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Tetrahedron 60 (2004) 1365–1373
Tetrahedron

Cationic zirconocene- or hafnocene-based Lewis acids in organic synthesis: glycoside–flavonoid analogy

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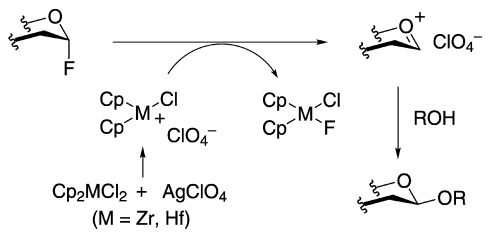
Received 23 July 2003; accepted 7 August 2003

Abstract—Cationic metallocene species, generated from Cp_2MCl_2 and $AgClO_4$ (M=Zr, Hf), were used for the glycosylation of catechin derivative **2**, enabling a concise synthesis of a glycosyl flavonoid, astilbin (**1**). Further study revealed the efficiency of this Lewis acidic species for S_N1-type activation of the C(4) position of catechin derivative **11**, enabling selective substitution with various nucleophiles.

1. Introduction

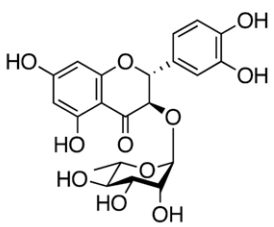
Lewis acidic activation of various functionalities is one of the current focuses in organic synthesis,[1] and has experienced considerable advance[2] during the last two decades. In the case of our study in carbohydrate synthesis, we found that the metallocene-based promoters,[3] Cp_2MCl_2–AgX (M=Ti, Zr, Hf; X^-=ClO_4^-, OTf^-), serve as efficient activator of glycosyl fluorides[3a,b] or acetates.[3c] These reagents have found various applications in the synthesis of complex oligosaccharides.[4]



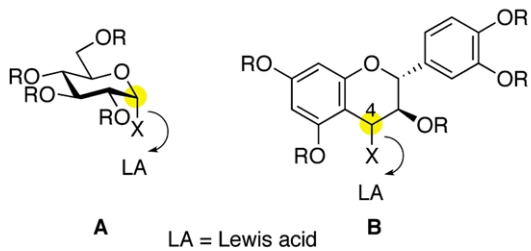
The high reactivity is ascribed to the cationic metallocene species of high electrophilicity, which could be further reinforced by generating the corresponding dicationic species (Eq. 1).[5]

$$Cp_2MCl_2 + 2\ AgClO_4 \longrightarrow Cp_2M^{2+} \cdot 2\ ClO_4^- + 2\ AgCl \quad (1)$$
(M = Zr, Hf)

We wished to develop a novel application of these metallocene-based Lewis acids, that is, the extension of this methodology to the functionalization of flavonoids. In particular, we endeavored to utilize this approach to an implement of our recently reported synthesis of astilbin (**1**), a glycosyl flavonoid isolated from Chinese folk medicine.[6,7] Described in the following report are (1) the synthetic route of **1**, including glycosidation study, and (2) the implication of unsuccessful glycosylation within the context of polyphenol synthesis. The latter aspect can be summarized as the controlled S_N1-type activation of the C(4) position of catechin derivatives **B**, which represents an interesting analogy to the glycosidic activation **A**.



astilbin (**1**)



Keywords: Zirconocene; Hafnocene; Astilbin; Flavonoid; Catechin.
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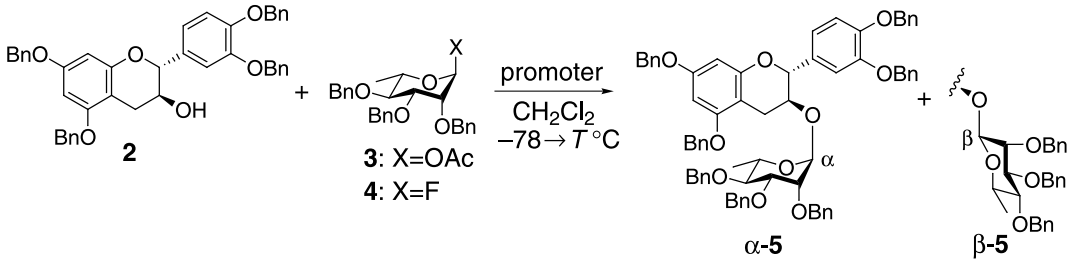
doi:10.1016/j.tet.2003.08.076

Table 1. Lewis acid-promoted glycosylation of **2**



Run	X	Promoter	T (°C)[a]	**5** (yield, %)	Recovery of **2** (%)
1	OAc	Cp_2ZrCl_2,[b] $AgClO_4$[c]	−35	α (74)	8
2	OAc	Cp_2HfCl_2,[b] $AgClO_4$[c]	−35	α (82)	7
3	OAc	$BF_3{\cdot}OEt_2$[d]	25	α (38)	16
4	OAc	TMSOTf[b]	−30	α (55), β (16)	16
5	OAc	$SnCl_4$[e]	−30	α (10), β (20)	18
6	F	Cp_2HfCl_2,[b] $AgClO_4$[c]	−55	α (57), β (31)	10
7	F	Cp_2HfCl_2,[b] AgOTf[c]	−72	α (47), β (36)	10

[a] The reaction mixture was gradually warmed to the temperature over 60 min.
[b] 1.1 mol equiv.
[c] 2.2 mol equiv.
[d] 2.0 mol equiv.
[e] 1.0 mol equiv.

2. Results and discussion

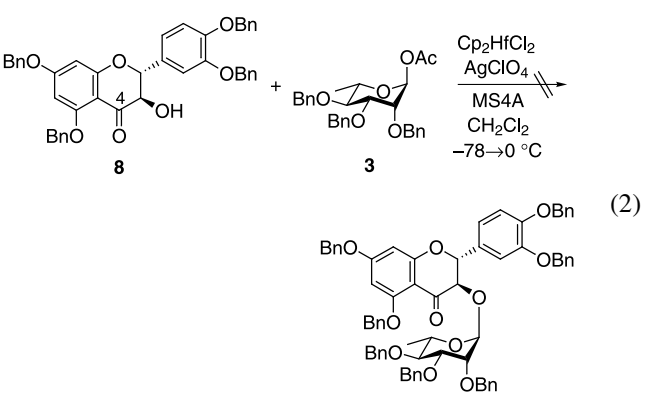
2.1. Successful route to astilbin (1)

Our synthetic route to **1** consisted of two stages, (1) glycosylation of the catechin derivative **2**,[8] and (2) oxidation of the C(4) position of the flavan skeleton. The first stage, that is, the glycosylation required considerable optimization as summarized in Table 1. The optimum conditions were the use of Cp_2ZrCl_2 or Cp_2HfCl_2 coupled with $AgClO_4$ as the activator for L-rhamnosyl acetate **3**,[9] and the reaction in CH_2Cl_2 (−78→−35 °C) afforded good yield of the desired α-glycoside **5** (runs 1 and 2). In contrast, other promoters gave only unsatisfactory results (runs 3–5). $BF_3{\cdot}OEt_2$ required higher temperature for the activation of acetate **3**, giving poor yield of α-**5** (run 3). The reactions smoothly proceeded with TMSOTf at low temperature, giving the glycoside α-**5**, which, however, was accompanied by a considerable amount of the β-anomer (run 4). $SnCl_4$ was even more β-selective, although the yield was poor. These results were amazing that rhamnosidation is generally α-selective, which is favored under both kinetic as well as thermodynamic conditions. The factor relevant to this α/β selectivity seemed quite delicate, since it was found that the stereoselectivity diminished by replacing the acetate donor **3** by the corresponding fluoride donor **4**[10] under the hafnocene-promoted conditions (runs 6 and 7, cf. run 2).

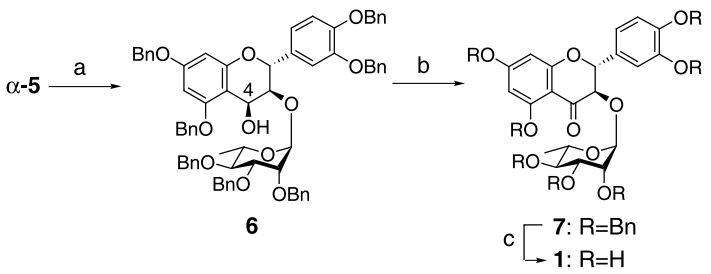
Having the desired glycoside α-**5** in hand, the stage was set for its conversion to the final target (**1**) (Scheme 1). Thus, oxidation of the C(4) position of the flavan skeleton of α-**5** was easily effected by the following two steps; upon treatment of α-**5** with DDQ (H_2O, CH_2Cl_2, 25 °C, 5 h), alcohol **6** was obtained in 66% yield as a single diastereomer, which was then treated with PDC (CH_2Cl_2, 25 °C, 19 h) to give ketone **7** in 85% yield. It is interesting to note that the C(4)-hydroxylation occurred from the β-side, which is a general tendency of reactions at this position (vide infra, Tables 2 and 3). Final removal of the seven benzyl protecting groups in **7** was effected by employing Pd–black as the catalyst, and the target **1** was obtained in 91% yield. All the physical data of **1** (^1H and ^{13}C NMR, IR, $[\alpha]_D$, mp) were fully identical with those of the authentic specimen by direct comparison, $[\alpha]_D^{18}$ −11 (*c* 0.52, EtOH), [lit. $[\alpha]_D^{25}$ −13.6 (*c* 0.52, EtOH)],[6d] mp 179–182 °C, [lit. mp 179–180 °C].[6b]

2.2. Implication from unsuccessful glycosidation attempts

At the preliminary stage of this synthetic study, we attempted also the glycosylation of the flavanols, **8** and **9**, with higher oxidation levels at C(4).[7] Upon attempted glycosylation of keto alcohol **8** by using Cp_2HfCl_2 and $AgClO_4$ as the promoter in CH_2Cl_2 at −78 °C followed by warming to 0 °C, no glycosylated product was obtained, although acetate **3** was completely consumed (Eq. 2). This failure was in line with the general difficulty in glycosylation of a hydrogen-bonded hydroxy group. Furthermore, poor recovery of the glycosyl acceptor **8** (40%) suggested its instability under glycosylation conditions.

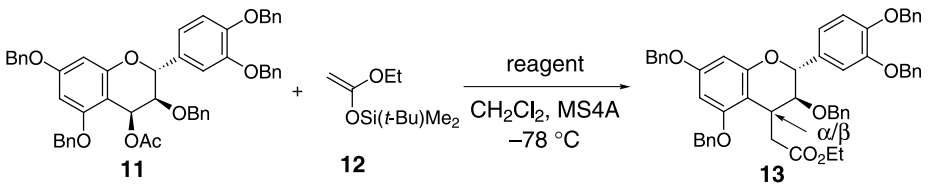


(2)



Scheme 1. *Reagents and conditions*: (a) DDQ, H_2O, CH_2Cl_2, 25 °C, 5 h (66%); (b) PDC, CH_2Cl_2, 25 °C, 40 h (85%); (c) H_2, Pd–black, MeOH, 25 °C, 50 h (91%).

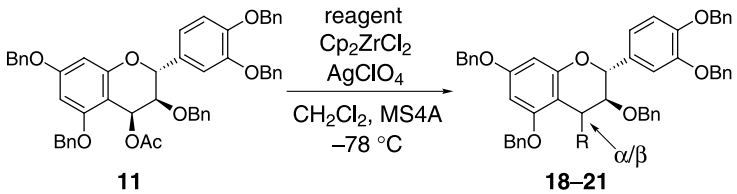
Table 2. Activation of **11** by using various Lewis acids

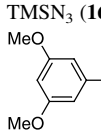
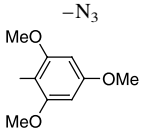


Run	Reagent (mol equiv.)	Time (min)	Yield (%)	α/β
1	Cp_2ZrCl_2 (1.2), $AgClO_4$(2.4)	<10	80	16:84
2	Cp_2ZrCl_2 (0.1), $AgClO_4$(0.2)	15	85	16:84
3	Cp_2ZrCl_2 (0.1), AgOTf(0.2)	240[a]	98	15:85
4	Cp_2ZrCl_2 (0.1)	15	n.r.[b]	—
5	$AgClO_4$ (0.2)	15	n.r.[b]	—
6	$BF_3{\cdot}OEt_2$ (1.2)	60	95	13:87
7	$BF_3{\cdot}OEt_2$ (0.1)	15	n.r.[b]	—
8	TMSOTf (1.2)	60	95	13:87
9	TMSOTf (0.1)	15	n.r.[b]	—

[a] At −78→0 °C.
[b] n.r., no reaction.

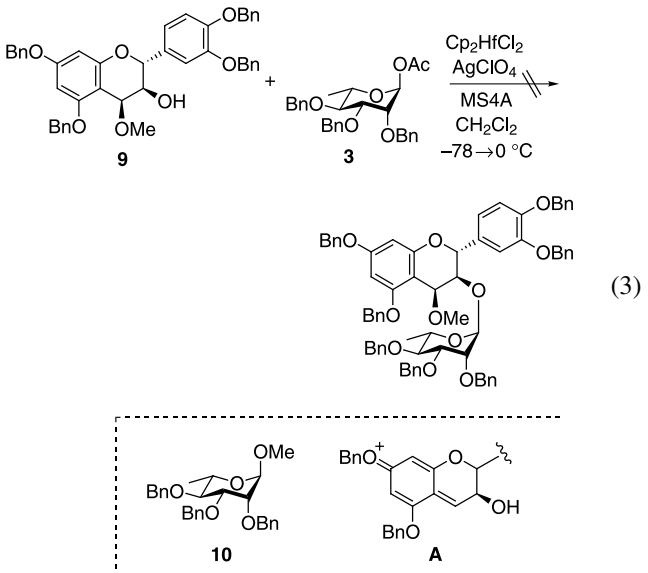
Table 3. Stoichiometric reaction of **11**[a]



Run	Reagent	Product	R	Time (min)	Yield (%)	α/β
1	 (**14**)	**18**	$-C(Me)_2CO_2i$-Pr	10	92	<1/>99
2	PhSH (**15**)	**19**	−SPh	10	83	5/95
3	$TMSN_3$ (**16**)	**20**	$-N_3$	10	52	6/94
4	 (**17**)	**21**		10	80	84/16

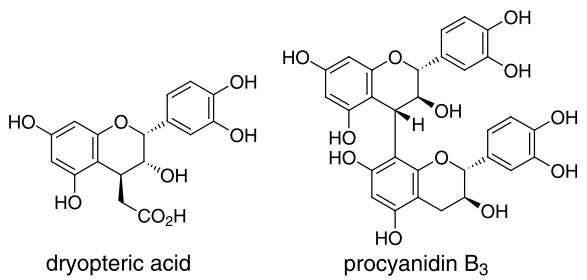
[a] Reagent (3 mol equiv.), Cp_2ZrCl_2 (1.2 mol equiv.), $AgClO_4$ (2.4 mol equiv.).

The glycosylation was also unsuccessful for the acceptor **9**, however, for a different reason. Decomposition of **9** was the main event observed, as rationalized by the Lewis acid-induced departure of the C(4)-methoxy group to generate a quinonemethide **A**, which undergoes various side reactions. Convincing evidence was the formation of the methyl glycoside **10**, albeit in 12% yield, suggesting that the methanol liberated from **9** was glycosylated.

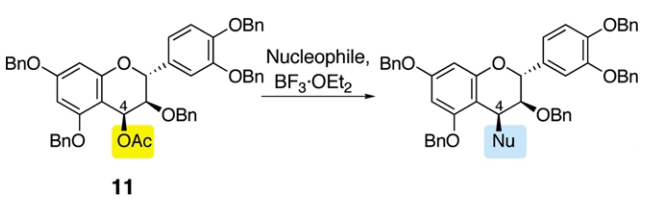


(3)

This result, though unfortunate for the total synthesis, gave us an interesting hint in flavonoid synthesis. Namely, the potential reactivity of the C(4)-position of flavan is similar to that of the anomeric position of a sugar. Activation by a Lewis acid could generate a resonance stabilized cationic species as **A**, providing opportunity for bond formation at this particular position. Given the case, this potential reactivity must be relevant to the enormous structure diversity of natural flavonoids, as exemplified by two natural products shown below.[11]



Through preliminary experiments along these lines, it soon became clear that stereoselective substitution was possible for acetate **11** in the presence of a common Lewis acid, for example, $BF_3{\cdot}OEt_2$, giving substitution products in good yield (Eq. 4).[12]



(4)

In further pursuit of the more effective protocols, we were delighted to find that the cationic metallocene species serve as effective catalyst for this reaction.

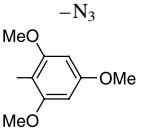
As a model reaction to compare various Lewis acids, the reaction of acetate **11** with ketene silyl acetal **12** (3 mol equiv.) was employed (Table 2). Upon treatment of **11** and **12** with Cp_2ZrCl_2 (1.2 mol equiv.) and $AgClO_4$ (2.4 mol equiv.), the reaction completed almost instantaneously at −78 °C, giving the substitution product **13** in 80% yield (run 1). The activation level offered by this protocol seemed to be too high, judging from the substantial formation of oligomeric products derived from self-condensation of **11** (ca. 15%). We were pleased to find that this side reaction could be effectively suppressed by employing catalytic conditions (run 2): In the presence of Cp_2ZrCl_2 (0.1 mol equiv.) and $AgClO_4$ (0.2 mol equiv.), the reaction smoothly proceeded at −78 °C within 15 min, giving the product **13** in a higher yield than that of the stoichiometric case. Change in the counter anion from ClO_4^- to TfO^- led to much slower reaction, which, however, led to a cleaner formation of **13** in almost quantitative yield (run 3).

It should be noted that the combination of Cp_2ZrCl_2 and a Ag(I) salt was essential for this catalytic reaction. Thus, independent use of these did not work as a promoter (runs 4 and 5). The catalytic activity is quite high, because other promoters, such as $BF_3{\cdot}OEt_2$ and TMSOTf, were only effective when they were used in a stoichiometric amount (runs 6 and 8, cf. runs 7 and 9).

Table 3 shows the reactions of **11** with various other nucleophiles **14**–**17** by using stoichiometric amount of Cp_2ZrCl_2 (1.2 mol equiv.) and $AgClO_4$ (2.4 mol equiv.).[12] Under these conditions, a sterically demanding ketene silyl acetal **14** took part in the reaction at −78 °C within 15 min, and gave the substitution product in excellent yield. An electron-rich aromatic **15** was also smoothly introduced, giving the arylated product in high yield. A sulfur nucleophile, PhSH, and a nitrogen nucleophile, $TMSN_3$, cleanly took part in the reaction. Notably, in all cases, the reactions again proceeded faster than $BF_3{\cdot}OEt_2$ promoted conditions described in our previous report.[12]

Table 4 shows the efficacy of the cationic zirconocene species, which was further highlighted by the catalytic conditions. The reactions listed in Table 3 were just repeated in the presence of Cp_2ZrCl_2 (0.1 mol equiv.) and

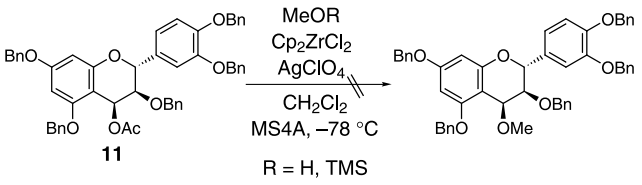
Table 4. Catalytic reaction of **11**[a]

Run	Reagent	Product	R	Time	Yield (%)	α/β
1	**14**	**18**	$-C(Me)_2CO_2i$-Pr	3 h	94	<1/>99
2	**15**	**19**	−SPh	15 min	88	4/96
3	**16**	**20**	$-N_3$	15 min	81	2/98
4	**17**	**21**		21 h	96	94/6

[a] Reagent (3 mol equiv.), Cp_2ZrCl_2 (10 mol%), $AgClO_4$ (20 mol%).

$AgClO_4$ (0.2 mol equiv.), which gave good to excellent yields of products, albeit longer reaction periods were required. It is noted that the reaction rate with hetero nucleophiles, azide and sulfide, remained rather rapid (runs 2 and 3), while the reactions with carbon nucleophiles became considerably slower, although still synthetically acceptable (runs 1 and 4).

In contrast to these positive results, introduction of oxygen nucleophiles has been so far unsuccessful. For example, MeOH or its TMS ether (TMSOMe) failed to react under the stoichiometric conditions. Formation of considerable amount of oligomeric products by self-condensation of **11** was observed, which could be rationalized by the lability of C(4)-methoxylated product. Even if formed, it would undergo reactivation under Lewis acidic conditions to cause oligomerization.



3. Conclusion

Through the synthetic study of a biologically active glycosyl flavonoid, we uncovered the high reactivity of cationic metallocene-based Lewis acids, not only as a glycosylation agent, but also as a catalyst for the S_N1-type reaction of flavan acetate **11** with various nucleophiles. Further study of these reactions is under way in our laboratory.

4. Experimental

4.1. General

All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Dichloromethane was distilled successively from P_2O_5 and CaH_2 and stored over 4 Å molecular sieves. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. For silica gel preparative TLC (PTLC) was performed on Merck silica gel 60 PF_{254} (Art 7747). Melting point (mp) determinations were performed by using a Yanako MP-S3 instrument and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL lambda300 spectrometer or Bruker DRX500. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. High resolution mass spectra (HRMS) were obtained with a JEOL JMS AX505HA spectrometer. Optical rotations ($[\alpha]_D$) were measured on a DIP-1000 polarimeter.

4.2. Glycosylation of 2

The promoter was prepared in situ by stirring the mixture of Cp_2HfCl_2 (83.0 mg, 0.218 mmol) and $AgClO_4$ (90.8 mg, 0.439 mmol) in the presence of powdered molecular sieves 4 Å (214 mg) in CH_2Cl_2 (1.5 mL) for 10 min at room temperature. To this suspension was added a solution of alcohol **2** (127 mg, 0.195 mmol) in CH_2Cl_2 and glycosyl acetate **3** (93.7 mg, 0.197 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C. The reaction mixture was gradually warmed to −35 °C during 1 h, and the stirring was continued for 1 h. The reaction was stopped by the addition of saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad, and extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 98:2) to afford α-glycoside **5** (70.1 mg, 82%) as white solid.

4.2.1. Glycoside 5α. $[\alpha]_D^{22}$ +26.2 (*c* 1.05, $CHCl_3$); mp 36–38 °C; IR (KBr) 3030, 2910, 2865, 1950, 1875, 1810, 1750, 1620, 1590, 1515, 1500, 1455, 1430, 1375, 1310, 1260, 1215, 1145, 1120, 1095, 910, 840, 810, 735, 695, 615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (d, 3H, *J*=6.3 Hz), 2.66 (dd, 1H, *J*=16.5, 9.0 Hz), 3.06 (dd, 1H, *J*=16.5, 6.0 Hz), 3.36 (dd, 1H, *J*=3.0, 1.5 Hz), 3.52 (dd, 1H, *J*=9.5, 9.5 Hz), 3.75 (dd, 1H, *J*=9.5, 3.0 Hz), 3.79 (dq, 1H, *J*=9.5, 6.5 Hz), 3.95 (ddd, 1H, *J*=9.0, 9.0, 6.0 Hz), 4.20 (d, 1H, *J*=12.5 Hz), 4.259 (d, 1H, *J*=12.5 Hz), 4.263 (d, 1H, *J*=1.5 Hz), 4.47 (d, 1H, *J*=11.5 Hz), 4.54 (d, 1H, *J*=11.5 Hz), 4.58 (d, 1H, *J*=11.0 Hz), 4.60 (d, 1H, *J*=9.0 Hz), 4.89 (d, 1H, *J*=11.0 Hz), 4.98 (s, 2H), 5.03 (d, 1H, *J*=12.0 Hz), 5.05 (d, 1H, *J*=12.0 Hz), 5.09 (s, 2H), 5.12 (s, 2H), 6.18 (d, 1H, *J*=2.5 Hz), 6.24 (d, 1H, *J*=2.5 Hz), 6.88–6.94 (m, 2H), 7.06 (d, 1H, *J*=1.5 Hz), 7.19–7.21 (m, 5H), 7.25–7.43 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 27.9, 68.5, 70.0, 70.1, 71.3, 71.4, 71.9, 72.4, 74.2, 75.4, 75.5, 79.7, 80.1, 80.4, 93.9, 94.4, 98.1, 102.5, 114.0, 114.7, 120.8, 127.12, 127.14, 127.39, 127.41, 127.50, 127.54, 127.7, 127.80, 127.84, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.475, 128.483, 128.5, 128.6, 131.9, 136.9, 136.96, 137.00, 137.1, 138.2, 138.5, 138.7, 149.1, 149.2, 155.3, 157.6, 158.8. Anal. Calcd for $C_{70}H_{66}O_{10}$: C, 78.78; H, 6.23. Found C, 78.82, H, 6.36.

4.2.2. Glycoside 5β. $[\alpha]_D^{21}$ +46.3 (*c* 1.04, $CHCl_3$); mp 96–98 °C; IR (KBr) 3030, 2860, 1950, 1870, 1620, 1590, 1515, 1500, 1455, 1430, 1375, 1315, 1260, 1215, 1140, 1120, 1075, 1025, 910, 855, 805, 735, 695, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, 3H, *J*=6.5 Hz), 2.57 (dd, 1H, *J*=16.5, 4.0 Hz), 2.74 (dd, 1H, *J*=16.5, 5.0 Hz), 3.28 (dq, 1H, *J*=9.5, 6.5 Hz), 3.40 (dd, 1H, *J*=9.5, 3.0, 6.0 Hz), 3.58 (dd, 1H, *J*=9.0, 9.0 Hz), 3.74 (d, 1H, *J*=3.0 Hz), 4.33 (d, 1H, *J*=12.0 Hz), 4.39 (ddd, 1H, *J*=5.0, 5.0, 4.0 Hz), 4.42 (d, 1H, *J*=12.0 Hz), 4.51 (s, 1H), 4.61 (d, 1H, *J*=11.0 Hz), 4.63 (d, 1H, *J*=12.5 Hz), 4.71 (d, 1H, *J*=12.5 Hz), 4.94 (d, 1H, *J*=11.0 Hz), 4.99 (d, 1H, *J*=12.0 Hz), 5.00 (d, 1H, *J*=12.0 Hz), 5.02 (d, 2H, *J*=12.0 Hz), 5.07 (s, 2H), 5.10 (s, 2H), 5.26 (d, 1H, J=5.0 Hz), 6.27 (d, 1H, *J*=2.0 Hz), 6.29 (d, 1H, *J*=2.0 Hz), 6.85 (d, 2H, *J*=1.0 Hz), 6.97 (s, 1H), 7.16–7.45 (m, 35H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 21.1, 70.0, 70.1, 71.07, 71.13, 71.2, 71.3, 72.1, 73.1, 73.4, 75.4, 79.6, 80.0, 93.5, 94.5, 98.5, 101.1, 113.5, 114.9, 119.6, 127.18, 127.19, 127.3, 127.46, 124.47, 127.5, 127.6, 127.7, 127.9, 127.97, 128.04, 128.26, 128.32, 128.39, 128.44, 128.54, 128.57, 128.63, 132.4, 136.9, 137.0, 137.2, 137.3, 138.2, 138.5, 138.6, 148.6, 148.8, 155.2, 157.7, 158.9. Anal. Calcd for $C_{70}H_{66}O_{10}$: C, 78.78; H, 6.23. Found C, 78.56, H, 6.05.

4.2.3. Synthesis of alcohol 6. To a solution of **5**α (28.5 mg, 0.0267 mmol) in CH_2Cl_2 (2.7 mL) was added water (0.14 mL) and DDQ (12.6 mg, 0.0555 mmol) at 25 °C, and the mixture was stirred for 5 h. After cooling to 0 °C, the mixture was diluted with water and Et_2O. The mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to afford **6** (19.1 mg, 66%) as white solid.

Compound **6**. $[\alpha]_D^{23}$ +36.7 (*c* 1.04, $CHCl_3$); mp 40–42 °C; IR (KBr) 3435, 3030, 2915, 1615, 1595, 1515, 1495, 1455, 1430, 1375, 1265, 1210, 1150, 1120, 1050, 1030, 905, 810, 735, 695, 624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, 3H, *J*=6.0 Hz), 2.46 (br s, 1H, OH), 3.36 (dd, 1H, *J*=3.0, 1.5 Hz), 3.51 (dd, 1H, *J*=9.5, 9.5 Hz), 3.73 (dd, 1H, *J*=9.5, 3.0 Hz), 3.83 (dq, 1H, *J*=9.5, 6.0 Hz), 3.95 (dd, 1H, *J*=10.0, 3.0 Hz), 4.09 (d, 1H, *J*=12.5 Hz), 4.18 (d, 1H, *J*=12.5 Hz), 4.20 (d, 1H, *J*=1.5 Hz), 4.45 (d, 1H, *J*=12.0 Hz), 4.53 (d, 1H, *J*=12.0 Hz), 4.58 (d, 1H, *J*=11.0 Hz), 4.88 (d, 1H, *J*=11.0 Hz), 4.97 (d, 1H, *J*=13.0 Hz), 4.99 (d, 1H, *J*=13.0 Hz), 5.06–5.11 (m, 5H), 5.12–5.15 (m, 3H), 6.15 (d, 1H, *J*=2.0 Hz), 6.25 (d, 1H, *J*=2.0 Hz), 6.95 (d, 1H, *J*=8.0 Hz), 7.01 (dd, 1H, *J*=8.0, 2.0 Hz), 7.14 (d, 1H, *J*=2.0 Hz), 7.16–7.42 (m, 35H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 61.9, 69.0, 70.1, 70.3, 71.2, 71.4, 72.0, 74.7, 75.31, 75.34, 77.1, 79.5, 80.1, 94.3, 94.4, 98.5, 104.7, 114.5, 114.6, 121.1, 127.1, 127.37, 127.41, 127.45, 127.48, 127.5, 127.6, 127.7, 127.8, 127.88, 127.93, 128.0, 128.1, 128.2, 128.3, 128.4, 128.47, 128.49, 128.59, 128.61, 131.3, 136.6, 136.7, 136.9, 137.0, 138.0, 138.4, 138.5, 149.1, 149.4, 155.9, 158.6, 160.9. Anal. Calcd for $C_{70}H_{66}O_{11}$: C, 77.61; H, 6.14. Found C, 77.42, H, 6.44.

4.2.4. Synthesis of ketone 7. To a solution of alcohol **6** (35.7 mg, 0.0330 mmol) in CH_2Cl_2 (3 mL) was added pyridinium dichromate (24.9 mg, 0.0662 mmol) at 0 °C. After stirring for 21 h at room temperature, second portion of pyridinium dichromate (24.9 mg, 0.0662 mmol) was added. After stirring for 19 h, the reaction was cooled to 0 °C, and diluted with Et_2O. The mixture was filtered through the Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give ketone **7** (30.2 mg, 85%) as while solid.

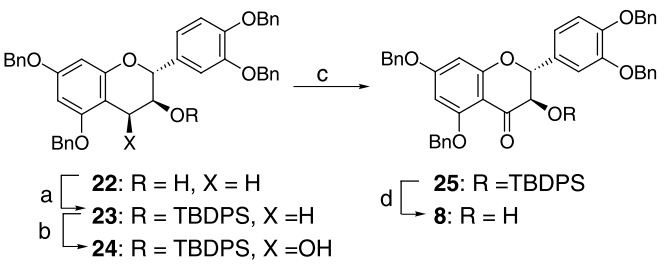
Compound **7**. $[\alpha]_D^{24}$ +25.7 (*c* 1.03, $CHCl_3$); mp 47–49 °C; IR (KBr) 3030, 2930, 1955, 1695, 1610, 1575, 1515, 1455, 1430, 1380, 1265, 1235, 1215, 1165, 1115, 1030, 820, 750, 695, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, 3H, *J*=6.0 Hz), 3.47 (dd, 1H, *J*=3.3, 1.5 Hz), 3.52 (dd, 1H, *J*=9.5, 9.5 Hz), 3.91 (dd, 1H, *J*=9.5, 3.3 Hz), 4.179 (d, 1H, *J*=1.5 Hz), 4.180 (d, 1H, *J*=12.5 Hz), 4.23 (d, 1H, *J*=12.5 Hz), 4.33 (dq, 1H, *J*=9.5, 6.0 Hz), 4.44 (d, 1H, *J*=11.0 Hz), 4.49 (d, 1H, *J*=11.5 Hz), 4.61 (d, 2H, *J*=11.5 Hz), 4.90 (d, 1H, *J*=11.5 Hz), 5.01 (s, 2H), 5.08 (s, 2H), 5.12 (d, 1H, *J*=11.0 Hz), 5.13 (s, 2H), 5.19 (s, 2H), 6.16 (d, 1H, *J*=2.2 Hz), 6.21 (d, 1H, *J*=2.2 Hz), 6.94 (d, 1H, *J*=8.0 Hz), 6.98 (dd, 1H, *J*=8.0, 2.0 Hz), 7.12 (d, 1H, *J*=2.0 Hz), 7.18–7.43 (m, 33H), 7.52 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 68.8, 70.3, 70.5, 71.2, 71.4, 72.2, 72.4, 74.9, 76.0, 78.2, 79.7, 80.4, 82.3, 94.7, 95.6, 98.0, 105.5, 114.0, 114.5, 126.5, 127.1, 127.3, 127.29, 127.33, 127.38, 127.39, 127.50, 127.52, 127.6, 127.8, 127.86, 127.93, 128.1, 128.2, 128.4, 128.50, 128.52, 128.6, 128.7, 129.6, 135.7, 136.4, 136.8, 136.9, 138.3, 138.9, 139.0, 149.2, 149.8, 161.2, 163.9, 164.8, 186.7. Anal. Calcd for $C_{70}H_{64}O_{11}$: C, 77.76; H, 5.97. Found C, 77.54, H, 6.27.

4.2.5. Synthesis of astilbin (1). To a solution of **7** (39.5 mg, 0.0365 mmol) in MeOH (5.0 mL) was added Pd–black (6.0 mg) at 25 °C. After stirring under H_2 atmosphere for 50 h, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was purified by LH-20 column chlomatography (MeOH) to give **1** (14.9 mg, 91%) as white solid.

Compound **1**. $[\alpha]_D^{18}$ −11 (*c* 0.52, EtOH); mp 178.5–181.5 °C; IR (KBr) 3380, 1645, 1520, 1455, 1260, 1160, 1085, 1035, 809 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.18 (d, 3H, *J*=6.0 Hz), 3.30 (dd, 1H, *J*=9.5, 9.5 Hz, overlapped with MeOH), 3.54 (dd, 1H, *J*=3.3, 1.3 Hz), 3.65 (dd, 1H, *J*=9.5, 3.3 Hz), 4.05 (d, 1H, *J*=1.3 Hz), 4.23 (dq, 1H, *J*=9.5, 6.0 Hz), 4.56 (d, 1H, *J*=10.5 Hz), 5.06 (d, 1H, *J*=10.5 Hz), 5.89 (d, 1H, *J*=2.0 Hz), 5.91 (d, 1H, *J*=2.0 Hz), 6.80 (d, 1H, *J*=8.3 Hz), 6.83 (dd, 1H, *J*=8.3, 1,8 Hz), 6.95 (d, 1H, *J*=1.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 18.6, 71.3, 72.6, 73.0, 74.6, 79.4, 84.7, 97.1, 98.2, 102.9, 103.3, 116.3, 117.1, 121.3, 130.0, 147.3, 148.2, 164.9, 166.3, 169.5, 196.7. Anal. Calcd for $C_{21}H_{22}O_{11}$: C, 56.00; H, 4.92. Found C, 56.00, H, 5.22; HRFAB-MS (*m*-nitrobenzyl alcohol, added NaI) exact mass calcd for $C_{21}H_{22}O_{11}$+Na requires *m*/*z* 473.1059. Found *m*/*z* 473.1053.

4.3. Preparation of the glycosyl acceptors, 8 and 9

Acceptor **8** was prepared from tetrabenzyl catechin (**22**) by the following sequence (Scheme 2).



Scheme 2. (a) *tert*-$BuPh_2SiCl$, imidazole, DMF (90%). (b) DDQ, H_2O, CH_2Cl_2 (76%). (c) *n*-Pr_4NRuO_4, NMO, CH_2Cl_2 (32%). (d) PPTS, EtOH (60%).

4.3.1. Silyl ether 23. To a solution of alcohol **22** (1.014 g, 1.56 mmol) in DMF (3.3 mL) was added imizazole (321 mg, 4.71 mmol) and TBDMSCl (352 mg, 2.34 mmol) at 25 °C. After stirring for 12 h at this temperature, the reaction was stopped by adding aqueous pH 7 phosphate buffer. The mixture was extracted with Et_2O (×3). The combined organic extracts were washed with brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 95:5) to give **23** (1.07 mg, 90%) as colorless oil.

Compound **23**. $[\alpha]_D^{20}$ +21.9 (*c* 1.00, $CHCl_3$); IR (neat) 3030, 2855, 1620, 1595, 1500, 1455, 1430, 1375, 1260, 1215, 1150, 1125, 1050, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.48 (s, 3H), −0.18 (s, 3H), 0.72 (s, 9H), 2.62 (dd, 1H, *J*=16.4, 9.5 Hz), 3.10 (dd, 1H, *J*=16.4, 5.8 Hz), 3.89 (ddd, 1H, *J*=9.5, 9.0, 5.8 Hz), 4.56 (d, 1H, *J*=9.0 Hz), 4.95 (d, 1H, *J*=11.7 Hz), 4.99 (d, 1H, *J*=11.7 Hz), 5.04 (d, 1H, *J*=11.7 Hz), 5.08 (d, 1H, *J*=11.9 Hz), 5.12 (d, 1H, *J*=11.9 Hz), 5.159 (d, 1H, *J*=10.3 Hz), 5.162 (d, 1H, *J*=11.9 Hz), 5.19 (d, 1H, *J*=10.3 Hz), 6.20 (d, 1H, *J*=2.2 Hz), 6.23 (d, 1H, *J*=2.2 Hz), 6.92 (s, 2H), 7.05 (s, 1H), 7.27–7.48 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.9, 17.8, 25.6, 30.3, 69.4, 69.9, 70.1, 71.2, 71.4, 82.1, 93.8, 94.3, 102.9, 114.2, 115.1, 121.1, 126.8, 127.3, 127.5, 127.72, 127.76, 127.8, 127.9, 128.42, 128.46, 128.50, 128.6, 132.7, 136.9, 137.16, 137.26, 137.29, 147.7, 149.0, 155.6, 157.5, 158.7. Anal. Calcd for $C_{49}H_{52}O_6Si$: C, 76.93; H, 6.85. Found C, 76.92, H, 7.08.

4.3.2. Alcohol 24. To a solution of **23** (35.8 mg, 0.0478 mmol) in CH_2Cl_2 (9.0 mL) was added DDQ (80.9 mg, 0.356 mmol) and H_2O (0.45 mL, 25.0 mmol) at 25 °C. After stirring for 1.5 h at this temperature, the reaction was stopped by adding water. The mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give **24** (106 mg, 76%) as white solid.

Compound **24**. $[\alpha]_D^{21}$ +31.4 (*c* 1.02, $CHCl_3$); IR (neat) 3540, 3060, 3030, 2940, 2855, 1620, 1590, 1515, 1455, 1430, 1375, 1310, 1265, 1200, 1150, 1120, 1090, 1060, 1030, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.56 (s, 3H), −0.14 (s, 3H), 0.76 (s, 9H), 2.91 (s, 1H), 3.86 (dd, 1H, *J*=9.8, 3.4 Hz), 4.93–5.00 (m, 4H), 5.09–5.21 (m, 6H), 6.16 (d, 1H, *J*=2.0 Hz), 6.24 (d, 1H, *J*=2.0 Hz), 6.94 (s, 2H), 7.08 (s, 1H), 7.29–7.48 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.7, −5.1, 17.9, 25.7, 62.3, 70.0, 71.1, 71.3, 72.7, 75.8, 94.3, 94.3, 94.4, 104.3, 114.3, 115.0, 121.4, 126.7, 127.2, 127.5, 127.6, 127.7, 127.8, 128.0, 128.4, 128.5, 129.2, 131.9, 136.5, 137.0, 137.1, 137.2, 148.8, 149.0, 156.1, 158.8, 160.7. Anal. Calcd for $C_{49}H_{52}O_7Si$: C, 73.35; H, 6.71. Found C, 75.18, H, 6.96.

4.3.3. Ketone 25. To a solution of **24** (39.8 mg, 0.0510 mmol) in CH_2Cl_2 (1.0 mL) was added *N*-methyl morpholine *N*-oxide (6.5 mg 0.081 mmol) and TPAP (1.6 mg, 0.0046 mmol) at 25 °C. After stirring for 10 h, an additional portion of TPAP (1.6 mg, 0.0046 mmol) was added, and stirred for 4.5 h. The mixture was diluted with CH_2Cl_2, filtered through the Celite pad. The filtrate was concentrated in vacuo, and extracted with Et_2O (×3), and the combined organic extracts were successively washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 98:2) to give **25** (12.6 mg, 32%) as white solid.

Compound **25**. $[\alpha]_D^{20}$ +19.7 (*c* 1.02, $CHCl_3$); IR (KBr) 3065, 3030, 2925, 2855, 1695, 1610, 1575, 1515, 1455, 1430, 1375, 130.5, 1260, 1210. 1160, 1115, 1025, 875, 840, 780, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.31 (s, 3H), 0.13 (s, 3H), 0.63 (s, 9H), 4.30 (d, 1H, *J*=11.2 Hz), 4.99 (s, 2H), 5.03 (d, 1H, *J*=11.2 Hz), 5.14 (d, 1H, *J*=12.0 Hz), 5.19 (s, 2H), 5.20 (d, 1H, *J*=12.0 Hz), 5.21 (s, 2H), 6.16 (d, 1H, *J*=2.0 Hz), 6.19 (d, 1H, *J*=2.0 Hz), 6.94 (d, 1H, *J*=8.3 Hz), 6.99 (dd, 1H, *J*=8.3, 2.0 Hz), 7.11 (d, 1H, *J*=2.0 Hz), 7.28–7.53 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −6.1, −4.2, 18.3, 25.5, 70.2, 70.4, 71.3, 76.0, 76.6, 83.7, 94.6, 95.7, 105.0, 114.1, 115.0, 121.2, 126.4, 127.2. 127.3, 127.5, 127.8,128.3, 128.5, 128.7, 130.9, 135.7, 136.6, 137.10, 137.13, 149.0, 149.3, 160.9, 164.1, 164.6, 189.6. Anal. Calcd for $C_{49}H_{50}O_7Si$: C, 75.55; H, 6.47. Found C, 75.26, H, 6.71.

4.3.4. Alcohol 8. To a solution of **25** (8.6 mg, 0.011 mmol) in EtOH (0.5 mL) was added PPTS (5 mg) at 25 °C. After stirring for 66 h, the reaction was stopped by adding water. The mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give **8** (4.5 mg, 60%) as white solid.

$[\alpha]_D^{21}$ −9.0 (*c* 0.46, $CHCl_3$); mp 193.5–194.2 °C; IR (KBr) 3465, 3035, 2925, 1675, 1610, 1580, 1515, 1440, 1375, 1310, 1260, 1215, 1170, 1135, 1120, 1010, 810, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (br s, 1H), 4.42 (d, 1H, *J*=12.2 Hz), 4.95 (d, 1H, *J*=12.2 Hz), 5.05 (s, 2H), 5.10–5.25 (m, 6H), 6.19 (d, 1H, *J*=2.2 Hz), 6.26 (d, 1H, *J*=2.2 Hz), 7.00 (d, 1H, *J*=8.3 Hz), 7.09 (dd, 1H, *J*=8.3, 1.9 Hz), 7.18 (d, 1H, *J*=1.9 Hz), 7.27–7.58 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.4, 70.5, 71.2, 71.4, 72.7, 83.1, 94.8, 95.2, 103.4, 114.1, 114.7, 121.0, 126.6, 127.2, 127.5, 127.6, 127.8, 127.85, 127.92, 128.48, 128.51, 128.7, 128.8, 129.6, 135.5, 136.0, 137.1, 137.2, 149.1, 149.8, 160.9, 164.8, 165.9, 190.6. Anal. Calcd for $C_{43}H_{36}O_7$: C, 77.69; H, 5.46. Found C, 77.41; H, 5.73.

4.3.5. Preparation of alcohol 9. To a solution of **22** (56 mg, 0.086 mmol) in $CHCl_3$ (10 mL) was added MeOH (0.5 mL) and DDQ (39 mg, 0.017 mmol) at 25 °C. After stirring for 4 h, the mixture was diluted with water and Et_2O, and the products were extracted with Et_2O (×4). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), concentrated in vacuo. The residue was purified by preparative TLC (benzene/EtOAc, 95:5) to give **9** (45 mg, 79%) as white solid.

Compound **9**. $[\alpha]_D^{21}$ −53.1 (*c* 1.02, $CHCl_3$); mp 142–144 °C; IR (KBr) 3415, 3030, 2910, 1620, 1590, 1515, 1500, 1430, 1380, 1260, 1220, 1165, 1120, 1070, 1030, 815, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (d, 1H, *J*=9.0 Hz), 3.50 (s, 6H), 3.89 (ddd, 1H, *J*=10.3, 9.0, 3.7 Hz), 4.73 (d, 1H, *J*=3.7 Hz), 4.94 (d, 1H, *J*=10.3 Hz), 4.99 (s, 2H), 5.01 (d, 1H, *J*=11.2 Hz), 5.07 (d, 1H, *J*=11.2 Hz), 5.16 (s,

4H), 6.17 (d, 1H, *J*=2.1 Hz), 6.27 (d, 1H, *J*=2.1 Hz), 6.96 (d, 1H, *J*=8.3 Hz), 7.01 (dd, 1H, *J*=8.3, 1.5 Hz), 7.08 (d, 1H, *J*=1.5 Hz), 7.27–7.64 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.4, 69.8, 70.1, 70.6, 71.2, 71.3, 93.3, 94.2, 103.0, 114.3, 114.7, 121.2, 127.2, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.5, 128.6, 131.4, 136.4, 136.5, 137.2, 137.3, 149.0, 149.3, 156.2, 158.7, 160.9. Anal. Calcd for $C_{44}H_{40}O_7$: C, 77.63; H, 5.92. Found C, 77.35, H, 6.12.

4.4. Cp_2ZrCl_2–$AgClO_4$-Mediated substitution reaction of 11 with ketene silyl acetal 12 under the stoichiometric conditions

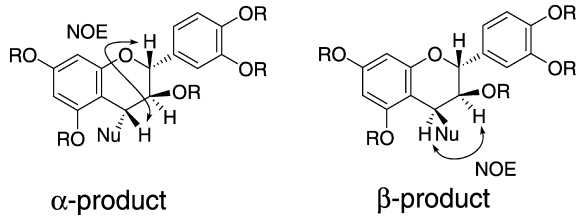
The promoter was prepared in situ by stirring the mixture of Cp_2ZrCl_2 (22 mg, 0.075 mmol) and $AgClO_4$ (31 mg, 0.15 mmol) in the presence of powdered molecular sieves 4 Å (63 mg) in CH_2Cl_2 (0.5 mL) for 5 min at room temperature. To this suspension was added a mixture of **11** (50 mg, 0.063 mmol) and **12** (38 mg, 0.19 mmol) in CH_2Cl_2 (0.75 mL) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C. The reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad, and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc, 3:1) to afford **13** (42 mg, 80%) as amorphous solid.

4.5. Cp_2ZrCl_2–$AgClO_4$-Mediated substitution reaction of 11 with ketene silyl acetal 12 under the catalytic conditions

The promoter was prepared in situ by stirring the mixture of Cp_2ZrCl_2 (3.7 mg, 0.013 mmol) and $AgClO_4$ (5.2 mg, 0.025 mmol) in the presence of powdered molecular sieves 4 Å (125 mg) in CH_2Cl_2 (1.0 mL) for 5 min at room temperature. To this suspension was added a mixture of **11** (100 mg, 0.125 mmol) and **12** (76 mg, 0.38 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C. The reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad, and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc, 3:1) to afford **13** (88 mg, 85%) as amorphous solid.

4.5.1. Ethyl ester 13. The title compound is a mixture of two diastereomers, α/β, 16:84. IR (neat) 3064, 3031, 2903 (br), 1732, 1616, 1592, 1514, 1498, 1455, 1439, 1376, 1264, 1216, 1152, 1028, 811, 736, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, conspicuous signal of minor isomer was marked with an asterisk) δ 1.06* (t, 3H, *J*=7.1 Hz), 1.07 (t, 3H, *J*=7.1 Hz), 2.24* (dd, 1H, *J*=15.8, 8.5 Hz), 2.61* (dd, 1H, *J*=15.8, 3.2 Hz), 2.64–2.71 (m, 2H), 3.44–3.48* (m, 1H), 3.71 (dd, 1H, *J*=9.9, 5.9 Hz), 3.77 (dq, 1H, *J*=10.8, 7.1 Hz), 3.85 (d, 1H, *J*=11.4 Hz), 3.88 (dq, 1H, *J*=10.8, 7.1 Hz), 3.96* (dd, 1H, *J*=6.5, 5.9 Hz), 3.99* (d, 1H, *J*=11.5 Hz), 4.17–4.21 (m, 1H), 4.29 (d, 1H, *J*=11.4 Hz), 4.77 (d, 1H, *J*=9.9 Hz), 4.84* (d, 2H, *J*=6.6 Hz), 4.95 (d, 1H, *J*=11.8 Hz), 4.97 (d, 1H, *J*=11.8 Hz), 5.01 (d, 1H, *J*=12.1 Hz), 5.08 (s, 2H), 5.09 (d, 1H, *J*=12.1 Hz), 5.10* (s, 2H), 5.17* (s, 2H), 5.20 (s, 2H), 6.16 (d, 1H, *J*=2.3 Hz), 6.26* (d, 1H, *J*=2.4 Hz), 6.27 (d, 1H, *J*=2.3 Hz), 6.27* (d, 1H, *J*=2.4 Hz), 6.81–6.84 (m, 2H), 6.84* (d, 1H, *J*=2.0 Hz), 6.86* (d, 1H, *J*=1.8 Hz), 6.92–6.99 (m, 3H), 7.10–7.15 (m, 3H), 7.27–7.47 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 30.7, 36.6, 60.0, 69.8, 70.0, 70.9, 71.3, 72.2, 75.9, 77.2, 93.8, 94.1, 105.5, 113.9, 114.7, 121.2, 126.7, 127.2, 127.3, 127.5, 127.70, 127.74, 127.8, 128.0, 128.2, 128.42, 128.44, 128.46, 128.6, 132.0, 136.7, 137.2, 137.3, 137.7, 148.8, 155.0, 157.5, 159.2, 172.4. Anal. Calcd for $C_{54}H_{50}O_8$: C, 78.43; H, 6.09. Found C, 78.21, H, 6.30.

The stereochemical assignment and the ratio of the isomers were determined by NMR. Although the α- and β- were generally inseparable, the spectra were resolved enough to assess the selectivity, and both stereoisomers showed diagnostic NOE as shown below.



4.5.2. Isopropyl ester 18. IR (neat) 3064, 3031, 2979, 2934 (br), 1715, 1615, 1590, 1514, 1498, 1454, 1374, 1261, 1218, 1144, 1106, 1028, 910, 817, 734, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.11 (d, 3H, *J*=6.2 Hz), 1.15 (s, 3H), 1.15 (d, 3H, *J*=5.1 Hz), 3.92 (s, 1H), 4.03 (d, 1H, *J*=11.2 Hz), 4.15 (d, 1H, *J*=8.1 Hz), 4.36 (d, 1H, *J*=8.1 Hz), 4.50 (d, 1H, *J*=11.2 Hz), 4.91–4.97 (m, 1H), 4.96 (d, 1H, *J*=11.9 Hz), 4.98 (d, 1H, *J*=11.9 Hz), 5.04 (s, 2H), 5.12 (s, 2H), 5.18 (s, 2H), 6.31 (d, 1H, *J*=1.1 Hz), 6.36 (d, 1H, *J*=1.1 Hz), 6.93 (d, 1H, *J*=8.2 Hz), 7.01 (d, 1H, *J*=8.2 Hz), 7.13–7.16 (m, 3H), 7.19–7.24 (m, 3H), 7.27–7.48 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.6, 25.7, 44.3, 47.9, 68.0, 70.0, 70.1, 71.0, 71.1, 71.2, 84.2, 84.5, 95.4, 96.3, 108.1, 113.3, 115.0, 119.7, 126.9, 127.2, 127.3, 127.59, 127.64, 127.70, 127.72, 128.0, 128.2, 128.41, 128.44, 128.6, 133.8, 136.7, 137.0, 137.2, 137.3, 138.3, 148.5, 148.9, 158.6, 158.9, 159.9, 177.0. Anal. Calcd for $C_{57}H_{56}O_8$: C, 78.78; H, 6.49. Found C, 78.86, H, 6.68.

4.5.3. Sulfide 19. The title compound is a mixture of two diastereomers, α/β, 5:95. IR (neat) 3063, 3031, 2925, 2868, 1615, 1591, 1513, 1498, 1454, 1438, 1377, 1310, 1263, 1217, 1182, 1151, 1118, 1027, 812, 741, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, conspicuous signal of minor isomer was marked with an asterisk) δ 3.60 (d, 1H, *J*=11.7 Hz), 3.67 (d, 1H, *J*=11.7 Hz), 3.80 (dd, 1H, *J*=9.5, 3.9 Hz), 3.90* (d, 1H, *J*=11.5 Hz), 4.02* (dd, 1H, *J*=10.0, 7.4 Hz), 4.33* (d, 1H, *J*=11.5 Hz), 4.54* (d, 1H, *J*=3.9 Hz), 4.82 (d, 1H, *J*=3.9 Hz), 4.97 (s, 2H), 5.03 (d, 1H, *J*=11.9 Hz), 5.04 (d, 1H, *J*=11.2 Hz), 5.09 (d, 1H, *J*=11.2 Hz), 5.11 (d, 1H, *J*=11.9 Hz), 5.21 (s, 2H), 5.35 (d, 1H, *J*=9.5 Hz), 6.14 (d, 1H, *J*=2.0 Hz), 6.23* (d, 1H, *J*=2.2 Hz), 6.26 (d, 1H, *J*=2.0 Hz), 6.30* (d, 1H, *J*=2.2 Hz), 6.48 (d, 2H, *J*=8.3 Hz), 6.93–7.52 (m, 31H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.7, 70.0, 70.6, 70.9, 71.3, 71.4, 77.7, 93.7, 93.9, 102.6, 114.2, 114.7, 121.3, 126.9,

127.2, 127.3, 127.5, 127.7, 127.8, 128.0, 128.2, 128.26, 128.32, 128.40, 128.45, 128.6, 131.9, 133.6, 136.4, 136.6, 136.8, 137.2, 137.3, 137.4, 148.77, 148.81, 155.1, 157.5, 160.2. Anal. Calcd for $C_{56}H_{48}O_6S$: C, 79.22; H, 5.70; S, 3.78. Found C, 78.95, H, 5.85; S, 3.89.

4.5.4. Azide 20. IR (neat) 3031, 2872, 2099, 1618, 1593, 1513, 1498, 1454, 1377, 1315, 1263, 1216, 1190, 1152, 1123, 1090, 1028, 911, 814, 736, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73* (dd, 1H, J=8.5, 6.2 Hz), 3.68 (dd, 1H, J=10.1, 3.9 Hz), 3.95* (d, 1H, J=11.0 Hz), 4.08 (d, 1H, J=11.9 Hz), 4.21 (d, 1H, J=11.9 Hz), 4.34* (d, 1H, J=11.0 Hz), 4.76* (d, 1H, J=8.5 Hz), 4.77* (d, 1H, J=6.2 Hz), 4.97 (s, 2H), 5.00 (d, 1H, J=10.1 Hz), 5.03 (d, 1H, J=11.8 Hz), 5.05 (d, 1H, J=3.9 Hz), 5.06 (d, 1H, J=12.2 Hz), 5.10 (d, 1H, J=11.8 Hz), 5.12 (d, 1H, J=12.2 Hz), 5.22 (s, 2H), 6.14 (d, 1H, J=2.2 Hz), 6.26 (d, 1H, J=2.2 Hz), 6.92–6.94 (m, 2H), 6.95–7.03 (m, 3H), 7.15–7.19 (m, 3H), 7.27–7.44 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.0, 70.2, 70.5, 71.1, 71.4, 72.1, 75.9, 76.7, 93.8, 94.4, 101.0, 114.2, 115.0, 121.1, 127.3, 127.4, 127.53, 127.57, 127.78, 127.84, 128.0, 128.1, 128.2, 128.3, 128.49, 128.51, 128.65, 131.3, 136.4, 136.5, 137.16, 137.20, 137.28, 148.9, 149.1, 155.8, 158.4, 161.2. Anal. Calcd for $C_{50}H_{43}N_3O_6$: C, 76.81; H, 5.54; N, 5.37. Found C, 76.90, H, 5.81; N, 5.34.

4.5.5. Trimethyl ether 21. The title compound is a mixture of two diastereomers, α/β, 84:16. IR (neat) 3030, 2935, 1606, 1591, 1512, 1496, 1454, 1377, 1263, 1215, 1149, 1119 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$, conspicuous signal of minor isomer was marked with an asterisk) δ *3.28 (s, 3H), 3.39 (s, 6H), 3.51 (d, 1H, J=10.8 Hz), *3.56 (s, 3H), 3.66 (d, 1H, J=10.8 Hz), 3.79 (s, 3H), 3.98 (dd, 1H, J=8.2, 9.7 Hz), *4.07 (d, 1H, J=11.8 Hz), *4.34 (d, 1H, J=11.8 Hz), 4.55 (d, 1H, J=11.4 Hz), 4.59 (d, 1H, J=9.7 Hz), 4.76 (d, 1H, J=11.4 Hz), 4.77 (d, 1H, J=8.2 Hz), 4.95 (s, 2H), 5.09 (d, 1H, J=12.5 Hz), 5.15 (d, 1H, J=12.5 Hz), 5.19 (s, 2H), 5.88–5.95 (br s, 1H), 6.00–6.07 (br s, 1H), *6.11 (d, 1H, J=2.1 Hz), 6.12 (d, 1H, J=2.4 Hz), *6.17 (d, 1H, J=2.1 Hz), 6.23 (d, 1H, J=2.4 Hz), 6.59–6.63 (m, 2H), 6.73–7.46 (m, 26H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 55.2, 56.0, 69.9, 70.0, 71.1, 71.4, 73.8, 81.3, 81.5, 91.2, 92.1, 94.4, 94.5, 109.5, 114.2, 114.5, 115.1, 120.9, 127.1, 127.3, 127.37, 127.39, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.37, 128.40, 128.43, 133.0, 136.9, 137.1, 137.26, 137.32, 138.0, 148.7, 148.8, 157.1, 157.65, 157.74, 158.6, 159.3; Anal. calcd for $C_{59}H_{54}O_9$: C, 78.12; H, 6.00. Found: C, 78.39; H, 6.27.

Acknowledgements

Partial financial supports from 21st Century COE Program (Chemistry) and that Suntory Corporation are gratefully acknowledged.

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