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Regioselective fluorination in synthesis of deoxyfluoro quercitols from D-(−)-quinic acid

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ABSTRACT

A facile synthesis of six new deoxyfluoro querciotls from D-(−)-quinic acid is described. The key steps involve the regioselective fluorination as well as highly stereoselective dihydroxylation. These synthetic deoxyfluoro quercitols are considered as potential glycosidase inhibitors.

1. Introduction

Fluorine-containing compounds are widely applied in material[1] and medicinal chemistry.[1a,2] Evidences have proved that the fluorine substituents drugs can influence the chemical, physical, and pharmaceutical properties of molecules.[3] The fluorine atom has comparable size and higher electronegativity than oxygen atom. This more electrostatic character of the C–F bond leads to high polarization (large dipole moment) change.[4] Also the C–F bond is a weak hydrogen bonding donor and acceptor.[4] This is meaningful to medicinal chemists for drugs' designs because the fluorine substituents may enhance the drug performance and reduce side effects.[2,5] Since the fluorinated molecules are not naturally occurring, however, the demands of fluorinated drugs are increasing dramatically during the past few years.[2a,3] On the other hand, sugars contained fluorine atom(s) and their analogues are not unusual.[6] One of the most important sugars' analogues is *myo*-inositol in which derivatives, phosphatidylinositols, were recognized as secondary messengers for related cellular modulation.[7] In order to probe the phosphatidylinositol pathway mechanism, a number of deoxyfluoro *myo*-inositols or their phosphatidyl derivatives were synthesized.[8] In addition, analogues of inositols, so called quercitols (the generic term for cyclohexanepentols or deoxyinositols) are considered as potential glycosidase inhibitors.[9] We rationalize that the fluorinated quercitols may play the similar roles as *myo*-inositol analogues. However, the syntheses of quercitols containing fluorine atom(s) and their phosphated derivatives are rare.[8a,10]

We have experienced in syntheses of several candidates of glycosidase inhibitors, such as azasugars (azepanes)[11] and thiosugars (thiepanes),[12] from D-(−)-quinic acid. We realized that we could use D-(−)-quinic acid as starting material to synthesize a series of deoxyfluoro quercitols. The advantage of our synthesis is to utilize the rigid conformation of D-(−)-quinic acid derivatives to selectively fluorinate the designated configuration of hydroxy group.

2. Results and discussion

When compound **1**[11c] was treated with diethylaminosulfur trifluoride (DAST, 2 equiv),[13] the retention configuration product compound **3**[10a,14] was isolated in 8% yield and an inseparable mixture of **4**[10a,15] and **5**[16] was obtained in 87% combined yield (ratio of **4**/**5** was about 1.72:1 by NMR) (Scheme 1). When compound **3** was subjected to dihydroxylation under $RuCl_3/NaIO_4/NaH_2PO_4$, compound **6** was isolated as a single product in 40% yield. The oxidation occurred at the less hindered side, which was *anti* relationship to the cyclohexylidene group.[17,18] While OsO_4/NMO[10a] was used as oxidants instead, the higher yield of **6** (71%) was received. We observed OsO_4/NMO is a more reliable method for dihydroxylation in these cases than $RuCl_3/NaIO_4/NaH_2PO_4$ because the later gave more unidentified polar products. The mixture of **4** and **5** was dihydroxylated (OsO_4/NMO) to afford a mixture of diol products in about 74% yield, which could not be separated by flash

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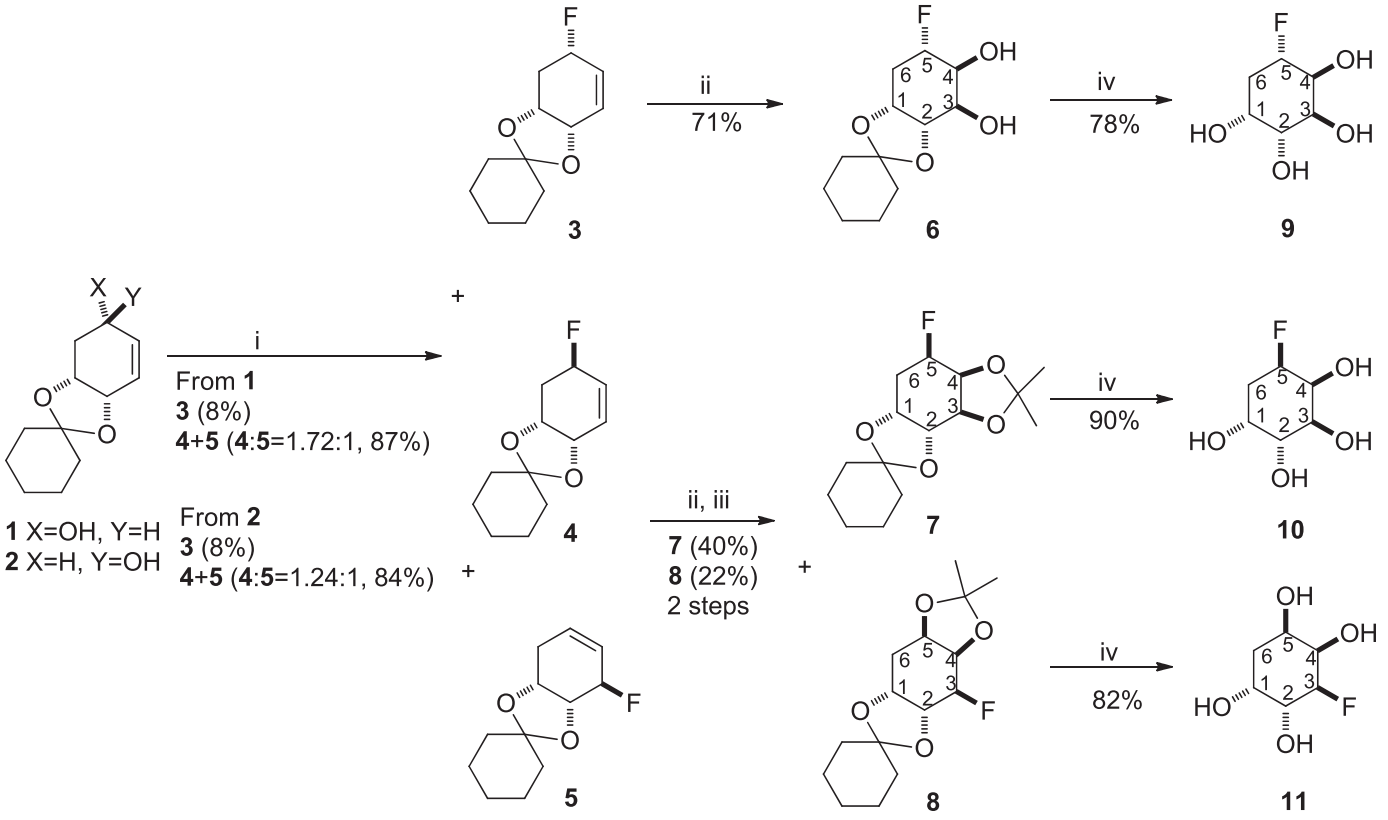


Reagents and conditions: (i) DAST (2 equiv.), CH_2Cl_2, 0 °C to rt.; (ii) 5 mol% OsO_4/NMO/acetone/H_2O; (iii) 2,2-dimethoxypropane, CH_2Cl_2, PPTS; (iv) 80% TFA (aq)

Scheme 1. Regioselective syntheses of deoxyfluoro quercitols **9**–**11**.

column chromatography. Therefore, the above mixture was further treated with 2,2-dimethoxypropane with catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) to yield **7**[19] (40%) and **8**[20] (22%) (two steps), respectively. This protecting step is not only to allow us for easy separation of the stereoisomers **7** and **8** but also to confirm their structures. No other possible diastereoisomers **12**–**14** were isolated from reaction might be due to small quantities (Fig. 1). In order for comparison, compound **2**,[11c] the epimer of **1**, was fluorinated by the same manner as **1** to yield **3** in 8%. Again, a mixture of **4** and **5** from **2** was obtained with almost equivalent yield in 84% (ratio of **4**/**5** was about 1.24:1 by NMR) comparing from **1**. Therefore, compound **4** was obtained as the major product no matter starting from **1** or **2**.

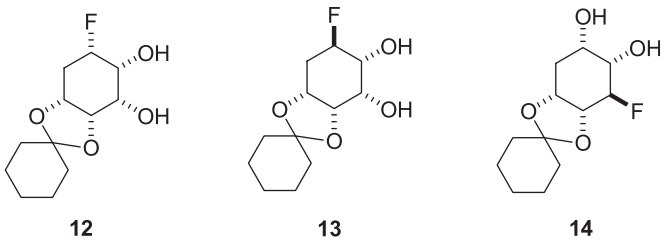
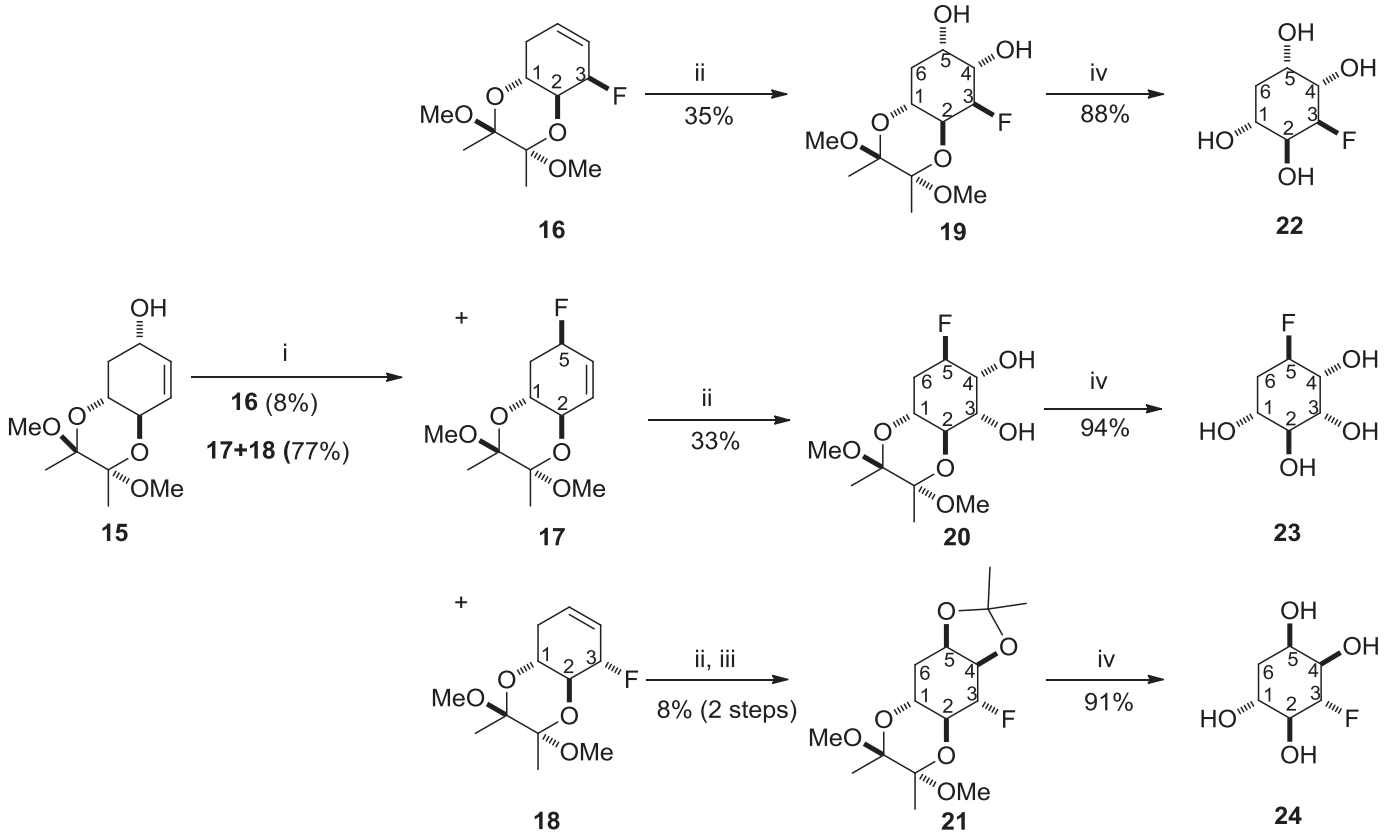


Fig. 1. Possible stereoisomers not isolated from reaction.

A TMB protected **15**[18] was fluorinated by the same manner as in Scheme 1 to afford **16**[21] (8%) and an inseparable mixture contained predominately **17** and **18** in about 77% combined yield (ratio was not determined)[22] (Scheme 2). Again, compound **16** was subjected to dihydroxylation by different oxidants to give **19**.[23] However, the yield from OsO_4/NMO condition (35%) is almost equivalent to $RuCl_3/NaIO_4/NaH_2PO_4$ (34%). A mixture of **17** and **18** was dihydroxylated by either OsO_4/NMO or $RuCl_3/NaIO_4/NaH_2PO_4$ to yield compound **20**[24] in 33% and 30%, respectively, both along with a complicated mixture. This mixture then further treated with 2,2-dimethoxypropane and a catalytic amount of PPTS to yield **21**[25] (8%, two steps) as well as a trace amount of unidentified mixture. We may not rule out the possibility in formation of stereoisomers **25**–**29**, but we were not able to isolate neither of them throughout the reaction media (Fig. 2). We are also aware that the stereochemistry of fluoride influenced the dihydroxylation outcomes. Dihydroxylation preferentially occurred against the stereochemistry of fluoride. A similar case has been reported.[18] We found both oxidation conditions (OsO_4/NMO vs $RuCl_3/NaIO_4/NaH_2PO_4$) for dihydroxylation in Scheme 2 gave lower yields at this stage. It might be compounds **16**–**18** were labile under these conditions. Finally, compounds **6**–**8** and **19**–**21** were deprotected by using 80% TFA to obtain **9**[26] (78%), **10**[27] (90%), **11**[28] (82%), **22** (88%), **23** (94%), and **24** (91%) in high yields, respectively. The stereochemistry of compounds **9**–**11** and **22**–**24** has been confirmed by NMR experiments (COSY, NOESY, HMQC, and HMBC) and HRMS.

We deduced the plausible mechanisms based on the formation of compounds **3**–**5** and **16**–**18** in Figs. 3 and 4, respectively.[29] Apparently, compounds **3**–**5** might obtain from a combination of S_N1, S_N2, and S_N2' mechanisms (Fig. 3). Obviously, the formation of **3** from fluorination of **1** must derive from S_N1 mechanism (Fig. 3a). However, both S_N1 and S_N2 mechanisms were involved to produce **3** from **2** (Fig. 3b). The least hindered compound **4** was obtained as the major product from either **1** or **2**. A slightly high ratio yield obtained from **1** was probably because both S_N2 and S_N1 mechanisms were involved simultaneously. However, only S_N1



Reagents and conditions: (i) DAST (2 equiv.), CH_2Cl_2, 0 °C to rt; (ii) 5 mol% OsO_4/NMO/acetone/H_2O; (iii) 2,2-dimethoxypropane, CH_2Cl_2, PPTS; (iv) 80% TFA.

Scheme 2. Regioselective syntheses of deoxyfluoro quercitols **22**–**24**.

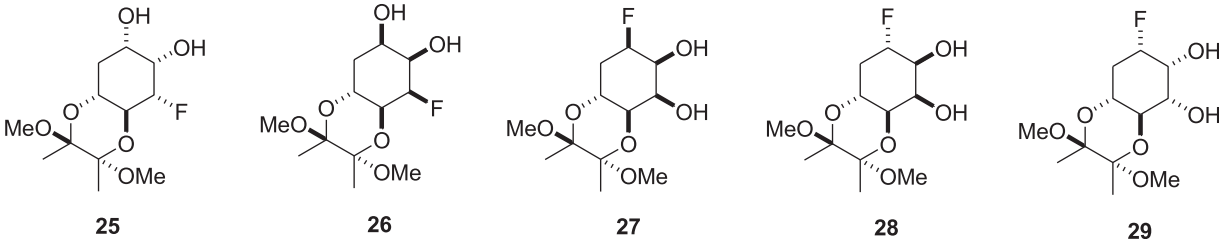


Fig. 2. Possible stereoisomers not isolated from reaction.

mechanism participated in formation of **4** from **2** (Fig. 3a). The path d in both cases likely does not occurre due to the steric effect (Fig. 3a). Compound **15** could possibly involve both S_N2 and S_N2' mechanisms to afford **17** and a mixture of **16**/**18**, respectively (Fig. 4). Since no epimer of **17** was received, we could possibly assume that the S_N1 mechanism might not involve in fluorination of **15**.

3. Conclusion

In conclusion, we have accomplished the synthesis of six new deoxyfluoro quercitols **9**–**11** and **22**–**24** from D-(−)-quinic acid with a facile manner. The regioselectivity of fluorination of **1**,**2** and **15** is not high, however, the total yields are high. Dihydroxylation of compounds **3**–**5** and **16**–**18** using OsO_4/NMO was a more reliable and highly diastereoselective method in accordance with our previous report.[18] These molecules will be evaluated as glycosidase inhibitors and published in due course.

4. Experimental section

4.1. General

All chemicals were purchased from commercial providers and used without further purification except otherwise stated. Melting points were uncorrected. ^1H (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Bruker 600 instrument. Chemical shifts were reported in parts per million (ppm) and referenced to the residual of solvents as following: CD_3OD (3.34 ppm for ^1H; 49.0 ppm for ^{13}C); D_2O (4.63 ppm for ^1H). Flash column chromatography all performed on 230–400 mesh silica gel except otherwise mentioned. Reactions were monitored in progress by thin

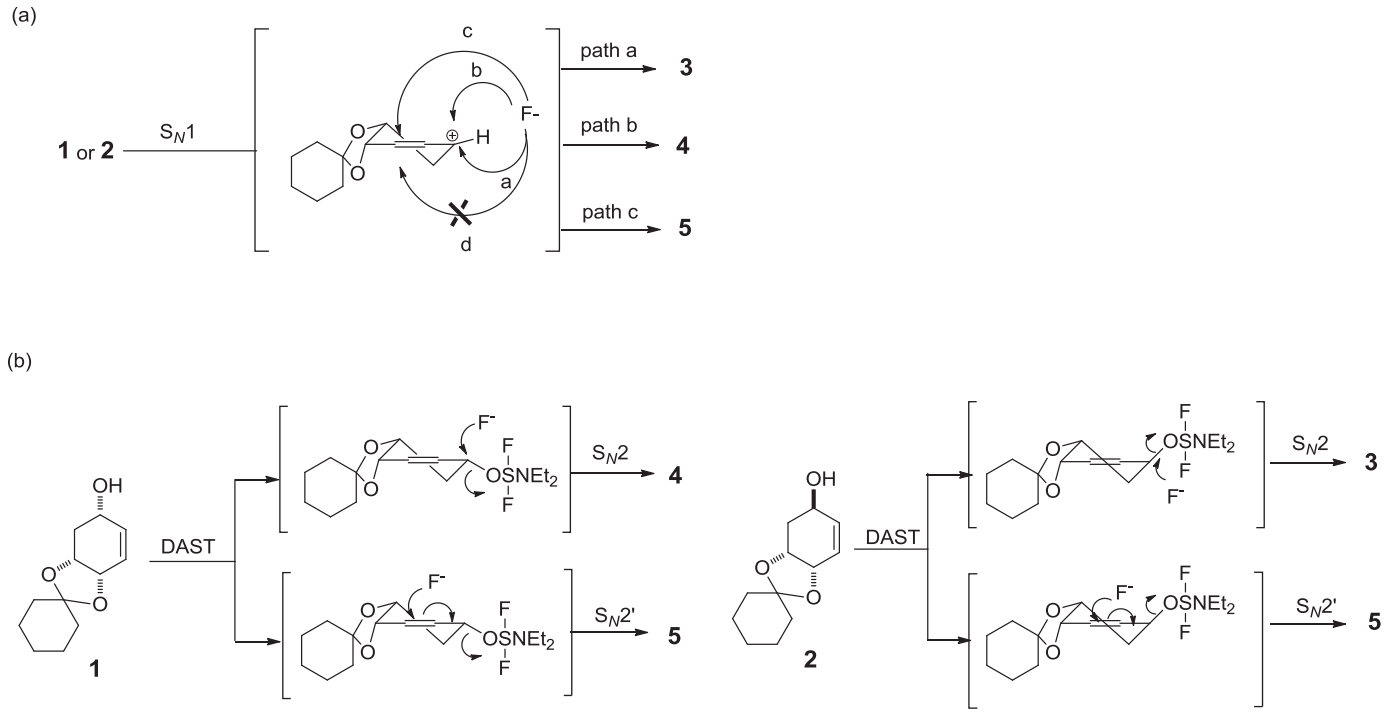


Fig. 3. The plausible mechanisms in fluorination of **1** and **2**.

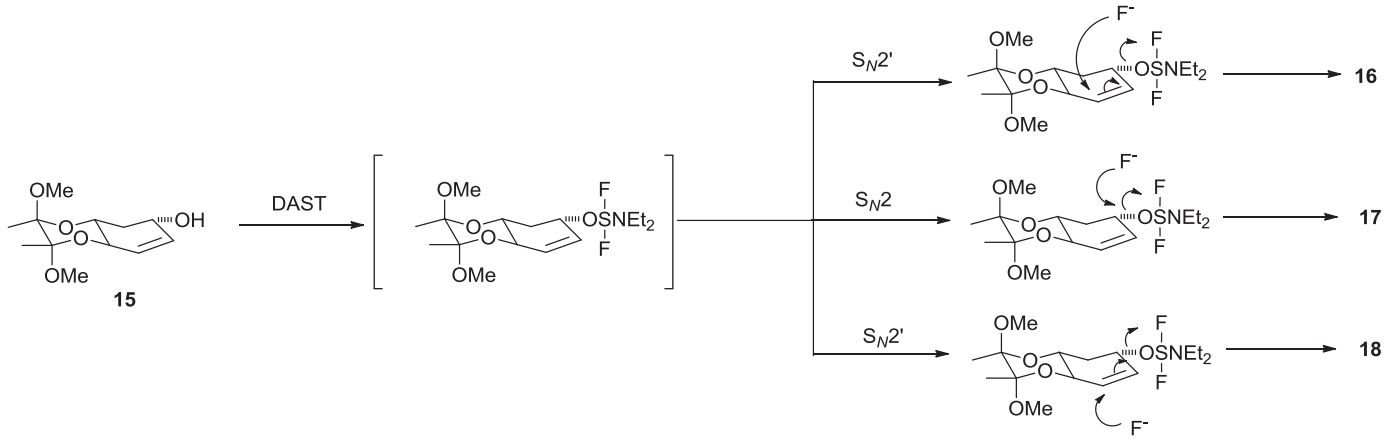


Fig. 4. The plausible mechanisms in fluorination of **15**.

layer chromatography (TLC). Optical rotations were measured by Horbia Sepa-300 instrument at 23 °C. The LRMS and HRMS data were measured by the National Taiwan University, the National Tsing Hua University, and the National Chung Hsing University.

4.2. General procedure of fluorination

Compound **1** (2.087 g, 9.93 mmol) in CH_2Cl_2 (100 mL), for example, was added DAST (2.62 mL, 19.86 mmol) at 0 °C and gradually warmed up to ambient temperature then stirred for 24 h. At the end of reaction time, the mixture was diluted with saturated $NaHCO_3$, extracted with CH_2Cl_2, and dried ($MgSO_4$). Flash column chromatography (pentane/ether=25:1) provided **3** (0.178 g, 8%) and a mixture of **4** and **5** (1.823 g, 87%). It is noteworthy that compounds **3**–**5** as well as compounds **16**–**18** are slightly volatile under reduced pressure and handle with care (400–500 bar, 40 °C water bath).

4.3. General procedure of dihydroxylation

Compound **3** (49 mg, 0.231 mmol), for example, was dissolved in acetone/H_2O (7.5 mL:2.5 mL) and treated with OsO_4 (0.12 mL, prepared in 0.1 M in THF) and NMO (81.2 mg, 0.693 mmol) sequentially at ambient temperature. This mixture was stirred at that temperature for 12 h and monitored by TLC. The reaction was quenched by addition of saturated solution of $Na_2S_2O_3$ and stirred for 3 h. Acetone was removed, diluted with EtOAc, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (Hex/EtOAc=3:1 to 1:1) to afford **6** (40.2 mg, 0.163 mmol, 71%).

4.4. General procedure of deprotection

Compound **6** (47 mg, 0.191 mmol), for example, was treated with 80% TFA (8 mL) and stirred at ambient temperature until

reaction completed by TLC indication (~1 h). The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc=3:1 to 1:1) to afford **9** (24.9 mg, 0.15 mmol, 78%).

4.5. (1*R*,2*R*,3*S*,4*S*,5*S*)-1,2-*O*-Cyclohexylidene-5-fluorocyclohexane-1,2,3,4-tetraol (6)

Compound **3** (49 mg, 0.231 mmol) was dihydroxylated and purified by flash column chromatography (Hex/EtOAc=3:1 to 1:1) to afford **6** (40.2 mg, 0.163 mmol, 71%) as a white solid. Mp=77–78 °C. $[\alpha]_D$ −22.3 (*c* 0.52, MeOH). ^{1}H NMR (CD_3OD) δ 4.67 (ddt, *J*=50.0, 11.0, 5.3 Hz, H_5), 4.37 (dd, *J*=8.7, 4.2 Hz, H_1), 4.14 (t, *J*=5.2 Hz, H_2), 3.96 (ddd, *J*=13.0, 6.4, 2.8 Hz, H_4), 3.90 (dd, *J*=7.3, 3.9 Hz, H_3), 2.32 (ddt, *J*=28.8, 15.3, 5.3 Hz, H_{6eq}), 2.07 (ddt, *J*=23.8, 15.3, 4.7 Hz, H_{6axial}), 1.68–1.62 (m, 4H), 1.60–1.54 (m, 4H), 1.43–1.38 (m, 2H). ^{13}C NMR (CD_3OD) δ 110.5, 92.2 ($^1J_{C-F}$=172.5 Hz, C_5), 78.7 (C_2), 73.1 ($^3J_{C-F}$=3 Hz, C_1), 72.3 ($^2J_{C-F}$=22.5 Hz, C_4), 72.0 ($^3J_{C-F}$=7.5 Hz, C_3), 38.9, 35.6, 32.0 ($^2J_{C-F}$=19.5 Hz, C_6), 26.4, 25.2, 24.9. HRMS (ESI) calcd for $C_{12}H_{20}FO_4$ $[M+H]^+$ 247.1346. Found: 247.1376.

4.6. (1*R*,2*R*,3*S*,4*S*,5*S*)-1,2-*O*-Cyclohexylidene-3,4-*O*-isopropylidene-5-fluorocyclohexane-1,2,3,4-tetraol (7)

Compounds **4**+**5** (0.460 g, 2.17 mmol) were dihydroxylated then treated with 2,2-dimethoxypropane (0.99 mL, 8.06 mmol) and PPTS (0.0201 g, 0.081 mmol) in CH_2Cl_2 (15 mL). Flash column chromatography (Hex/EtOAc=30:1 to 20:1) afforded **7** (0.248 g, 0.86 mmol) as a pale-yellow syrup. Yield=40% (two steps). $[\alpha]_D$ +77.3 (*c* 0.54, MeOH). ^{1}H NMR (C_6D_6) δ 4.94 (ddt, *J*=46.5, 11.9, 2.8 Hz, H_5), 4.43 (d, *J*=7.6 Hz, H_3), 4.30–4.24 (m, $H_{2,4}$), 4.20–4.19 (m, H_1), 2.21 (tt, *J*=9.2, 3.7 Hz, H_{6eq}), 1.91 (t, *J*=13.4 Hz, H_{6axial}), 1.59–1.53 (m, 4H), 1.46–1.37 (m, 7H), 1.22–1.21 (m, 2H), 1.10 (s, 3H). ^{13}C NMR (C_6D_6) δ 109.1, 108.6, 86.7 ($^1J_{C-F}$=178.5 Hz, C_5), 76.2 ($^3J_{C-F}$=6 Hz, C_3), 73.3 ($^2J_{C-F}$=15 Hz, C_4), 72.9 (C_2), 72.8 ($^3J_{C-F}$=6 Hz, C_1), 36.8, 33.5, 29.0 ($^2J_{C-F}$=19.5 Hz, C_6), 26.2, 25.9, 24.7, 24.2, 23.9. HRMS (ESI) calcd for $C_{15}H_{23}FNaO_4$ $[M+Na]^+$ 309.1478. Found: 309.1466.

4.7. (1*R*,2*R*,4*R*,5*R*)-1,2-*O*-Cyclohexylidene-1,2-*O*-isopropylidene-3-fluorocyclohexane-1,2,4,5-tetraol (8)

A mixture of compounds **4** and **5** (0.460 g, 2.17 mmol). Flash column chromatography (Hex/EtOAc=30:1 to 20:1) afforded **8** (0.138 g, 0.48 mmol) as a pale-yellow syrup. Yield=22% (two steps). $[\alpha]_D$ −47.0 (*c* 0.56, MeOH). ^{1}H NMR (C_6D_6) δ 4.46 (ddd, *J*=44.5, 5.9, 2.8 Hz, H_3), 4.45 (dd, *J*=10.7, 7.4 Hz, H_4), 4.35 (dt, *J*=7.7, 4.4 Hz, H_5), 4.21 (ddd, *J*=16.8, 7.6, 2.2 Hz, H_2), 4.08 (dt, *J*=9.2, 4.8 Hz, H_1), 2.07 (dt, *J*=14.2, 4.7 Hz, H_{6eq}), 1.69–1.57 (m, 4H+H_{6axial}), 1.47–1.40 (m, 7H), 1.24–1.20 (m, 2H), 1.13 (s, 3H). ^{13}C NMR (C_6D_6) δ 109.8, 109.1, 91.8 ($^1J_{C-F}$=180 Hz, C_3), 74.2 ($^2J_{C-F}$=24 Hz, C_4), 73.6 ($^2J_{C-F}$=16.5 Hz, C_2), 72.2 ($^3J_{C-F}$=4.5 Hz, C_1), 71.7 ($^3J_{C-F}$=4.5 Hz, C_5), 37.5, 33.9, 31.2 (C_6), 26.6, 25.9, 24.7, 24.3, 24.2. HRMS (ESI) calcd for $C_{15}H_{23}FNaO_4$ $[M+Na]^+$ 309.1478. Found: 309.1465.

4.8. (1*R*,2*R*,3*S*,4*S*,5*S*)-5-Fluorocyclohexane-1,2,3,4-tetraol (9)

Compound **6** (47 mg, 0.191 mmol). Purification by flash column chromatography (Hex/EtOAc=1:1 to 0:1) afforded **9** (24.9 mg, 0.15 mmol) as a white solid. Yield=78%. Mp=186–187 °C. $[\alpha]_D$ −94.0 (*c* 0.52, MeOH). ^{1}H NMR (D_2O) δ 4.64–4.56 (m, signals overlapped with HOD, H_5), 4.00–3.95 (m, $H_{1,3}$), 3.91–3.85 (m, $H_{2,4}$), 2.12 (tt, *J*=13.6, 4.3 Hz, H_{6eq}), 1.88 (dt, *J*=22.5, 11.2 Hz, H_{6axial}). ^{13}C NMR (D_2O) δ 90.3 ($^1J_{C-F}$=169.5 Hz, C_5), 71.3, 70.5, 70.4, 65.9, 31.4 ($^2J_{C-F}$=18 Hz, C_6). ^{1}H NMR (CD_3OD) δ 4.63–4.51 (m, signals overlapped with HOD, H_5), 3.97–3.92 (m, H_{1+2}). 3.84–3.80 (m, H_{3+4}), 2.06 (ddd, *J*=17.0, 9.4, 4.9, H_{6eq}), 1.91 (dt, *J*=22.6, 14.6, Hz, H_{6axial}). ^{13}C NMR (150 MHz, CD_3OD) δ 92.0 ($^1J_{C-F}$=173.5 Hz, C_5), 74.0 ($^3J_{C-F}$=7.5 Hz, C_1), 73.7, 72.4 ($^3J_{C-F}$=18 Hz, C_3), 67.3 ($^2J_{C-F}$=12.0 Hz, C_4), 34.0 ($^2J_{C-F}$=18 Hz, C_6). HRMS (ESI) calcd for $C_7H_{12}FO_6$ $[M+HCO_2]^+$ 211.0618. Found: 211.0666.

4.9. (1*R*,2*R*,3*S*,4*S*,5*R*)-5-Fluorocyclohexane-1,2,3,4-tetraol (10)

Compound **7** (52 mg, 0.182 mmol). Purification by column chromatography (Hex/EtOAc=3:1 to 0:1) afforded **10** (26.6 mg, 0.16 mmol) as a white solid. Yield=88%. Mp=171–172 °C. $[\alpha]_D$ −52.3 (*c* 0.51, MeOH). ^{1}H NMR (D_2O) δ 4.78 (ddt, *J*=46.7, 8.0, 2.7 Hz, H_5), 4.10 (d, *J*=10.9 Hz, H_4), 3.99 (t, *J*=3.2 Hz, H_1), 3.67 (s, $H_{2,3}$), 1.98–1.94 (m, $H_{6eq+6axial}$). ^{13}C NMR (D_2O) δ 89.2 ($^1J_{C-F}$=186 Hz, C_5), 70.5 (C_{2+4}), 69.4 (C_3), 66.8 (C_1), 30.3 ($^2J_{C-F}$=20 Hz, C_6). HRMS (ESI) calcd for $C_6H_{12}FO_6$ $[M+H]^+$ 167.0720. Found: 167.0708.

4.10. (1*R*,2*R*,4*R*,5*R*)-3-Fluorocyclohexane-1,2,4,5-tetraol (11)

Compound **8** (21 mg, 0.073 mmol). Flash column chromatography (Hex/EtOAc=3:1 to 0:1) afforded **11** (10.1 mg, 0.061 mmol) as a white solid. Yield=82%. Mp=163–164 °C. $[\alpha]_D$ −40.7 (*c* 0.29, MeOH). ^{1}H NMR (D_2O) δ 4.51 (ddd, *J*=48.2, 9.8, 2.9 Hz, H_3), 4.16 (d, *J*=10.2 Hz, H_4), 3.98 (dt, *J*=9.6, 3.2 Hz, H_1), 3.92–3.88 (m, H_5), 3.86 (dt, *J*=10.3, 3.2 Hz, H_2), 1.80–1.74 (m, $H_{6'eq+6axial}$). ^{13}C NMR (D_2O) δ 91.8 ($^1J_{C-F}$=177 Hz, C_3), 70.8 (C_4), 68.9 ($^2J_{C-F}$=18 Hz, C_2), 67.5 (C_1), 65.1 (C_5), 32.0 (C_6). HRMS (ESI) calcd for $C_6H_{10}FO_4$ $[M-H]^+$ 165.0563. Found: 165.0558.

4.11. (1*R*,2*S*,3*R*)-1,2-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-dioxy]-3-fluorocyclohex-4-ene (16)

Compound **15** (1.950 g, 7.987 mmol). Flash column chromatography (pentane/Et_2O=30:1 to 20:1) afforded **16** (0.163 g, 0.663 mmol) as a pale-yellow solid. Yield=8%. $[\alpha]_D$ +39.7 (*c* 0.51, MeOH). ^{1}H NMR (C_6D_6) δ 5.56–5.52 (m, H_5), 5.47–5.42 (m, H_4), 4.78 (ddd, *J*=52.1, 4.9, 3.6 Hz, H_3), 4.32 (dt, *J*=14.7, 10.5 Hz, H_1), 3.65 (ddd, *J*=23.6, 10.9, 3.3 Hz, H_2), 3.06 (s, 3H), 3.05 (s, 3H), 2.19 (ddd, *J*=23.9, 11.9, 6.1 Hz, H_{6eq}), 2.08–1.96 (m, H_{6axial}), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (C_6D_6) δ 132.9 ($^3J_{C-F}$=9 Hz, C_5), 124.2 ($^2J_{C-F}$=15 Hz, C_4), 100.6, 99.8, 85.3 ($^1J_{C-F}$=176 Hz, C_3), 71.0 ($^2J_{C-F}$=18 Hz, C_2), 63.4, 48.0, 47.9, 32.1 (C_6), 18.5, 18.4. HRMS (ESI) calcd for $C_{12}H_{19}FNaO_4$ $[M+Na]^+$ 269.1165. Found: 269.1152.

4.12. (1*R*,2*S*,3*S*,4*S*,5*S*)-1,2-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-dioxy]-3-fluorocyclohexane-1,2,4,5-tetraol (19)

Compound **16** (25.2 mg, 0.102 mmol). Flash column chromatography (Hex/EtOAc=3:1 to 1:1) afforded **19** (21 mg, 0.074 mmol) as a white solid. Yield=72%. Mp=172–173 °C. $[\alpha]_D$ +125.3 (*c* 0.33, MeOH). ^{1}H NMR (CD_3OD) δ 4.63 (dd, *J*=50.4, 2.3 Hz, H_3), 4.57 (s, −OH), 3.99 (dd, *J*=7.3, 3.7 Hz, H_2), 3.88–3.78 (m, $H_{1,4,5}$), 3.22 (s, 6H), 1.86–1.75 (m, $H_{6eq+6axial}$), 1.29 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (CD_3OD) δ 101.7, 100.7, 92.7 ($^1J_{C-F}$=177 Hz, C_3), 71.4 ($^2J_{C-F}$=25.5 Hz, C_2), 70.3 ($^2J_{C-F}$=15 Hz, C_4), 67.8 (C_5), 64.8 ($^3J_{C-F}$=3 Hz, C_1), 48.3 (×2), 32.9 (C_6), 18.2, 18.1. HRMS (ESI) calcd for $C_{12}H_{20}FO_6$ $[M-H]^+$ 279.1244. Found: 279.1238.

4.13. (1*R*,2*S*,3*R*,4*R*,5*R*)-1,2-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-dioxy]-5-fluorocyclohexane-1,2,3,4-tetraol (20)

A mixture of compounds **17** and **18** (1.490 g, 6.054 mmol). Flash column chromatography (Hex/EtOAc=3:1 to 1:2) afforded **20** (0.558 g, 1.993 mmol) as a white solid. Yield=33%. Mp=196–197 °C. $[\alpha]_D$ +175.0 (*c* 0.51, MeOH). ^{1}H NMR (CD_3OD) δ 4.73 (dd, *J*=45.4,

2.6 Hz, H_5), 4.00 (dd, J=7.6, 3.8 Hz, H_4), 3.78–3.74 (m, $H_{1,2}$), 3.64 (dd, J=6.7, 2.9 Hz, H_3), 3.27 (s, 3H), 3.21 (s, 3H), 2.10–1.82 (m, $H_{6eq+6axial}$), 1.28 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (CD_3OD) δ 101.0, 91.8 ($^1J_{C-F}$=171 Hz, C_5), 72.3 (C_1), 71.6 ($^2J_{C-F}$=27 Hz, C_4), 70.2 (C_3), 66.5 (C_2), 48.4, 48.2, 30.8 ($^2J_{C-F}$=19.5 Hz, C_6), 18.2 (x2). HRMS (ESI) calcd for $C_{12}H_{20}FO_6$ $[M-H]^+$ 279.1244. Found: 279.1238.

4.14. (1*R*,2*S*,3*R*,4*R*,5*R*)-1,2-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-dioxy]-3-fluorocyclohexane-1,2,4,5-tetraol (21)

A mixture of compounds **17** and **18** (1.490 g, 6.054 mmol). Flash column chromatography (Hex/EtOAc=30:1 to 1:10) afforded **21** (0.114 g, 0.357 mmol) as a white solid. Yield=6% (two steps). Mp=117–118 °C. $[\alpha]_D$ +102.3 (*c* 0.50, MeOH). ^{1}H NMR (D_2O) δ 4.80 (ddd, J=52.5, 10.1, 6.5 Hz, H_3), 4.06 (dt, J=15.5, 4.7 Hz, H_1), 3.87 (dt, J=21.2, 6.1 Hz, H_4), 3.78 (s, H_5), 3.66 (dd, J=21.0, 10.4 Hz, H_2), 3.19 (s, 3H), 3.00 (s, 3H), 2.22 (dd, J=14.7, 4.7 Hz, H_{6eq}), 1.50 (ddd, J=18.6, 12.4, 4.0 Hz, H_{6axial}), 1.36 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (D_2O) δ 109.7, 99.9, 99.8, 95.4 ($^1J_{C-F}$=183 Hz, C_3), 79.3 ($^2J_{C-F}$=21 Hz, C_4), 73.7 ($^3J_{C-F}$=10.5 Hz, C_5), 71.8 ($^2J_{C-F}$=16.5 Hz, C_2), 64.3 ($^3J_{C-F}$=7.5 Hz, C_1), 48.1, 48.0, 29.9 (C_6), 28.3, 26.4, 18.3, 18.2. HRMS (ESI) calcd for $C_{15}H_{25}FNaO_6$ $[M]^+$ 343.1533. Found: 343.1527.

4.15. (1*R*,2*S*,3*S*,4*S*,5*S*)-3-Fluorocyclohexane-1,2,4,5-tetraol (22)

Compound **19** (32 mg, 0.114 mmol). Purification by flash column chromatography (Hex/EtOAc=1:2 to 0:1) afforded **22** (16.7 mg, 0.101 mmol) as a white solid. Yield=88%. Mp=215–216 °C. $[\alpha]_D$ −42.7 (*c* 0.25, MeOH). ^{1}H NMR (D_2O) δ 4.73–4.60 (m, H_3), 3.99 (dd, J=7.6, 4.1 Hz, H_2), 3.87 (ddd, J=11.0, 7.4, 3.7 Hz, H_1), 3.73–3.65 (m, H_5), 3.67–3.59 (m, H_4), 1.90 (dt, J=12.4, 4.2 Hz, H_{6eq}), 1.62 (dd, J=22.5, 11.2 Hz, H_{6axial}). ^{13}C NMR (D_2O) δ 92.5 ($^1J_{C-F}$=172.5 Hz, C_3), 71.3 ($^2J_{C-F}$=16.5 Hz, C_4), 69.2 ($^2J_{C-F}$=25.5 Hz, C_2), 67.6 (C_5), 66.3 (C_1), 33.2 (C_6). HRMS (ESI) calcd for $C_6H_{11}FNaO_4$ $[M+Na]^+$ 189.0539. Found: 189.0533.

4.16. (1*R*,2*S*,3*R*,4*R*,5*R*)-5-Fluorocyclohexane-1,2,3,4-tetraol (23)

Compound **20** (40 mg, 0.143 mmol). Purification by flash column chromatography (Hex/EtOAc=1:2 to 0:1) afforded **23** (22.3 mg, 0.134 mmol) as a white solid. Yield=94%. Mp=177–178 °C. $[\alpha]_D$ +23.7 (*c* 0.51, MeOH). ^{1}H NMR (D_2O) δ 4.71 (ddd, J=45.4, 6.4, 3.7 Hz, H_5), 3.99 (dd, J=7.4, 3.6 Hz, H_4), 3.58 (ddd, J=11.6, 9.4, 4.9 Hz, H_1), 3.53 (ddd, J=9.7, 3.2 Hz, H_3), 3.44 (t, J=9.5 Hz, H_2), 2.15–2.08 (m, H_{6eq}), 1.88 (dddd, J=47.5, 14.3, 11.6, 2.2 Hz, H_{6axial}). ^{13}C NMR (D_2O) δ 90.3 ($^1J_{C-F}$=167 Hz, C_5), 74.0 (C_2), 70.8 (C_3), 69.5 ($^2J_{C-F}$=27 Hz, C_4), 68.5 (C_1), 32.0 ($^2J_{C-F}$=20 Hz, C_6). HRMS (ESI) calcd for $C_6H_{11}FNaO_4$ $[M+Na]^+$ 189.0539. Found: 189.0534.

4.17. (1*R*,2*S*,3*R*,4*R*,5*R*)-3-Fluorocyclohexane-1,2,4,5-tetraol (24)

Compound **21** (35 mg, 0.109 mmol). Purification by flash column chromatography (Hex/EtOAc=1:2 to 0:1) afforded **24** (16.4 mg, 0.099 mmol) as a white solid. Yield=91%. Mp=219–220 °C. $[\alpha]_D$ −100.3 (*c* 0.25, MeOH). ^{1}H NMR (D_2O) δ 4.33 (dt, J=53.0, 9.4 Hz, H_3), 3.97 (s, H_1), 3.73–3.94 (m, $H_{2,5}$), 3.44 (dt, J=13.4, 9.3 Hz, H_4), 1.99 (dt, J=14.1, 4.1 Hz, H_{6eq}), 1.46 (td, J=14.3, 2.2 Hz, H_{6axial}). ^{13}C NMR (D_2O) δ 94.9 ($^1J_{C-F}$=174 Hz, C_3), 75.4 ($^2J_{C-F}$=15 Hz, C_4), 72.0 ($^2J_{C-F}$=16.5 Hz, C_2), 68.1 ($^3J_{C-F}$=10.5 Hz, C_1), 67.7 ($^3J_{C-F}$=9.0 Hz, C_5), 34.8 (C_6). HRMS (ESI) calcd for $C_6H_{11}FNaO_4$ $[M+Na]^+$ 189.0539. Found: 189.0533.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR data for all new products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.11.001.

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14. ^{1}H and ^{13}C NMR data of compound **3** are all in accordance with the reported value in Ref. 10a.
15. ^{1}H NMR data of compound **4** are consistent with the reported value in Ref. 10a.
16. ^{1}H NMR data of compound **5** was subtracted the signals from the mixture of **4** and **5**. Also the stereochemistry of $H_{3pseudo\ eq}$ of **5** is *anti* relationship to the its H_{2eq} based on the small coupling constant (~3.8 Hz). Its stereochemistry could be further confirmed until the formation of **8**.
17. Similar examples, see Ref. 10a. In compound **6**, the steric effect (cyclohexylidene group) strongly influenced the stereoselectivity. The evidence was supported by the large coupling constant of H_{4axial}/H_{5axial} (~13.0 Hz).
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19. The stereochemistry of H_{2eq}/H_{3eq} of compound **7** was resolved based on the coupling constant (~0 Hz), which is corresponding to the diequatorial relationship. On the other hand, the coupling constant of H_{4axial}/H_{5eq} is ~2.8 Hz. These results also supported the observation in Ref. 16.
20. The dihydroxylation of compound **5** occurred to the *syn* addition of the same side with fluoride group (*anti* to the cyclohexylidene group) and followed by protection to lead to compound **8**. The assignment was supported by the coupling constants (H_{4axial}/H_{5eq}=7.4 Hz and H_{5eq}/H_{6axial}=~0 Hz). Furthermore, the small coupling constant of H_{2eq}/H_{3eq} (~2.8 Hz) was an evidence to firmly prove the assignment in compound **5**.
21. The stereochemistry of H_3 was based on the coupling constant of $H_{2axial}/H_{3pseudo\ eq}$ of compound **16** (~3.4 Hz). No NOE was observed between H_{1axial} and $H_{3pseudo\ eq}$.
22. The spectrum of this mixture is complicated. Assignments for **17** and **18** were not available at this stage.
23. We had previously reported a similar case to **16** in dihydroxylation and two diastereomers were obtained (Ref. 18). However, only one diastereomer **19** was received in many attempts in this article. The stereochemistry of **19** is difficult to be resolved since signals of $H_{1,4,5}$ (NOSEY and COSY) were overlapping. Fortunately, the stereochemistry was determined after its deprotecting to yield **22**. The NOESY spectrum of **22** indicated the cross relationship between H_{1axial} and H_{5axial}. This allowed us to conclude that the dihydroxylation occurred at the α face in **19**.
24. The coupling constant of H_{4eq}/H_{5eq} of **20** is ~2.6 Hz. Its NOESY spectrum showed H_1/H_3 relationship to confirm the assignment. Further information was provided after deprotecting **20** to give **23** in which the coupling constants of H_{2axial}/H_{3axial} and H_{4eq}/H_{5eq} are 9.7, 3.2 Hz, respectively.
25. The NOESY spectrum of compound **21** showed the relationship of H_{1axial}/H_{3axial} but not of H_{3axial}/H_{5eq}. This evidence indicated the dihydroxylation of 18 occurred at the β face. In addition, the coupling constant of compound **21** of H_{2axial}/H_{3axial} (~10.1 Hz) confirmed the assignment. Furthermore, the coupling constants of H_{2axial}/H_{3axial} (~9.4 Hz) and H_{3axial}/H_{4axial} (~9.4 Hz) of **24** are consistent with the assignment of structure **21**.
26. The NOESY spectrum showed cross relationship of H_{1axial}/H_{5axial} and H_{4axial}/H_{6axial} of **9**.
27. The assignment of compound **10** is mainly based on its precursor **7**. In compound **10**, although the coupling constants of H_{3axial}/H_{4eq} and H_{4eq}/H_{5axial} are ambiguous, however, the NOESY spectrum showed the cross relationship between H_{3axial}/H_{5axial}.
28. The NOESY spectrum of **11** indicated no cross relationship between H_{1eq}/H_{3axial} and H_{1eq}/H_{5axial} but H_{3axial}/H_{5axial}. The configurations of H_{1eq} and H_{2axial} of **11** are confirmed to lead to our assignment, which is consistent with its preceding compound **8**.
29. Similar examples see: Kiss, L.; Forró, E.; Fustero, S.; Fülöp, F. *Org. Biomol. Chem.* **2011**, *9*, 6528–6534.