Synthesis of Asperuloside Aglucon Silyl Ether and Garjasmine from (+)-Genipin via Gardenoside Aglucon Bis(silyl ether) as a Common Intermediate

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Syntheses of C6-functionalized iridoids represented by asperuloside aglucon silyl ether (**4**) and garjasmine were accomplished from (+)-genipin by utilizing the gardenoside aglucon bis(silyl ether) (**3**) as a common intermediate. During the transformation of **3** into **4**, the acid-catalyzed transposition reaction of the tertiary hydroxyl group was found to proceed from more hindered concave side to give C6-hydroxylated compound having the same stereochemistry as that of C6 in **4**. This observed hydroxyl group transposition reaction was interesting since such migration of hydroxyl group in the proposed biosynthetic pathway of gardenoside from geniposide proceeded to the opposite direction.

Iridoids are widespread in nature and are available in large quantity. Geniposide (**1**), one of such monoterpene iridoids, is abundant in the fruit of *Gardenia jasminoides Ellis* and could be easily supplied in industrial scale. From the viewpoint of efficient use of natural resources, we have investigated syntheses of iridoids as well as diterpenes with high added value such as secologanin,[1] petiodial,[2] and antipode of udoteatrial hydrate[3] starting from genipin (**2**), an aglucon of geniposide, as a chiral building block. To demonstrate the versatility of **2** as a building block, we recently focused our attention on the syntheses of C6-functionalized iridoids.[4] In this article we would like to describe the detail of synthesis of asperuloside aglucon silyl ether (**4**)[5] and garjasmine (**5**)[6] from gardenoside aglucon silyl ether (**3**) as a common intermediate (Chart 1).

It was recognized that **1** placed at the key position in the proposed biosynthesis of the C6-functionalized iridoids such as scandoside (**7**) and gardenoside (**8**) from loganin (**6**) (Scheme 1).[7] Although the key step in the proposed biosynthesis of **8** is the enzymatic allylic oxidation at C6 of **1** to give scandoside (**7**), direct oxidation at C6 of heavily functionalized iridoid such as **2** with chemical reactions is difficult. After extensive investigations, synthetic scheme involving dihydroxylation-elimination sequence was found to work nicely on the derivative of **2** to afford $\Delta^{6,7}$-iridoids (Scheme 2).

Thus, dihydroxylation of (+)-genipin bis(silyl ether) (**9**), obtained from **2** by silylation of both hydroxyl

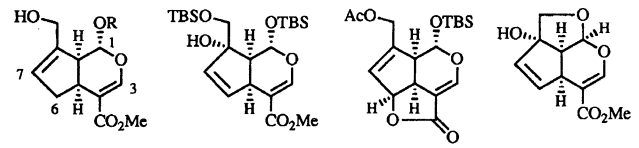
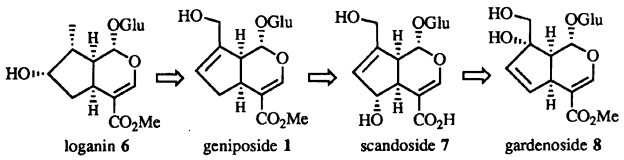
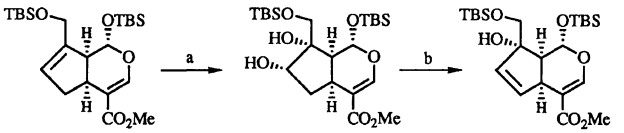


Chart 1.



Scheme 1. Proposed biosynthesis of gardenoside (**8**) from loganin (**6**).



Scheme 2. Conditions: a) cat. OsO_4, NMO, *t*-BuOH : acetone : H_2O=10 : 3 : 1, 85%; b) Tf_2O (1.5 equiv), DMAP (3 equiv), CH_2Cl_2 then DBU (3.6 equiv), 70%.

group, with catalytic amount of OsO_4 in the presence of *N*-methyl-morpholine *N*-oxide (NMO) smoothly proceeded to give diol (**10**).[8] The stereochemistry of **10** was assigned by assuming that osmium reagent approached from the less hindered side of the double bond and was later confirmed by its successful conversion into **5**. Dehydration of the secondary alcohol moiety in **10** was effected by treatment with trifluoromethane sulfonic anhydride (Tf_2O) and 4-dimethylaminopyridine (DMAP) followed by DBU[9] to afford gardenoside aglucon bis(silyl ether) (**3**) in good yield.

With the $\Delta^{6,7}$-compound in hand, we then focused our attention on the introduction of oxygen functionality at C6 aiming at synthesis of asperuloside derivative. We at first examined chromium trioxide oxidation of **3** accompanied by allylic rearrangement. Upon treatment of **3** with pyridinium dichromate (PDC) in DMF the expected enone (**11**) was obtained in moderate yield accompanied by unidentified side products. Pyridinium chlorochromate (PCC), general reagent for these purpose,[10] was found not to be effective in this particular case. Since **11** was not stable for storage, it was directly subjected to the reduction of the ketone

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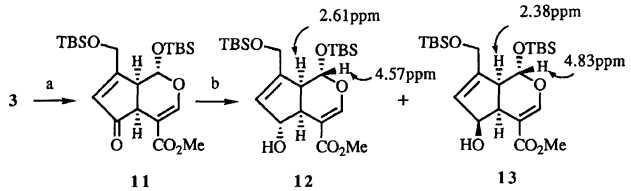
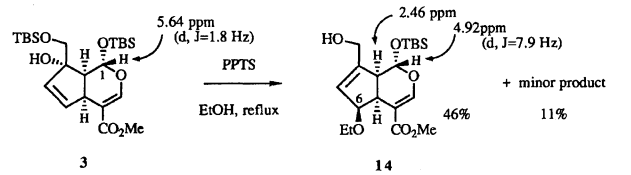
with $NaBH_4$ in the presence of cerium(III) chloride.[11] The reduction of **11**, however, was not stereoselective to produce two diastereomeric alcohols **12** and **13** in 2:3 ratio (Scheme 3). The stereochemistries of these compounds were assigned based on the chemical shifts of hydrogens at Cl and C9 in their ^1H NMR spectra and confirmed by the conversion of **13** into asperuloside aglucon silyl ether (**4**). Although **13** was our proposed intermediate for asperuloside synthesis, overall yield of **13** from **10** was not acceptable.

In other experiments, we have examined deprotection of the primary hydroxyl group in **3** to obtain gardenoside aglucon silyl ether **15**. In these studies, we observed that upon treatment of **3** with pyridinium *p*-toulenesulfonate (PPTS) in ethanol, compounds involving ethoxyl group were obtained in 4:1 ratio. Comparing the coupling constant of C_1–H in their ^1H NMR spectra (7.9 and 1.8 Hz for major and minor products, respectively) revealed that their conformations at pyran ring were different each other and the minor product seemed to retain the original conformation. Since large upfield shift of C_1–H (4.92 ppm) in the major product suggested migration of $\Delta^{6,7}$-double bond to $\Delta^{7,8}$-position, we assigned this compound as **14** involving a C6-β-ethoxyl group, while the structure of the minor product involving C6-α-ethoxyl group could not be determined from its NMR spectra. Although the stereochemistry of **14** was not confirmed, its tentative assignment was made by comparison of its chemical shift as well as coupling constant at C_1–H with those of **12** and **13** (Scheme 4). Should this reaction work in water instead of ethanol, we could confirm the stereochemistries of products by converting them into **12** and **13** and develop the method to introduce hydroxyl group at C6.

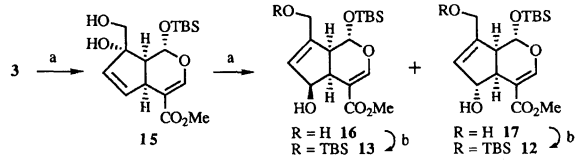
Thus, on treatment of **3** with PPTS in acetone–H_2O (2:1) the silyl group attached to the primary hydroxyl group was first hydrolyzed to give gardenoside aglucon silyl ether (**15**) and the prolonging the reaction time further caused hydroxyl group transposition of **15** to



Scheme 3. Conditions: a) PDC, DMF, r.t., 41%; b) $NaBH_4$, $CeCl_3$, MeOH, **12** 30%, **13** 45%.



Scheme 4.

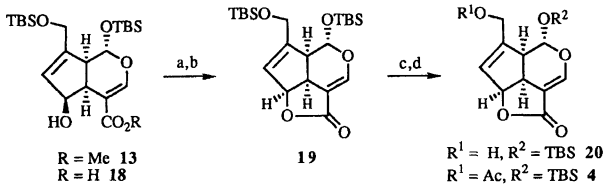


Scheme 5. Condition: a) PPTS, acetone:H_2O=3:1, reflux, **16** 49%, **17** 12%; b) TBSCl, Imidazole, DMF, r.t., **13** 85%, **12** 59% (95% conv.).

afford the expected C6-hydroxylated compounds as a mixture of stereoisomers (**16** and **17**) in about 4 to 1 ratio. The structure of each isomer was unambiguously assigned as shown in Scheme 5 by the conversion of major isomer (**16**) into **13**.

The remaining task to convert **13** into **4** was hydrolysis of the methyl ester and lactonization of the resulting hydroxy acid. Attempts to hydrolyze the methyl ester with external nucleophiles (*n*-PrSLi in HMPA, KOH in aqueous methanol, Me_3SiCl–NaI in CH_3CN, or LiOH in aqueous THF) resulted in either recovery or decomposition of the starting material. In contrast, hydrolysis utilizing the neighboring hydroxyl group at C6 as an internal nucleophile was found to be successful. Thus, treatment of **13** with potassium hydride in THF cleanly afforded hydroxy acid (**18**),[12] which was then lactonized with dicyclohexylcarbodiimide (DCC) to give the desired lactone (**19**). Finally hydrolysis of the silyl group on the primaty hydroxyl group followed by acetylation of the resulting alcohol accomplished the synthesis of **4**, 400 MHz ^1H NMR spectrum of which was in good agreement with that of the aglucon portion of asperuloside tetraacetate obtained by acetylation of asperuloside (**21**) (Scheme 6).[13]

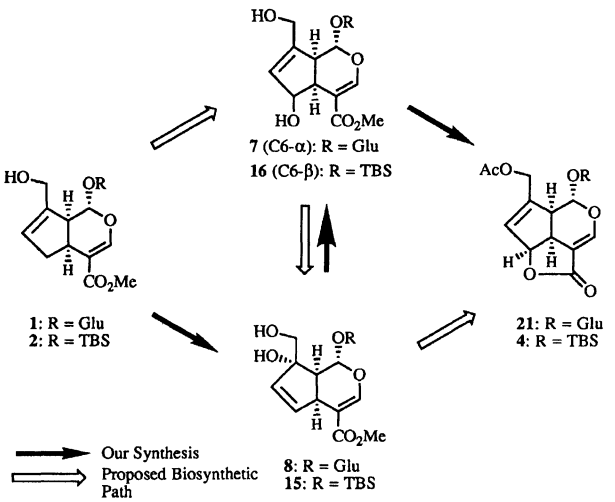
The hydroxyl group transposition reaction observed upon treatment of **13** with acid catalysts deserves some comments. Computational calculations using PM3 (MOPAC ver 5.01)[14] have supported that the hydroxyl transposition to produce either **16** or **17** from **15** was thermodynamically favorable reaction pathway by comparing their heats of formation of **15**, **16**, and **17** (**15**: -212.37 kcal mol^{-1}, **16**: -218.31 kcal mol^{-1}, **17**: -219.31 kcal mol^{-1}).[15] Since equilibration between **16** and **17** was not detected under the same reaction conditions, introduction of hydroxyl group from more hindered side of the cis-fused bicyclo[4.3.0]nona-3,7-diene system to give **16** might be accounted by *anti*-S_N2' re-



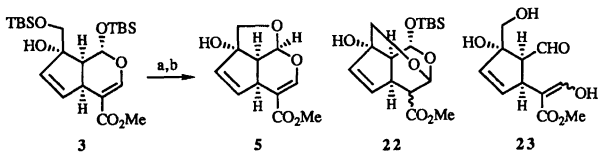
Scheme 6. Conditions: a) KH, THF, 0 °C; b) DCC, CH_2Cl_2, 85% (2 steps); c) PPTS, acetone:H_2O= 3:1, reflux; d) Ac_2O, Py, DMAP, 54% (2 steps).

action of water to protonated **15** from concave side (β face), while the minor product **17** seemed to be formed by *syn*-S_N2' reaction. Such *anti*-S_N2' pathway was often observed in the intramolecular allylic substitution reactions,[16] participation of ester carbonyl in these hydroxyl transposition reaction to produce **16**, however, was not detected when **15** was treated with acid catalysts in acetone without any external nucleophile.[17] On the other hand, direct formation of either **12** or **13** from **3** without hydrolysis of the *t*-butyldimethylsilyl (TBS) ether moiety on the primary hydroxyl group was not observed on TLC analyses. Thus, it was probable that the primary alcohol moiety somehow played an important role to result in acceleration the hydroxyl group transposition reaction. This observed hydroxyl group transposition in chemical reactions is in good contrast to that in the proposed biosynthetic pathway of gardenoside (**8**) from geniposide (**1**). Thus, in enzymatic reactions such migration of hydroxyl group is considered to proceed to the opposite direction (from **7** to **8**) (Scheme 7).

As discussed above asperuloside derivative was successfully obtained from **3**, which was also found to be an intermediate for the synthesis of garjasmine (**5**). This compound was recently isolated in China, its biological activities, however, were remained uncertain. Since acidic conditions for hydrolysis of the silyl group in **3** could not be used because of the hydroxyl group transposition, deprotection with tetrabutylammonium fluoride (TBAF) was thus examined. Treatment of **3** with two equivalents of TBAF afforded a mixture of two stereoisomers of cyclic acetal (**22**) resulted from the intramolecular Michael addition of alkoxide. Furthermore the silyl group on the hemiacetal oxygen in **3** was found to be inert even in the presence of theoretical amount of TBAF. After examining conditions of desilylation of **3** with TBAF, use of excess amounts of TBAF (5 equiv) was found to be successful and the desilylated



Scheme 7.



Scheme 8. Conditions: a) TBAF (5 equiv), THF; b) *p*-TsOH (7 equiv), THF, 53% (2 steps).

compound was, without isolation, treated with *p*-toluenesulfonic acid (*p*-TsOH) to give **5**(mp 135.0—135.5 °C, lit, 132—133 °C). Although the spectral data of **5** were not reported, those of our synthetic material were in good agreement with the proposed structure of garjasmine in all respects (Scheme 8). Since treatment of **22** with excess TBAF followed by *p*-TsOH did not afford **5**, it was apparent that the production of **22** was suppressed when **3** was treated with excess amount of TBAF. Probably this is because that desilylation of both silyl ether with large excess amounts of TBAF might produce monocyclic trihydroxy aldehyde (**23**) of which unsaturated ester portion was less electrophilic than that of **3**. Upon acidification of **23** cyclic acetal formation became favorable to afford **5**. Since the biological properties of **5** were not investigated yet, synthetic **5** was subjected to the antibacterial as well as antitumor examinations, in which **5** showed only weak activities.

In conclusion, the functionalization at C6 position in **2** can be achieved to give **3**, which was demonstrated to be a common intermediate for syntheses of **4** as well as **5**. The observed acid catalyzed hydroxyl group transposition reaction might present possibilities that such transposition reaction involved in the biosynthesis of those C6-oxygenated iridoids. We believe those synthetic method reported here would widen the utility of (+)-genipin as a chiral source for highly added-value materials.

Experimental

All melting points were determined with a Yanagimoto 279 micro melting point apparatus and were uncorrected. Optical rotations were measured with a JASCO MODEL DIP polarimeter. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. ^{1}H NMR spectra were measured with Hitachi R-90H (90 MHz), JEOL FX-100 (100 MHz) and JEOL GX-400 (400 MHz) spectrometers. The chemical shifts were expressed in parts per million downfield from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual solvent such as chloroform (δ=7.25) as an internal standard. Splitting pattern were indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Mass spectra were taken with a JEOL AX-500 mass spectrometer. Unless otherwise noted, all experiments were carried out using anhydrous solvents under an atmosphere of dry argon. Especially, tetrahydrofuran and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Throughout this work, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used for

thin-layer chromatographic (TLC) analyses. Daiso Gel IR-60 was used as an adsorbent for flash column chromatography.

Methyl (1*S*,5*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-butyldimethylsilyloxy)methyl]-2-oxabicyclo[4.3.0]-nona-3,7-diene-4-carboxylate (9). To a solution of (+)-genipin (**2**) (10.0 g, 44 mmol) in DMF (65 ml) was added a DMF (35 ml) solution of *t*-butyldimethylsilyl chloride (20.0 g, 133 mmol) and the mixture was stirred for 14 h at room temperature. After the reaction was quenched by addition of sat. $NaHCO_3$, the resulting mixture was extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue gave **9** as a colorless oil (19.6 g, 98%). $[\alpha]_D^{20}$ +34.9° (c=1.49, $CHCl_3$). IR ($CHCl_3$) 2940, 2860, 1690, 1630, 1460, 1385, 1250, 1160, 1135, 1090, 1020, 965, 935, 890, 830 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.04, 0.05, 0.10, 0.12 (s×4, each 3H, $-SiMe_2$×2), 0.89, 0.90 (s×2, each, 9H, $-Si^tBu$×2), 2.02 (m, 1H), 2.44 (t, 1H, J=7.3 Hz), 2.81 (dd, 1H, J=15.9, 8.5 Hz), 3.16 (q, 1H, J=7.9 Hz), 3.70 (s, 3H, –OMe), 4.21, 4.33 (d×2, each 1H, J=14.6 Hz), 4.82 (d, 1H, J=7.9 Hz), 5.79 (s, 1H), 7.46 (s, 1H). MS (m/z) (%) 455 [(M+H)$^+$], 454 (M$^+$), 439, 397 [(M$-{}^t$Bu)$^+$] (44), 365 (22), 265 (40), 233 (17), 205 (14), 191 (21), 147 (21), 131 (9), 89 (17), 73 (100). HRMS Calcd for $C_{19}H_{33}O_5Si_2$: (M$-{}^t$Bu)$^+$, 397.1866. Found: m/z 397.1866.

Methyl (1*S*,5*S*,7*S*,8*R*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-butyldimethylsilyloxy)methyl]-7,8-dihydroxy-2-oxabicyclo[4.3.0]non-3-ene-4-carboxylate (10). To a solution of **9** (11.3 g, 25 mmol) and *N*-methyl-morpholine *N*-oxide (3.1 g, 27 mmol) in *t*-BuOH (113 ml), acetone (34 ml), and H_2O (11.3 ml) was added OsO_4 (565 mg, 2.2 mmol) and the mixture was stirred for 21 h at room temperature. After the reaction was quenched with aq $NaHSO_3$ and the resulting mixture was stirred for another 36 h. After neutralization with aq NH_4Cl the reaction mixture was extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue gave **10** as a colorless needles (10.3 g, 85%). Analytical sample of **10** was obtained from recrystallization from hexane. Mp 79.5—80.5 °C $[\alpha]_D^{23}$ −43.2° (c=0.87, $CHCl_3$). IR ($CHCl_3$) 3540, 3000, 2950, 2930, 2880, 1700, 1640, 1460, 1440, 1390, 1360, 1285, 1255, 1180, 1115, 1075, 1005, 940, 835, 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.05 (s, 3H×2, $-SiMe_2$), 0.07, 0.10 (s×2, each 3H, $-SiMe_2$), 0.84, 0.88 (s×2, each 9H, $-Si^tBu$×2), 1.60 (s, 1H), 1.81 (m, 1H), 2.17 (m, 1H), 2.53 (dd, 1H, J=9.2, 3.1 Hz), 2.58 (d, 1H, J=3.1 Hz), 3.16 (m, 1H), 3.27 (s, 1H), 3.55, 3.78 (d×2, each 1H, J=10.4 Hz), 3.70 (s, 3H, –OMe), 3.89 (m, 1H), 5.33 (d, 1H, J=3.1 Hz), 7.31 (s, 1H). MS (m/z) (%) 487 [(M−H)$^+$], 473 [(M−Me)$^+$], 457 (4), 431 [(M$-{}^t$Bu)$^+$] (25), 413 (26), 299 (27), 281 (100), 249 (27), 207 (20), 139 (66), 73 (35). HRMS Calcd for $C_{19}H_{35}O_7Si_2$: (M$-{}^t$Bu)$^+$, 431.1922. Found: m/z 431.1921. Anal. Calcd for $C_{23}H_{44}O_7Si_2$: C, 56.52; H, 9.07%. Found: C, 56.48; H, 9.12%.

Methyl (1*S*,5*S*,8*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-butyldimethylsilyloxy)methyl]-8-hydroxy-2-oxabicyclo[4.3.0]nona-3,6-diene-4-carboxylate (3). To a solution of **10** (469 mg, 0.96 mmol) and DMAP (353 mg, 2.9 mmol) in CH_2Cl_2 (6 ml) was added trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol, 0.25 ml) dropwise at −78 °C and the mixture was stirred for 30 min and another 30 min at 0 °C. DBU (540 mg, 3.5 mmol, 0.53 ml) was then added and the mixture was further stirred for 35 h at room temperature. After neutralization with aq NH_4Cl, the resulting mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue gave **3** as a colorless oil (316 mg, 70%). $[\alpha]_D^{27}$ −99.6° (c=1.02, $CHCl_3$). IR ($CHCl_3$) 3525, 2950, 2925, 2850, 1700, 1635, 1460, 1440, 1360, 1290, 1250, 1170, 1120, 1080, 1020, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.04, 0.06, 0.07, 0.10 (s×4, each 3H, $-SiMe_2$×2), 0.85, 0.90 (s×2, each, 9H, $-Si^tBu$×2), 2.60 (dd, 1H, J=8.6, 1.8 Hz), 3.40, 3.62 (d×2, each 1H, J=9.8 Hz), 3.46 (s, 1H, –OH), 3.65 (m, 1H), 3.70 (s, 3H, –OMe), 5.57 (dd, 1H, J=5.5, 1.2 Hz), 5.64 (d, 1H, J=1.8 Hz), 6.22 (dd, 1H, J=5.8, 2.7 Hz), 7.30 (d, 1H, J=1.2 Hz). MS (m/z) (%) 470 (M$^+$), 455 [(M−Me)$^+$], 452, 439, 413 [(M$-{}^t$Bu)$^+$] (87), 381 (23), 321 (32), 281 (92), 249 (63), 193 (100), 73 (59). HRMS Calcd for $C_{19}H_{33}O_6Si_2$: (M$-{}^t$Bu)$^+$, 413.1816. Found: m/z 413.1841.

Methyl (1*S*,5*S*,6*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-6-ethoxy-8-hydroxymethyl-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylate (14). A solution of **3** (76.3 mg, 0.16 mmol) and PPTS (16 mg, 0.06 mmol) in dry EtOH (10 ml) was refluxed for 5.5 h. After evaporation of solvent, the reaction mixture was extracted with hexane and EtOAc. The organic phase was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue gave **14** (29.1 mg, 46%) and minor product (7.0 mg, 11%) as both colorless oils. **14**: $[\alpha]_D^{26}$ +62.7° (c=1.17, $CHCl_3$). IR ($CHCl_3$) 3475, 2940, 2850, 1700, 1635, 1460, 1440, 1385, 1340, 1310, 1290, 1165, 1120, 1090, 950, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ= 0.12, 0.15 (s×2, each 3H, $-SiMe_2$), 0.91 (s, 9H, $-Si^tBu$), 1.04 (t, 3H, J=6.7 Hz, $-CH_3$), 2.45 (t, 1H, J=7.6 Hz), 3.00 (t, 1H, J=6.7 Hz), 3.32—3.47 (m, 2H, $-OCH_2CH_3$), 3.72 (s, 3H, $-CH_3$), 4.30, 4.38 (d×2, each 2H, J=15.6 Hz, $-CH_2OH$), 4.44 (dd, 1H, J=6.1, 2.4 Hz), 4.92 (d, 1H, J= 7.9 Hz), 6.07 (d, 1H, J=1.8 Hz), 7.57 (d, 1H, J=1.2 Hz). MS (m/z) (%) 384 (M$^+$), 366 (4), 353 (6), 337 (5), 327 [(M$-{}^t$Bu)$^+$] (48), 281 (50), 249 (38), 235 (73), 221 (32), 189 (27), 175 (31), 161 (23), 147 (32), 73 (100). HRMS Calcd for $C_{15}H_{23}O_6Si$: (M$-{}^t$Bu)$^+$, 327.1263. Found: m/z 327.1255.

The minor product: $[\alpha]_D^{27}$ −18.8° (c=0.46, $CHCl_3$). IR ($CHCl_3$) 3450, 2950, 2875, 1705, 1640, 1470, 1440, 1385, 1350, 1300, 1210, 1185, 1130, 1090, 950, 905, 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.09, 0.12 (s×2, each 3H, $-SiMe_2$), 0.87 (s, 9H, $-Si^tBu$), 1.22 (t, 3H, J=5.2 Hz), 3.13—3.22 (2H), 3.56—3.80 (2H, $-OCH_2CH_3$), 3.72 (s, 3H, $-CH_3$), 4.19—4.33 (3H), 5.81 (d, 1H, J=1.8 Hz), 5.82 (s, 1H), 7.36 (s, 1H). MS (m/z) (%) 384 (M$^+$), 366 (7), 353 (12), 337 (8), 327 [(M$-{}^t$Bu)$^+$] (65), 281 (71), 249 (49), 235 (60), 221 (34), 189 (34), 175 (41), 165 (23), 147 (37), 73 (100). HRMS Calcd for $C_{15}H_{23}O_6Si$: (M$-{}^t$Bu)$^+$, 327.1263. Found: m/z 327.1248.

Methyl (1*S*,5*S*,8*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-hydroxy-8-hydroxymethyl-2-oxabicyclo[4.3.0]nona-3,6-diene-4-carboxylate (15). A solution of **7** (58.0 mg, 0.12 mmol) and PPTS (15 mg, 0.06 mmol) in acetone (2.4 ml) and H_2O (1.2 ml) was refluxed for 2.5 h. After evaporation of acetone in vacuo, the reaction mixture

was extracted with hexane and EtOAc. The organic phase was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue gave **15** as colorless prisms (13.4 mg, 31%) accompanied with starting material (29.1 mg, 50% recovery). Analytical sample of **15** was obtained from recrystallization from hexane–EtOAc. Mp 70.0—71.0 °C. $[\alpha]_D^{27}$ −75.1° (c=1.12, $CHCl_3$). IR ($CHCl_3$) 3550, 2970, 2870, 1700, 1640, 1440, 1380, 1290, 1120, 1080, 940, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.13, 0.15 (s×2, each 3H, –$SiMe_2$), 0.88 (s, 9H, –Si^{t}Bu), 2.37 (dd, 1H, J=8.2, 4.2 Hz, –CH_2OH), 2.47 (dd, 1H, J=7.3, 4.9 Hz), 2.84 (s, 1H, –O*H*), 3.55 (dd, 1H, J=11.6, 7.9 Hz), 3.70 (m, 1H), 3.71 (s, 3H, –OMe), 3.81 (m, 1H), 5.23 (d, 1H, J=4.9 Hz), 5.62 (dd, 1H, J=5.8, 2.1 Hz), 6.22 (dd, 1H, J=5.5, 2.5 Hz), 7.37 (d, 1H, J=1.8 Hz). MS (m/z) (%) 339 (8), 325 [(M−CH_2OH)$^+$] (13), 299 [(M−^{t}Bu)$^+$] (15), 281 (28), 249 (55), 193 (59), 73 (100). HRMS Calcd for $C_{13}H_{19}O_6Si$: (M−^{t}Bu)$^+$, 299.0951. Found: m/z 299.0924.

Methyl (1*S*,5*S*,6*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-6-hydroxy-8-hydroxymethyl-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylate (16) and Methyl (1*S*,5*S*,6*R*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-6-hydroxy-8-hydroxymethyl-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylate (17). A solution of **3** (126 mg, 0.27 mmol) and PPTS (33 mg, 0.13 mmol) in acetone (3.5 ml) and H_2O (1.5 ml) was refluxed for 10 h. After evaporation of aceton in vacuo, the reaction mixture was extracted with hexane and EtOAc. The organic phase was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue gave **16** (46.8 mg, 49%) as colorless prisms and **17** (11.2 mg, 12%) as colorless prisms accompanied with starting material (10.0 mg, 8% recovery) and **15** (7.0 mg, 7%), respectively. Analytical samples of **16** and **17** were obtained from recrystallization from hexane–EtOAc. **16**: Mp 130—131 °C. $[\alpha]_D^{29}$ +48.6° (c=0.65, $CHCl_3$). IR ($CHCl_3$) 3620, 3480, 2860, 2850, 1685, 1620, 1420, 1280, 1150, 1100, 880, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.11, 0.14 (s×2, each 3H, –$SiMe_2$), 0.90 (s, 9H, –Si^{t}Bu), 2.54 (t, 1H, J=7.9 Hz), 2.96 (m, 1H), 3.73 (s, 3H, –OMe), 4.30, 4.39 (d×2, each 1H, J=15.2 Hz), 4.84 (d, 1H, J=7.9 Hz), 4.92 (m, 1H), 6.00 (br, 1H), 7.65 (br s, 1H). MS (m/z) (%) 339 (6), 299 [(M−^{t}Bu)$^+$] (10), 281 (16), 267 (100), 249 (23), 235 (30), 221 (17), 207 (25), 175 (31), 147 (28), 119 (26), 73 (94). HRMS Calcd for $C_{13}H_{19}O_6Si$: [(M−^{t}Bu)$^+$] 299.0951. Found: m/z 299.0931. Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.28; H, 7.92%. Found: C, 57.21; H, 7.93%.

17: Mp 109—110 °C. $[\alpha]_D^{30}$ −3.3° (c=0.34, $CHCl_3$). IR ($CHCl_3$) 3490, 2960, 2870, 1680, 1615, 1440, 1385, 1310, 1165, 1120, 945, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ= 0.11, 0.14 (s×2, each 3H, –$SiMe_2$), 0.91 (s, 9H, –Si^{t}Bu), 2.77 (dt, 1H, J=7.9, 1.0 Hz), 2.91 (m, 1H), 3.76 (s, 3H, –OMe), 4.26, 4.31 (d×2, each 1H, J=15.3 Hz), 4.42 (br, 1H), 4.57 (d, 1H, J=8.5 Hz), 4.61 (m, 1H), 5.90 (s, 1H), 7.53 (s, 1H). MS (m/z) (%) 338 [(M−H_2O)$^+$] (6), 325 (5), 306 (7), 281 (6), 267 (88), 249 (33), 221 (16), 175 (24), 147 (17), 119 (15), 75 (90), 73 (100). HRMS Calcd for $C_{17}H_{26}O_5Si$: [(M−H_2O)$^+$] 338.1549. Found: m/z 338.1570. Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.28; H, 7.92%. Found: C, 57.80; H, 8.23%.

Methyl (1*S*,5*S*,6*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-butyldimethylsilyloxy)methyl]-6-hydroxy-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylate (13) and Methyl (1*S*,5*S*,6*R*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-butyldimethylsilyloxy)methyl]-6-hydroxy-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylate (12).

a) via enone 11. To a solution of PDC (2.26 g, 6.0 mmol) in DMF (4 ml) was added a DMF solution (2 ml) of **3** (566 mg, 1.2 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 24 h. After dilution with ether, the resulting mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. Flash chromatography of the residue gave **11** (231 mg, 41%) as light yellow oil, which gradually decomposed on standing.

11: IR ($CHCl_3$) 2940, 2900, 1710, 1705, 1640, 1460, 1305, 1255, 1105, 950 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.07, 0.08, 0.10, 0.13 (s×4, each 3H, –$SiMe_2$×2), 0.90, 0.91 (s×2, each 9H, –Si^{t}Bu×2), 2.75 (t, 1H, J=6.7 Hz), 3.59 (dd, 1H, J=6.7, 1.8 Hz), 3.78 (s, 3H, –OMe), 4.41 (brd, 1H, J=18.9 Hz), 4.47 (d, 1H, J=7.3 Hz), 4.69 (dd, 1H, J=18.3, 1.8 Hz), 6.31 (brs, 1H), 7.44 (d, 1H, J=1.2 Hz).

To a methanol solution (1 ml) of **11** (48.0 mg, 0.1 mmol) and cerium(III) chloride heptahydrate (95.0 mg, 0.25 mmol) was added sodium borohydride (24.0 mg, 0.62 mmol) at 0 °C and the mixture was stirred for 40 min. The reaction was quenched with aq NH_4Cl and the resulting mixture was extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Preparative thin layer chromatography of the residue afforded **13** (21.6 mg, 45%) and **12** (14.2 mg, 30%) both as colorless oils.

3: $[\alpha]_D^{26}$ +31.1° (c=1.21, $CHCl_3$). IR ($CHCl_3$) 3400, 2960, 2940, 2870, 1690, 1615, 1420, 1300, 1255, 1160, 1100, 945, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.05 (s, 3H×2, –$SiMe_2$), 0.10, 0.12 (s×2, each 3H, –$SiMe_2$), 0.90, 0.91 (s×2, each 9H, –Si^{t}Bu×2), 1.53 (br, 1H), 2.38 (t, 1H, J=7.9 Hz), 2.98 (m, 1H), 3.73 (s, 3H, –OMe), 4.22, 4.44 (d×2, each 1H, J=15.9 Hz, –*CH*$_2$OSi), 4.83 (d, 1H, J=8.5 Hz), 4.90 (m, 1H), 6.06 (d, 1H, J=1.8 Hz), 7.65 (d, 1H, J=1.2 Hz). MS (m/z) (%) 470 (M$^+$) (13), 413 [(M−^{t}Bu)$^+$] (45), 395 (22), 381 (64), 321 (63), 281 (65), 249 (47), 235 (58), 207 (33), 147 (49), 73 (100). HRMS Calcd for $C_{23}H_{42}O_6Si_2$: (M$^+$) 470.2520. Found: m/z 470.2522.

12: $[\alpha]_D^{21}$ +4.6° (c=0.33, $CHCl_3$). IR ($CHCl_3$) 3480, 2940, 2850, 1680, 1615, 1310, 1255, 1120, 1100, 945, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.04, 0.05 (s×2, each 3H, –$SiMe_2$×2), 0.10, 0.12 (s×2, each 3H, –$SiMe_2$), 0.89, 0.90 (s×2, each 9H, –Si^{t}Bu×2), 1.23 (br, 1H, –OH), 2.61 (m, 1H), 2.90 (m, 1H), 3.76 (s, 3H, –OMe), 4.19 (m, 1H), 4.32—4.38 (2H), 4.56 (d, 1H, J=8.5 Hz), 4.59 (m, 1H), 5.93 (d, 1H, J=1.2 Hz), 7.52 (d, 1H, J=1.2 Hz). MS (m/z) (%) 470 (M$^+$) (8), 413 [(M−^{t}Bu)$^+$] (33), 381 (52), 325 (28), 281 (36), 249 (60), 73 (100). HRMS Calcd for $C_{23}H_{42}O_6Si_2$: (M$^+$) 470.2520. Found: m/z 470.2537.

b) from 16 and 17. To a suspension of *t*-butyldimethylsilyl chloride (41.0 mg, 0.27 mmol) and imidazole (24.8 mg, 0.36 mmol) in DMF (0.5 ml) was added a DMF (0.5 ml) solution of **16** (65.0 mg, 0.18 mmol) at room temperature. After stirring the mixture for 2.5 h, the reaction mixture was diluted with water and extracted with EtOAc and hexane. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue afforded **13** (76.5 mg,

85%) as a colorless oil. The similar procedure was applied to **17** to yield silyl ether (**12**) (59%, 39% recovery of starting material) as a colorless oil. The spectral data of these materials were identical in all respects with those of **13** and **12** obtained by method a, respectively.

(1*S*,5*S*,6*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-Butyldimethylsilyloxy)methyl]-6-hydroxy-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylic Acid (18). To a suspension of potassium hydride (35 wt%, 30 mg, 0.26 mmol, washed with hexane prior to use) in THF (1 ml) was added a THF solution (0.5 ml) of **13** (120 mg, 0.25 mmol) at −78 °C and the mixture was warmed up to room temperature for 1.5 h under stirring. The resulting mixture was quenched with water and extracted with EtOAc and hexane. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ filtered then concentrated in vacuo. Flash chromatography of the residue afforded **18** (66.0 mg, 57%) as a colorless oil. $[\alpha]_D^{26}+23.3°$ (c=0.93, $CHCl_3$). IR ($CHCl_3$) 3600—2400, 2970, 2950, 2870, 1670, 1630, 1295, 1260, 1170, 1125, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.05 (s, 3H×2, $-SiMe_2\times2$), 0.11, 0.14 (s×2, each 3H, $-SiMe_2$), 0.90, 0.91 (s×2, each 9H, $-Si^tBu\times2$), 1.23 (br, 1H), 2.39 (t, 1H, J=7.6 Hz), 2.97 (m, 1H), 4.23, 4.43 (d×2, each 1H, J=15.8 Hz), 4.86 (d, 1H, J=8.0 Hz), 4.91 (m, 1H), 6.06 (br, 1H), 7.74 (br, 1H). MS (m/z) (%) 456 (M^+), 438 [$(M-H_2O)^+$], 423 [$(M-H_2O-Me)^+$], 399 [$(M-{}^tBu)^+$] (14), 381 (73), 307 (28), 267 (30), 249 (52), 221 (85), 147 (90), 75 (80), 73 (100). HRMS Calcd for $C_{18}H_{31}O_6Si_2$: [$(M-{}^tBu)^+$] 399.1659. Found: m/z 399.1649.

(1*S*,5*S*,6*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-8-[(*t*-butyldimethylsilyloxy)methyl]-6-hydroxy-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylic Acid Lactone (19). To a solution of **18** (10.1 mg, 0.02 mmol) in CH_2Cl_2 (1 ml) was added DCC (4 mg, 0.03 mmol) and the mixture was stirred for 2 h at room temperature. After dilution with H_2O the reaction mixture was extracted with EtOAc and hexane. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the resiude afforded **19** (9.2 mg, 96%) as a colorless oil. $[\alpha]_D^{24}-88.1°$ (c=1.42, $CHCl_3$). IR ($CHCl_3$) 2950, 2930, 2850, 1745, 1655, 1200, 1110, 1080, 835 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.03, 0.04 (s×2, each 3H, $-SiMe_2$), 0.10, 0.14 (s×2, each 3H, $-SiMe_2$), 0.87, 0.88 (s×2, each 9H, $-Si^tBu\times2$), 3.13 (m, 1H), 3.54 (dt, 1H, J=6.7, 1.8 Hz), 4.20 (m, 2H), 5.46 (m, 1H), 5.54 (br, 1H), 5.69 (d, 1H, J=1.2 Hz), 7.22 (d, 1H). MS (m/z) (%) 439 [$(M+H)^+$] (2), 423 [$(M-Me)^+$] (2), 381 [$(M-{}^tBu)^+$] (100), 249 (98), 221 (26), 149 (28), 73 (84). HRMS Calcd for $C_{18}H_{29}O_5Si_2$: [$(M-{}^tBu)^+$] 381.1554. Found: m/z 381.1562.

(1*S*,5*S*,6*S*,9*S*)-1-(*t*-Butyldimethylsilyloxy)-6-hydroxy-8-hydroxymethyl-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylic Acid Lactone (20). A mixture of **19** (27.2 mg, 0.06 mmol) and PPTS (5 mg, 0.04 mmol) in acetone (3 ml) and H_2O (1 ml) was refluxed for 1.5 h. After concentration of the reaction mixture in vacuo, the residue was diluted with sat. $NaHCO_3$ and extracted with EtOAc and hexane. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue afforded **20** (13.5 mg, 67%) as a colorless oil. $[\alpha]_D^{23}-143.5°$ (c=1.45, $CHCl_3$). IR ($CHCl_3$) 3420, 2950, 2870, 1750, 1660, 1120, 1020, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.11, 0.15 (s×2, each 3H, $-SiMe_2$), 0.87 (s, 9H, $-Si^tBu$), 3.16 (m, 1H), 3.57 (dt, 1H, J=6.7, 1.8 Hz), 4.25 (m, 2H), 5.47 (m, 1H), 5.63 (br, 1H), 5.71 (d, 1H, J=1.8 Hz), 7.23 (br, 1H). MS (m/z) (%) 325 [$(M+H)^+$] (2), 267 [$(M-{}^tBu)^+$] (40), 249 (83), 221 (21), 193 (20), 175 (31), 147 (30), 75 (100), 73 (97). HRMS Calcd for $C_{12}H_{15}O_5Si$: [$(M-{}^tBu)^+$], 267.0689. Found: m/z 267.0676.

(1*S*,5*S*,6*S*,9*S*)-8-Acetoxymethyl-1-(*t*-butyldimethylsilyloxy)-6-hydroxy-2-oxabicyclo[4.3.0]nona-3,7-diene-4-carboxylic Acid Lactone (4). To a mixture of **20** (30.8 mg, 0.10 mmol) and pyridine (0.5 ml) was added acetic anhydride (0.03 ml, 0.03 mmol) and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with toluene and excess reagents were azeotropically removed in vacuo. Flash chromatography of the residue gave asperuloside aglucon silyl ether (**4**) (31.4 mg, 90 %) as a colorless oil. $[\alpha]_D^{24}-125.7°$ (c=1.58, $CHCl_3$). IR ($CHCl_3$) 2970, 2950, 2870, 1750, 1660, 1465, 1370, 1180, 1110, 1080, 1020, 990, 835 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.11, 0.15 (s×2, each 3H, $-SiMe_2$), 0.87 (s, 9H, $-Si^tBu$), 2.06 (s, 3H, $-OCOCH_3$), 3.10 (m, 1H), 3.57 (dt, 1H, J=6.7, 2.4 Hz), 4.61 (d, 1H, J=14.0 Hz), 4.65 (dd, 1H, J=14.0, 1.2 Hz), 5.47 (m, 1H), 5.61 (d, 1H, J=1.8 Hz), 5.70 (br, 1H), 7.22 (d, 1H, J=1.8 Hz). MS (m/z) (%) 309 [$(M-{}^tBu)^+$] (29), 291 (6), 267 (10), 249 (100), 221 (22), 175 (23), 117 (48), 75 (62), 73 (53). HRMS Calcd for $C_{14}H_{17}O_6Si$: [$(M-{}^tBu)^+$] 309.0795. Found: m/z 309.0811.

Garjasmine (5). To a solution of **3** (31.0 mg, 0.07 mmol) in THF (1.5 ml) was added TBAF (1 M in THF, 0.43 ml, 0.43 mmol) at 0 °C and the mixture was stirred for 4 h (M=mol dm^{-3}). A THF solution (0.5 ml) of *p*-TsOH was then added and the mixture was further stirred for 3 d. After quenched with sat. $NaHCO_3$ the reaction mixture was extracted with EtOAc and hexane. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Flash chromatography of the residue afforded **5** (9.1 mg, 48%) as colorless needles. Analytical sample was obtained by recrystallization from hexane–EtOAc. Mp 135.0—135.5 °C (lit, 132—133 °C). $[\alpha]_D^{24}+254.0°$ (c=0.40, $CHCl_3$). IR ($CHCl_3$) 3600, 3400, 3000, 2950, 1700, 1645, 1440, 1290, 1190, 1090, 1040, 990 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.87 (dd, 1H, J=9.8, 6.1 Hz), 3.73 (s, 3H, $-CO_2CH_3$), 3.82 (brd, 1H, J=9.8 Hz), 3.90, 3.92 (d×2, each 1H, J=9.8 Hz), 5.63 (d, 1H, J=6.1 Hz), 5.72 (dd, 1H, J=5.5, 2.4 Hz), 5.99 (dd, 1H, J=5.5, 1.8 Hz), 7.47 (s, 1H). MS (m/z) (%) 224 (M^+) (8), 193 (5), 162 (15), 138 (15), 102 (13), 85 (68), 83 (100). HRMS Calcd for $C_{11}H_{12}O_5$: (M^+), 224.0685. Found: m/z 224.0676. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39%. Found: C, 58.91; H, 5.40%.

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17) Because of difficulties to hydrolyze the ester without C6 hydroxyl group, we could not investigate the reaction using carboxylic acid as internal nucleophile in the hydroxyl transposition reaction.