Novel Synthesis of Chiral 5-Cyanomethyl-3,4-dihydroxy-2-iodomethyltetrahydrofuran from 3-Diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazolines *via* Iodoetheration Reaction

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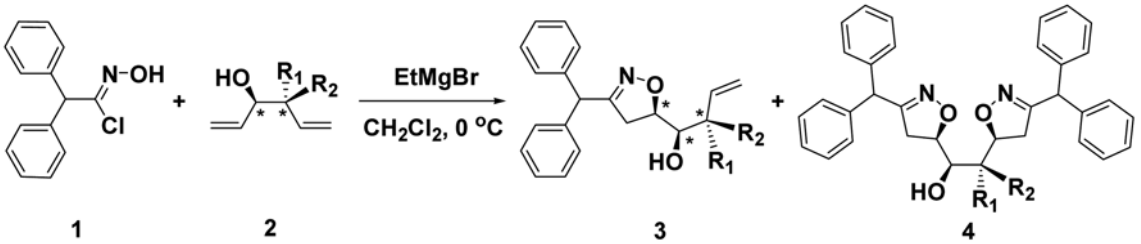
3-Butenyl-isoxazolines were known as good precursors for the syntheses of new types of 5-cyanomethyl-2-iodomethyltetrahydrofuran derivatives. 5-Cyanomethyl-2-iodomethyltetrahydrofuran was synthesized from isoxazolines by electrophilic iodoetheration using iodine or iodine monochloride,[1] which was the first example of electrophilic cleavage of isoxazoline ring by iodoetheration reaction. From the combination of this reaction and diastereoselective formation of isoxazoline in the support of magnesium chelation effect,[2] we synthesized 5-cyanomethyl-3-hydroxy-2-iodomethyltetrahydrofuran from *syn*-5-(1-hydroxy-3-butenyl)isoxazolines with diastereoselctivity.[3] We expected better diastereoselectivity could be achieved by adding one more hydroxyl group at the 2-position of butenyl group in isoxazoline close to the reaction center. First, we prepared chiral 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazolines (**3**)[4] by 1,3-dipolar cycloaddition reaction of diphenylacetohydroximoyl chloride (**1**) with (*3R,4R*)-1,5-hexadiene-3,4-diol[5] (**2a**) and *meso*-1,5-hexadiene-3,4-diol[6] (**2b**) by the aid of magnesium chelation effect, and after *O*-protection of isoxazolines, iodoetheration was examined to synthesize chiral 5-cyanomethyl-3,4-dihydroxy-2-iodomethyltetrahydrofurans **6**.

Diphenylacetohydroximoyl chloride (**1**), precursor of diphenylacetonitrile oxide was reacted with (*3R,4R*)-1,5-hexadiene-3,4-diol (**2a**) in the presence of ethylmagnesium bromide as shown in Scheme 1. The more ethylmagnesium bromide was used, the more diadduct **4a**[7] was formed in this reaction. When 2.2 equiv of ethylmagnesium bromide was used, the best result of **3a** was obtained (Entry 3 in Scheme 1). In case of *meso*-1,5-hexadiene-3,4-diol (**2b**), however, only 47% of **3b** was obtained (Entry 4 in Scheme 1). The isolated **3a** was a single stereoisomer that thought to be *syn*-isomer of 5-position and a-position due to the magnesium chelation effect, but **3b** must be a racemic mixture of *syn*-isomers according to which double bond was reacted.

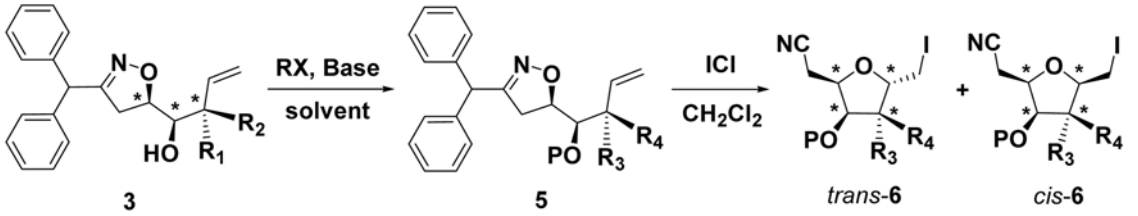
The hydroxyl groups of **3a** were protected with TBDMS and MOM group, and then reacted with iodine monochloride in dichloromethane to give 5-cyanomethyl-3,4-dihydroxy-2-iodomethyltetrahydrofurans **6** in moderate yields as shown in Scheme 2. **5a** (P=TBDMS) afforded only *trans*-**6a** (P=TBDMS) without any trace of *cis*-**6a** (P=TBDMS), while **5a** (P=MOM) afforded a mixture of two isomers (*trans*/*cis*, 5/1). As we expected, the bulkier TBDMS group showed better diastereoselectivity in iodoetheration. We examined the energy minimizations of *trans*-



Entry	**2**	**EtMgBr** (eq.)	Yield (%)[a] (**3**)	**3** : **4**[b]
1	**2a** (R_1=OH, R_2=H)	6.0	44 (**3a**)	2 : 1
2	**2a** (R_1=OH, R_2=H)	3.0	65 (**3a**)	5 : 1
3	**2a** (R_1=OH, R_2=H)	2.2	76 (**3a**)	9 : 1
4	**2b** (R_1=H, R_2=OH)	2.2	47 (**3b**)	3 : 1

[a]Isolated yields. [b]Isolated ratio.

Scheme 1



Entry	Reactant	5	Yield (%) of 6[a]	*trans* : *cis*
1	**3a** (R_1=OH, R_2=H)	**5a** (R_3=OP, R_4=H, P=TBDMS)	69	*trans* only
2	**3a** (R_1=OH, R_2=H)	**5a** (R_3=OP, R_4=H, P=MOM)	60	5 : 1
3	**3b** (R_1=H, R_2=OH)	**5b** (R_3=H, R_4=OP, P=TBDMS)	68	1 : 11

[a]Isolated yields (*trans*-**6** + *cis*-**6**).

Scheme 2

6a and *cis*-**6a** with other protection group by MM2. TBDMS-Protected **6a** showed about 1 kcal difference between *trans*-**6a** and *cis*-**6a**, and MOM-protected **6a** showed almost no difference between two isomers. Interestingly, **3b** derived from *meso*-1,5-hexadiene-3,4-diol (**2b**) was protected with TBDMS group and the iodoetheration of **5b** (P=TBDMS) with iodine monochloride afforded 1 : 11 mixture of *trans*-**6b** (P=TBDMS) and *cis*-**6b** (P=TBDMS). In the MM2 calculation, *cis*-**6b** (P=TBDMS) was more stable by 1.6 kcal than *trans*-**6b** (P=TBDMS). The individual five isomers of **6** such as *trans*-**6a** (P=TBDMS), *trans*-**6a** (P=MOM), *cis*-**6a** (P=MOM), *trans*-**6b** (P=TBDMS), and *cis*-**6b** (P=TBDMS) were separated, and the assignments of each proton and the relative stereochemistry of each isomer were confirmed by COSY and NOE experiment. For example, when methylene protons attached to iodine in *trans*-**6b** (P=TBDMS) appeared at 3.22 ppm was irradiated, protons on 4,5-positions (3.93-4.04 ppm) and 2,3-positions (4.28-4.34 ppm) showed 9.52% and 2.13% NOE respectively. However, when methylene protons attached to iodine in *cis*-**6b** (P=TBDMS) appeared at 3.28 ppm was irradiated, only protons on 4,5-positions (4.17-4.23 ppm) showed 5.45% NOE with 0.75% NOE of methylene attached to CN group. The weak NOE between two methylene groups was thought to be a critical evidence of *cis*-form. The configurations of other tetrahydrofurans **6** were confirmed by the same experiments.

As a conclusion, 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazoline was prepared diastereoselectively by 1,3-dipolar cycloaddition reaction of diphenylacetonitrile oxide with chiral 1,5-hexadiene-3,4-diol in the support of magnesium chelation effect.

Iodoetheration of *O*-protected 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazolines afforded the corresponding 5-cyanomethyl-3,4-di(*O*-protected-hydroxy)-2-iodomethyltetrahydrofurans with good diastereoselectivity. From these reactions, new series of highly substituted chiral tetrahydrofurans could be synthesized.

Experimental Section

General. Unless otherwise specified, all reagents were purchased from commercial sources and were used without further purification. ^{1}H NMR spectra were obtained with a Bruker AMX-500. All chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants are given in Hz. IR spectra were taken by a Sense ATR FT-IR spectrophotometer. MS spectra were recorded by EI method and HRMS spectra were measured on a Jeol JMX-DX 303 mass spectrometer. Chromatographic separations were carried out on a silica gel column (Merck silica gel 60).

Typical procedure of 1,3-dipolar cycloaddition (Entry 3 in Scheme 1): To a solution of (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**2a**, 114 mg, 1.0 mmol) in dichloromethane (20 mL) was added ethylmagnesium bromide (3.0 M solution in diethyl ether, 0.74 mL, 2.2 mmol) at 0 °C and the reaction mixture was stirred for 30 min at this temperature. Diphenylacetohydroximoyl chloride (246 mg, 1.0 mmol) in dichloromethane (5 mL) was added slowly by a syringe at 0 °C. The reaction mixture was stirred for 2 h at rt and saturated ammonium chloride solution (10 mL) was poured into the reaction mixture. The organic layer was extracted with dichloromethane (50 mL), washed with brine, dried over $MgSO_4$, and concentrated by a rotary evaporator. The residue was separated with silica gel chromatography (*n*-hexane/ethyl acetate, 2/1) to give **3a** (246 mg, 76%) as a white solid.

3a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (d, 1H, -OH, J = 7.7 Hz), 2.61 (d, H, -OH, J = 3.4 Hz), 2.98 (dd, 1H, J = 10.7, 16.9 Hz), 3.02 (dd, 1H, J = 8.1, 16.9 Hz), 3.38-3.42 (m, 1H), 4.21-4.24 (m, 1H), 4.71 (ddd, 1H, J = 10.7, 8.1, 2.9 Hz), 5.15 (s, 1H), 5.23-5.26 (m, 2H), 5.81-5.94 (m, 1H), 7.22-7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.07, 50.33, 73.81, 74.92, 80.68, 117.87, 127.25, 127.31, 128.63, 128.70, 128.71, 128.83, 136.51, 139.35, 160.96; IR (neat) 3399, 3028, 2921, 1599, 1494, 1452, 1324, 1079, 994, 905 cm^{-1}; HRMS calcd for $C_{20}H_{21}NO_3$ 323.152144, found 323.151957.

3b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (d, 1H, -OH, J = 7.7 Hz), 2.61 (d, H, -OH, J = 8.1 Hz), 2.96 (dd, 1H, J = 10.5, 16.9 Hz), 3.05 (dd, 1H, J = 8.5, 16.9 Hz), 3.44-3.53 (m, 1H), 4.21-4.31 (m, 1H), 4.82 (ddd, 1H, J = 10.5, 8.5, 2.4 Hz), 5.16 (s, 1H), 5.24-5.42 (m, 2H), 5.85-6.02 (m, 1H), 7.22-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.24, 50.35,

74.24, 74.35, 79.90, 117.05, 127.25, 127.30, 128.63, 128.70, 128.76, 128.81, 136.74, 139.34, 139.36, 161.15; IR (neat) 3410, 3028, 2923, 1494, 1452, 1320, 1080, 998 cm^{-1}; HRMS calcd for $C_{20}H_{21}NO_3$ 323.152144, found 323.151871.

Protection of hydroxyl group: The protection of **3** with TBDMS or MOM group was carried out in good yields by general procedure.

5a (P=TBDMS): ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.78 (s, 9H), 0.88 (s, 9H), 2.69 (dd, 1H, J = 10.2, 17.5 Hz), 2.91 (dd, 1H, J = 10.6, 17.5 Hz), 3.63-3.66 (m, 1H), 4.16-4.18 (m, 1H), 4.38 (dd, 1H, J = 10.2, 18.6 Hz), 5.10-5.21 (m, 2H), 5.14 (s, 1H), 5.99-6.05 (m, 1H), 7.20-7.31 (m, 10H); MS (FAB) 552.2 (M^+).

5a (P=MOM): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (dd, 2H, J = 10.6, 3.7 Hz), 3.27 (s, 3H), 3.29 (s, 3H), 3.64 (t, 1H, J = 5.3 Hz), 4.50-4.64 (m, 1H), 4.51 (d, 1H, J = 6.7 Hz), 4.61 (d, 1H, J = 6.7 Hz), 4.71-4.84 (m, 1H), 4.81 (s, 2H), 5.18 (s, 1H), 5.28-5.37 (m, 2H), 5.73-5.91 (m, 1H), 7.23-7.41 (m, 10H).

5b (P=TBDMS): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.0 (s, 3H), 0.04 (s, 3H), 0.09 (s, 6H), 0.87 (s, 9H), 0.89 (s, 9H), 2.73 (dd, 1H, J = 10.1, 16.9 Hz), 2.79 (dd, 1H, J = 10.1, 16.9 Hz), 3.65-3.70 (m, 1H), 4.05-4.11 (m, 1H), 4.38 (ddd, 1H, J = 7.3, 10.1, 10.1 Hz), 5.02-5.14 (m, 2H), 5.14 (s, 1H), 5.74-5.87 (m, 1H), 7.21-7.39 (m, 10H).

Typical procedure of iodoetheration (Entry 1 in Scheme 2): To a solution of 3-diphenylmethyl-5-[1,2-di(*t*-butyldimethylsilyloxy)-3-butenyl]isoxazoline, **5a** (P=TBDMS) (552 mg, 1.0 mmol) in dichloromethane (15 mL) was slowly added iodine monochloride (2.0 M in dichloromethane 0.65 mL, 1.3 mmol) at 0 °C and stirred for 3 h at rt. The reaction mixture was washed with aqueous 20% sodium bisulfite solution (10 mL × 2), dried over $MgSO_4$, and concentrated to give an oil. The oily residue was purified by flash column chromatography (*n*-hexane/ethyl acetate, 5/1) to afford ***trans*-6a** (P=TBDMS) (353 mg) as pale yellow oils.

***trans*-6a** (P=TBDMS): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 9H), 0.20 (s, 3H), 0.75 (s, 9H), 0.77 (s, 9H), 2.55 (dd, 1H, J = 8.0, 16.2 Hz), 2.62 (dd, 1H, J = 6.2, 16.2 Hz), 3.20 (d, 2H, J = 10.4 Hz), 4.03-4.06 (m, 1H), 4.11-4.13 (m, 1H), 4.34-4.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.6, −4.4, −4.1, 0.9, 18.0, 18.3, 25.6, 25.7, 77.2, 77.7, 77.9, 78.4, 82.6, 87.7, 117.2; IR (neat) 2952, 2922, 2858, 2253, 1471, 1259, 1116, 1065 cm^{-1}; MS *m/z* 512 (M^+), 455, 398, 241, 171.

***trans*-6a** (P=MOM): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (d, 2H, J = 11.8 Hz), 3.16-3.29 (m, 2H), 3.40 (s, 3H), 3.41 (s, 3H), 4.20-4.22 (m, 1H), 4.26-4.28 (m, 1H), 4.38-4.50 (m, 2H), 4.71 (dd, 2H, J = 11.4, 7.6 Hz), 4.74 (dd, 2H, J = 11.5, 4.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.3, 56.3, 56.4, 76.8, 77.1, 80.5, 80.8, 81.6, 96.8, 97.4, 117.1; IR (neat) 2922, 2851, 2249, 1466, 1151, 1021 cm^{-1}; MS *m/z* 371 (M^+), 310, 248, 214, 198, 182.

***cis*-6a** (P=MOM): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (d, 2H, J = 7.0 Hz), 3.22-3.33 (m, 2H), 3.44 (s, 6H), 4.22-4.25 (m, 1H), 4.28-4.31 (m, 1H), 4.40-4.52 (m, 2H), 4.70-4.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.3, 56.3, 56.4, 76.8, 77.2, 80.5, 80.8, 81.6, 96.8, 97.4, 117.1; IR (neat) 2926, 2852, 2249, 1465, 1150, 1022 cm^{-1}; MS *m/z* 371 (M^+), 310, 248, 198, 182.

***trans*-6b** (P=TBDMS): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 1.14 (s, 6H), 0.15 (s, 3H), 0.91 (s, 9H), 0.93 (s, 9H), 2.68 (dd, 1H, J = 17.3, 4.8 Hz), 2.84 (dd, 1H, J = 17.3, 7.6 Hz), 3.22 (d, 2H, J = 5.2 Hz), 3.93-4.04 (m, 2H), 4.28-4.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.8, −4.4, −4.3, −4.2, 7.5, 18.0, 18.3, 19.8, 25.9, 26.0, 72.9, 76.5, 76.9, 83.4, 118.3; IR (neat) 2929, 2857, 2250, 1471, 1253, 1161, 1051 cm^{-1}; MS *m/z* 512 (M^+), 454, 398, 270, 241, 171.

***cis*-6b** (P=TBDMS): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 12H), 0.94 (s, 18H), 2.70-2.76 (m, 2H), 3.28 (d, 2H, J = 6.0 Hz), 4.17-4.23 (m, 2H), 4.26-4.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.8, −4.6, −4.5, −4.1, 3.6, 18.4, 18.5, 20.8, 26.1, 26.2, 73.9, 74.3, 76.0, 81.9, 118.3; IR (neat) 2929, 2858, 2250, 1471, 1254, 1164, 1054 cm^{-1}; HRMS calcd for $C_{19}H_{38}NO_3Si_2I$ 511.143503, found 511.141785.

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