ring opening reaction mediated by zinc dust[19] gave diol (**7**). Diol (**7**) was converted to epoxide (**6**), which was ethynylated by lithium acetylide in the presence of $BF_3{\cdot}OEt_2$ to give (**13**). Finally, the A-ring synthon enyne (**5**) was obtained from (**13**) by converting the protecting group of the hydroxy groups to the *tert*-butyldimethylsilyl groups.

In summary, we developed a synthesis of the A-ring synthon enynes which have several 2α-carbon substituents. In the synthesis, introduction of 2α-carbon substituents was performed *via* Grignard



Scheme 2. Synthesis of A-ring synthon (**5**) from epoxy ring opened compound (**9**).

reaction, in which the use of toluene as the reaction medium showed marked effect. Utilizing this improved methodology, several novel vitamin D_3 analogues, especially 2α-aromatic substituent series, would be synthesized. The biological activities of the novel analogues that could be prepared from the enynes synthesized this time will be reported in due course.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micromelting point apparatus without correction. Elemental analyses were conducted with a Perkin Elmer PE 2400II CHNS/O analyzer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were measured on JASCO FT/IR-8000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX-400 or AL-400 NMR (400 MHz) with Me_4Si as an internal standard. ^{13}C NMR spectra taken in $CDCl_3$ (δ 77.0) were referenced to the residual solvents. Low- and high-resolution MS spectra were recorded on a JEOL JMX-SX 102A spectrometer. Merck silica gel 60 (230-400 mesh) was employed for flash column chromatography. The ratios of solvent mixtures for chromatography are shown in volume/volume.

General Procedure for the Addition Reaction of Grignard Reagent with Epoxide (10)

Epoxide (**10**) was prepared according to the literature procedure.[9]

(1) Toluene solution of Grignard reagent prepared by the procedure of Tuulmets[12]: Mg turnings (2 equiv) were suspended in toluene and activated by the addition of small amounts of iodine. To the suspension was added THF (1 equiv. to chloride) and the mixture was warmed at 70 °C. Toluene solution of chloride was added dropwise for 2 h, followed by additional stirring at the same temperature overnight. The concentration of Grignard reagent formed was determined by titration with 2-butanol using 1,10-phenanthroline as an indicator. The solution of Grignard reagent (10 equiv to epoxide (**10**))

was transferred *via* syringe to another dried flask equipped with a reflux condenser, and to this solution was added epoxide (**10**). The mixture was heated under Ar at the temperature indicated in Table 1. After the completion of the reaction was confirmed by TLC, the mixture was cooled to rt. The reaction flask was immersed in an ice-water bath and saturated aqueous NH_4Cl solution was added cautiously to hydrolyze excess Grignard reagent. Aqueous layer was extracted with AcOEt and organic layers were combined, washed with brine, dried (Na_2SO_4) and concentrated. Purification by silica gel flash column chromatography (10% - 30% EtOAc in hexane) gave the product.

(2) Toluene solution of Grignard reagent by solvent displacement: To a dried flask equipped with a reflux condenser was added the THF solution of Grignard reagent (10 equiv to epoxide (**10**)), and the flask was connected to a vacuum line and the solvent was removed gently under reduced pressure. To the residue was added dry toluene so that the concentration of the Grignard reagent would be about 1 M. Epoxide (**10**) was added to the solution and the mixture was heated under Ar at the temperature indicated in Table 1. The same work-up procedure was employed as shown above.

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside (9a)

The spectral data were identical to that reported in the literature.[10a,b]

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-ethyl-α-D-altropyranoside (9b)

Colorless oil (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.4 Hz), 1.67-1.87 (2H, m), 2.06 (1H, m), 2.30 (1H, br s), 3.35 (3H, s), 3.76 (1H, dd, *J* = 10.1, 10.1 Hz), 3.92 (1H, br s), 3.97 (1H, ddd, *J* = 4.8, 10.1, 10.1 Hz), 4.08 (1H, dd, *J* = 5.4, 10.1 Hz), 4.26 (1H, dd, *J* = 4.8, 10.1 Hz), 4.55 (1H, s), 5.57 (1H, s), 7.31-7.44 (3H, m), 7.45-7.55 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 17.5, 44.8, 55.2, 59.5, 69.5, 69.7, 76.5, 101.9, 102.1, 126.0, 128.1, 128.8, 137.6. IR (neat) 3447, 2965, 2932, 2876, 1457, 1383, 1105, 1055, 752, 700 cm^{-1}. LRMS (EI) *m*/*z*: 294 (M^+), 262 (M^+–CH_3OH). HRMS (EI) calcd for $C_{16}H_{22}O_5$; 294.1467. Found 294.1474. $[\alpha]^{22}_D$ +106.5° (c 1.4, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-propyl-α-D-altropyranoside (9c)

Colorless oil (53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.4 Hz), 1.31-1.37 (1H, m), 1.43-1.48 (1H, m), 1.68-1.72 (2H, m), 2.12-2.14 (1H, m), 2.59 (1H, d, *J* = 5.3 Hz), 3.35 (3H, s), 3.76 (1H, dd, *J* = 10.0, 10.0 Hz), 3.88 (1H, br d, *J* = 3.8 Hz), 3.97 (1H, ddd, *J* = 5.5, 10.0, 10.0 Hz), 4.07 (1H, dd, *J* = 5.5, 10.0 Hz), 4.26 (1H, dd, *J* = 5.2, 10.0 Hz), 4.53 (1H, s), 5.56 (1H, s), 7.33-7.37 (3H, m), 7.46-7.48 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.5, 26.5, 42.6, 55.1, 59.4, 69.5, 70.1, 76.4, 101.9, 102.1, 126.1, 128.2, 128.9, 137.7. IR (neat) 3467, 2936, 1454, 1379, 1109, 1032, 754, 698 cm^{-1}. LRMS (EI) *m*/*z*: 308 (M^+), 276 (M^+–CH_3OH). HRMS (EI) calcd for $C_{17}H_{24}O_5$; 308.1624. Found 308.1621. $[\alpha]^{25}_D$ +94.2° (c 1.0, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-*C*-butyl-3-deoxy-α-D-altropyranoside (9d)

Colorless oil (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.0 Hz), 1.23-1.47 (4H, m), 1.73 (2H, dt, *J* = 7.3, 7.3 Hz), 2,14 (1H, q, *J* = 5.5 Hz), 3.36 (3H, s), 3.76 (1H, dd, *J* = 10.2, 10.2 Hz), 3.92 (1H, br s), 3.98 (1H, ddd, *J* = 5.0, 10.2, 10.2 Hz), 4.07 (1H, dd, *J* = 5.5, 10.2 Hz), 4.27 (1H, dd, *J* = 5.0, 10.2 Hz), 4.56 (1H, s), 5.57 (1H, s), 7.31-7.40 (3H, m), 7.44-7.51 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.0, 24.1, 30.7, 43.0, 55.2, 59.5, 69.6, 70.3, 76.5, 101.9, 102.2, 126.0, 128.1, 128.8, 137.6. IR (neat) 3447, 2955, 2932, 2872, 1456, 1379, 1109, 1055, 752, 698 cm^{-1}. LRMS (EI) *m*/*z*: 322 (M^+), 290 (M^+–CH_3OH). HRMS (EI) calcd for $C_{18}H_{26}O_5$; 322.1780. Found 322.1792. $[\alpha]^{22}_D$ +78.5° (c 2.1, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-(1-methylethyl)-α-D-altropyranoside (9e)

Colorless oil (12% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.6 Hz), 1.14 (3H, d, *J* = 6.6 Hz), 1.80 (1H, d, *J* = 6.4 Hz), 1.95 (1H, ddd, *J* = 2.7, 5.5, 9.7 Hz), 2.27 (1H, ddq, *J* = 6.6, 9.7, 6.6 Hz), 3.38 (3H, s), 3.75 (1H, dd, *J* = 10.2, 10.2 Hz), 4.06 (1H, ddd, *J* = 5.3, 10.2, 10.2 Hz), 4.13 (1H, m), 4.23 (1H, dd, *J* = 5.3, 10.2 Hz), 4.29 (1H, dd, *J* = 5.5, 10.2 Hz), 4.56 (1H, s), 5.51 (1H, s), 7.33-7.39 (3H, m), 7.45-7.49 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.7, 25.7, 49.2, 55.1, 59.7, 69.7, 69.9, 78.0, 101.6, 102.4, 126.1, 128.1, 128.8, 137.8. IR (neat) 3411, 2959, 2872, 1455, 1381, 1103, 1055, 1036, 974 cm^{-1}. LRMS (EI) *m*/*z*: 308 (M^+), 276 (M^+–CH_3OH). HRMS (EI) calcd for $C_{17}H_{24}O_5$; 308.1624. Found 308.1624. $[\alpha]^{23}_D$ +73.7° (c 2.3, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-ethenyl-α-D-altropyranoside (9f)

Colorless needles (64% yield). mp 123.5-124.5 °C (hexane-ether). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.76; H, 6.97. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (1H, d, *J* = 6.0 Hz), 2.98 (1H, m), 3.41 (3H, s), 3.79 (1H, m), 3.91 (1H, ddd, *J* = 0.9, 2.3, 6.0 Hz), 4.04-4.12 (1H, m), 4.26-4.32 (1H, m), 4.63 (1H, s), 5.19 (1H, dd, *J* = 1.6, 10.4 Hz), 5.24 (1H, ddd, *J* = 1.0, 1.6, 17.0 Hz), 5.59 (1H, s), 6.23 (1H, ddd, *J* = 9.2, 10.4, 17.0 Hz), 7.31-7.38 (3H, m), 7.43-7.49 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.0, 55.3, 60.0, 69.5, 73.1, 75.5, 101.8, 102.0, 118.6, 126.2, 128.2, 128.9, 133.4, 137.5. IR (KBr) 3459, 2923, 1640, 1460, 1410, 1071, 916 cm^{-1}. LRMS (EI) *m*/*z*: 292 (M^+), 260 (M^+–CH_3OH). HRMS (EI) calcd for $C_{16}H_{20}O_5$; 292.1311. Found 292.1312. $[\alpha]^{23}_D$ +76.9° (c 0.9, $CHCl_3$).

Methyl 3-*C*-Allyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (9g)

The spectral data were identical to that reported in the literature.[10d]

Methyl 4,6-*O*-Benzylidene-3-*C*-(3-butenyl)- 3-deoxy-α-D-altropyranoside (9h)

Colorless oil (49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.94 (3H, m), 2.08-2.27 (3H, m), 3.38

(3H, s), 3.77 (1H, dd, *J* = 10.0, 10.0 Hz), 3.95 (1H, br d, *J* = 4.4 Hz), 4.00 (1H, ddd, *J* = 5.0, 10.0, 10.0 Hz), 4.10 (1H, dd, *J* = 5.4, 10.0 Hz), 4.28 (1H, dd, *J* = 5.0, 10.0 Hz), 4.59 (1H, s), 4.96-5.00 (1H, m), 5.00-5.08 (1H, m), 5.58 (1H, s), 5.82 (1H, ddt, *J* = 10.3, 17.0, 6.7 Hz), 7.32-7.40 (3H, m), 7.44-7.52 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 32.6, 42.2, 55.3, 59.6, 69.6, 70.4, 76.4, 102.0, 102.1, 114.7, 126.1, 128.2, 128.9. IR (neat) 3451, 2916, 1640, 1105 cm^{-1}. LRMS (EI) *m*/*z*: 320 (M^+), 288 (M^+–CH_3OH). HRMS (EI) calcd for $C_{18}H_{24}O_5$; 320.1624. Found 320.1622. $[\alpha]^{26}_D$ +78.4° (c 1.0, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-trimethylsilylethynyl-α-D-altropyranoside (9j)

Colorless oil (19% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (9H, s), 1.97 (1H, d, *J* = 6.0 Hz), 3.25 (1H, dd, *J* = 2.2, 5.2 Hz), 3.40 (3H, s), 3.79 (1H, m), 3.98 (1H, dd, *J* = 5.2, 9.0 Hz), 4.14 (1H, m), 4.29 (2H, m), 4.62 (1H, s), 5.59 (1H, s), 7.34-7.38 (3H, m), 7.49-7.53 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.00, 36.8, 54.8, 60.3, 69.0, 71.1, 73.9, 88.8, 101.4, 102.1, 126.4, 128.2, 129.1, 137.5. IR (neat) 3445, 2957, 2932, 2176, 1738, 1250 cm^{-1}. LRMS (EI) *m*/*z*: 362 (M^+), 330 (M^+–CH_3OH). HRMS (EI) calcd for $C_{19}H_{25}O_5Si$; 362.1550. Found 362.1549. $[\alpha]^{19}_D$ +139.6° (c 2.6, $CHCl_3$).

Methyl 3-*C*-Benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (9k)

Colorless oil (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (1H, br s), 2.42 (1H, m), 2.98-3.11 (2H, m), 3.44 (3H, s), 3.73 (1H, br d, *J* = 2.8 Hz), 3.78 (1H, dd, *J* = 10.2, 10.2 Hz), 4.07 (1H, ddd, *J* = 5.0, 10.2, 10.2 Hz), 4.15 (1H, dd, *J* = 5.0, 10.2 Hz), 4.29 (1H, dd, *J* = 5.0, 10.2 Hz), 4.54 (1H, s), 5.60 (1H, s), 7.14-7.21 (1H, m), 7.22-7.29 (4H, m), 7.32-7.40 (3H, m), 7.47-7.52 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 44.8, 55.3, 59.5, 68.4, 69.5, 76.1, 101.9, 102.4, 125.8, 126.2, 128.1, 128.2, 128.9, 129.5, 137.6, 140.6. IR (neat) 3443, 3068, 3030, 2910, 2872, 1130, 1099, 1062, 1041 cm^{-1}. LRMS (EI) *m*/*z*: 356 (M^+), 324 (M^+–CH_3OH). HRMS (EI) calcd for $C_{21}H_{24}O_5$; 356.1624. Found 356.1602. $[\alpha]^{26}_D$ +66.4° (c 1.0, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-(2-phenylethyl)-α-D-altropyranoside (9l)

Colorless oil (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96-2.30 (4H, m), 2.66 (1H, ddd, *J* = 6.4, 10.0, 13.5 Hz), 2.76 (1H, ddd, *J* = 6.1, 10.3, 13.6 Hz), 3.36 (3H, s), 3.76 (1H, dd, *J* = 10.4, 10.4 Hz), 3.94 (1H, br s), 4.00 (1H, ddd, *J* = 5.0, 9.9, 9.9 Hz), 4.15 (1H, dd, *J* = 5.4, 9.9 Hz), 4.27 (1H, dd, *J* = 5.0, 10.4 Hz), 4.56 (1H, s), 5.56 (1H, s), 7.14-7.22 (3H, m), 7.24-7.30 (2H, m), 7.32-7.39 (3H, m), 7.45-7.49 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 34.7, 42.2, 55.2, 59.5, 69.5, 70.4, 76.4, 102.0, 102.0, 125.6, 126.0, 128.1, 128.1, 128.3, 128.8, 137.5, 142.2. IR (neat) 3451, 2923, 2870, 1455, 1132 cm^{-1}. LRMS (EI) *m*/*z*: 370 (M^+), 352 (M^+–H_2O), 338 (M^+–CH_3OH). HRMS (EI) calcd for $C_{22}H_{26}O_5$; 370.1780.

Found 370.1774. $[\alpha]^{22}_{D}$ +80.3° (c 0.6, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-phenyl-α-D-altropyraonoside (9i)

Colorless needles (73% yield). mp 164.5-165.0 °C (hexane-AcOEt). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.02; H, 6.63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (1H, d, *J* = 5.6 Hz), 3.37 (3H, s), 3.65 (1H, dd, *J* = 2.3, 5.9 Hz), 3.79 (1H, t, *J* = 9.5 Hz), 4.24- 4.35 (4H, m), 4.69 (1H, d, *J* = 14.7 Hz), 5.60 (1H, s), 7.21-7.24 (1H, m), 7.28-7.35 (7H, m), 7.61 (2H, d, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.5, 55.2, 59.8, 69.8, 73.3, 75.8, 101.9, 102.0, 126.2, 127.6, 128.0, 128.8, 129.9, 137.3. IR (neat) 3424, 1406, 1364, 1254, 1192, 756, 704 cm^{-1}. LRMS (EI) *m*/*z*: 342 (M^+), 310 (M^+–CH_3OH). HRMS (EI) calcd for $C_{20}H_{22}O_5$; 342.1467. Found 342.1477. $[\alpha]^{19}_{D}$ +148.1° (c 0.9, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucopyranoside (12)

Epoxide (**10**) (2.50 g, 9.46 mmol) was added to the THF solution of PhMgCl (2.0 M, 28 mL) and the mixture was heated under Ar at reflux for 17 h. The reaction mixture was cooled to rt, and 0.5 M aqueous HCl solution (200 mL) was added slowly. The mixture was extracted with AcOEt (500 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (200 mL), water (200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated. Purification by silica gel flash column chromatography (hexane-AcOEt (9:1 to 4:1)) gave **12** (645 mg, 20%) as colorless needles. mp 199.5-201.0 °C (hexane-ether). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.25; H, 6.45. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (1H, s), 3.09 (1H, dd, *J* = 3.8, 10.5 Hz), 3.28 (3H, s), 3.69 (1H, dd, *J* = 9.4, 9.4 Hz), 3.84 (1H, dd, *J* = 9.9, 9.9 Hz), 4.02 (1H, ddd, *J* = 4.9, 9.9, 9.9 Hz), 4.33 (1H, dd, *J* = 4.9, 9.9 Hz), 4.53 (1H, dd, *J* = 9.9, 9.9 Hz), 4.71 (1H, d, *J* = 3.9 Hz), 5.62 (1H, s), 7.28-7.30 (1H, m), 7.34-7.40 (7H, m), 7.52-7.54 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.1, 55.4, 62.7, 68.8, 69.2, 83.6, 101.9, 102.1, 126.3, 127.4, 128.3, 128.4, 129.1, 129.6, 135.8, 137.2. IR (KBr) 3484, 2919, 1499, 1460, 1379, 1078, 1034, 972, 760, 700 cm^{-1}. LRMS (EI) *m*/*z*: 342 (M^+). HRMS (EI) calcd for $C_{20}H_{22}O_5$; 342.1467. Found 342.1468. $[\alpha]^{25}_{D}$ +112.7° (c 0.8, $CHCl_3$).

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-*C*-phenyl-α-D-mannopyranoside (11)

Under Ar, to a mixture of epoxide (**10**) (2.87 g, 10.9 mmol) and CuI (620 mg, 3.56 mmol) in ether (109 mL) was added THF solution of PhMgCl (2.0 M, 27 mL), and the mixture was stirred at reflux for 7.5 h, and then at rt for 16 h. The reaction was quenched by slowly adding saturated aqueous NH_4Cl solution (150 mL), and the mixture was extracted with AcOEt (500 mL). The organic layer was washed with saturated aqueous NH_4Cl solution (150 mL), water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated. Purification by silica gel flash column chromatography (hexane-AcOEt (9:1 to 3:1)) gave

11 (1.51 g, 41%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (1H, d, *J* = 4.0 Hz), 3.46 (1H, dd, *J* = 2.8, 11.6 Hz), 3.48 (3H, s), 3.91 (1H, ddd, *J* = 1.4, 2.8, 4.0 Hz), 3.93 (1H, dd, *J* = 10.3, 10.3 Hz), 4.03 (1H, ddd, *J* = 4.5, 9.1, 10.3 Hz), 4.33 (1H, dd, *J* = 4.5, 10.3 Hz), 4.43 (1H, dd, *J* = 9.1, 11.6 Hz), 4.74 (1H, d, *J* = 1.4 Hz), 5.64 (1H, s), 7.23-7.32 (4H, m), 7.33-7.40 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.0, 55.0, 64.8, 69.3, 73.0, 75.1, 100.5, 101.8, 125.9, 127.1, 128.0, 128.6, 128.7, 128.7, 136.9, 137.4. IR (neat) 3449, 2922, 1406, 1364, 1254, 1192, 756, 704 cm^{-1}. LRMS (EI) *m*/*z*: 342 (M^+). HRMS (EI) calcd for $C_{20}H_{22}O_5$; 342.1467. Found 342.1440. $[\alpha]^{26}_D$ –11.5° (c 0.8, $CHCl_3$).

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