Efficient Synthesis of Optically Active Gallocatechin-3-gallate Derivatives via 6-*endo*-Cyclization

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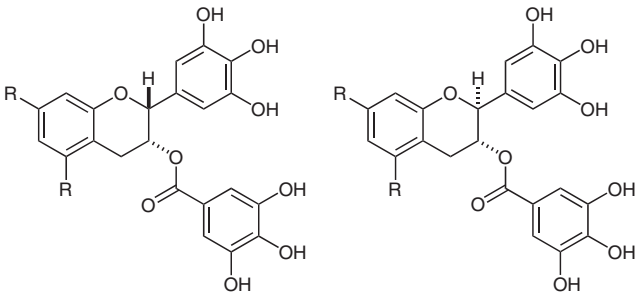
Abstract: Optically active dihydrobenzopyran derivatives are synthesized by 6-*endo* cyclization of corresponding epoxy-phenol, which is readily derived from the enantioselective epoxidation of 1,3-diarylpropene. Synthetic dihydrobenzopyrans are converted into (–)-5,7-dideoxy-gallocatechin gallate as well as (–)-5,7-dideoxy-epigallocatechin derivative.

Key words: dihydrobenzopyran, 6-*endo* cyclization, enantioselective epoxidation, (–)-5,7-dideoxy-gallocatechin gallate

(–)-Epigallocatechin gallate (EGCG, **1**) is a major constituent of green tea extract, which has various bioactivities such as cancer prevention and antiviral or antimicrobial activity.[2] Because these unique bioactivities are expected to be candidates for drug development, the detailed structure–activity relationship (SAR) study[3] has been a significant work. However, investigations of such bioactivities have been limited to natural products and/or their derivatives. Thus, developing an efficient and flexible synthetic method has strongly been desired. Although many synthetic efforts for catechin have been reported,[2,3] there are only a few examples of enantioselective syntheses.[4] During the course of our synthetic investigation on the gallocatechins, we have found that synthetic 5,7-dideoxy-epigallocatechin gallate (DO-EGCG, **3**) possesses more potent anti-influenza activities than natural EGCG (**1**).[5] Inspired by this finding, we have launched an investigation into the synthesis of 5,7-dideoxy-gallocatechin gallate derivatives. Herein we report enantioselective syntheses of **3** and **4** (Figure 1).



1 (–)-EGCG **1**: R = OH
3 (–)-DO-EGCG **3**: R = H

2 (–)-GCG **2**: R = OH
4 (–)-DO-GCG **4**: R = H

Figure 1 Structure of EGCG derivatives

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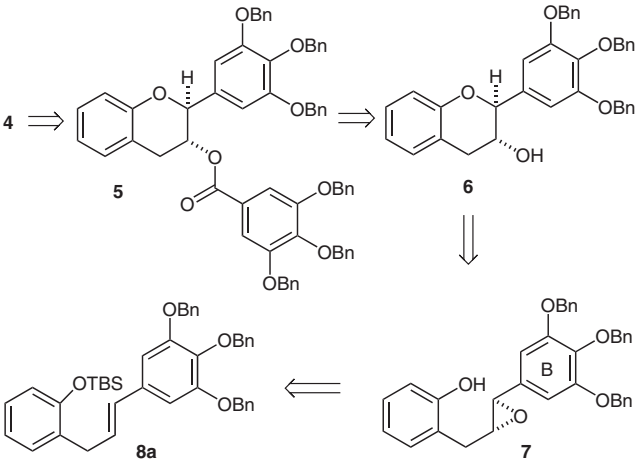
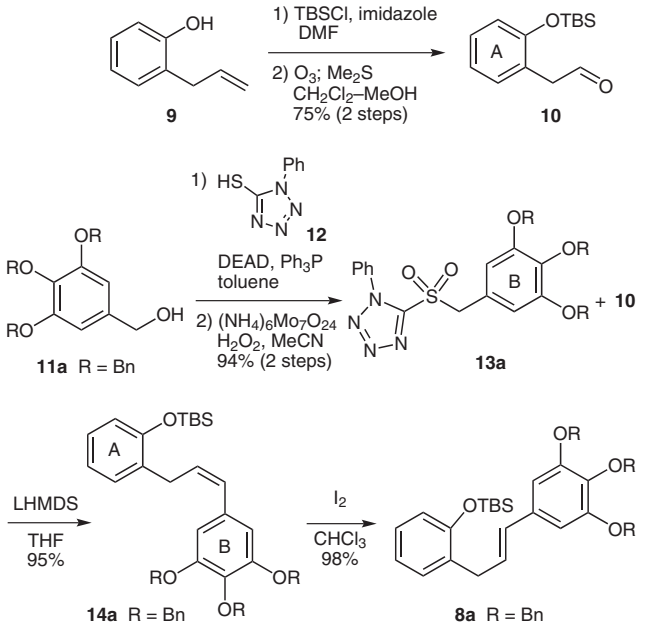
Scheme 1 illustrates the heart of our synthetic plan. Because a facile deprotection of the benzyl group and the incorporation of the galloyl moiety proceeded smoothly, the crucial problem in the synthesis of **4** should be the stereoselective construction of 2,3-*trans*-dihydrobenzopyran ring **6**. We anticipated that **6** could be synthesized by 6-*endo*-cyclization of epoxy-phenol **7**, which could be readily obtained by an asymmetric epoxidation[6] of **8a**. Several selective 6-*endo* cyclization-mediated pyran ring constructions have been reported.[7] Because the reaction should be accomplished by stabilizing the cation at the reaction site, an electron-rich B-ring group should enable dihydrobenzopyrane ring synthesis.



Scheme 1 Synthetic strategy of dideoxy-gallocatechin gallate (DO-GCG, **4**)

As shown in Scheme 2, condensation of the A- and B-rings was accomplished by Julia–Kocienski reaction[8] between aldehyde **10** and phenyltetrazole (PT)-sulfone **13**. The A-ring unit of aldehyde **10** was readily prepared in two steps from commercially available 2-allylphenol (**9**). Introducing a TBS group to **9** and oxidative cleavage of the double bond furnished aldehyde **10**.The PT-sulfone **13a** was prepared by a condensation reaction of 3,4,5-tribenzyloxybenzyl alcohol (**11a**) and PT-SH (**12**) under Mitsunobu conditions and subsequent oxidation to the sulfone. Upon treating the mixture of aldehyde **10** and PT-sulfone **13a** with LHMDS in THF, the *Z*-selective olefination reaction proceeded smoothly to provide **14a** as a single isomer in 95% yield. Although the reason for the high *Z*-selectivity of this Julia–Kocienski reaction is unclear,[8c] the selectivity and the reactivity depend on the protecting

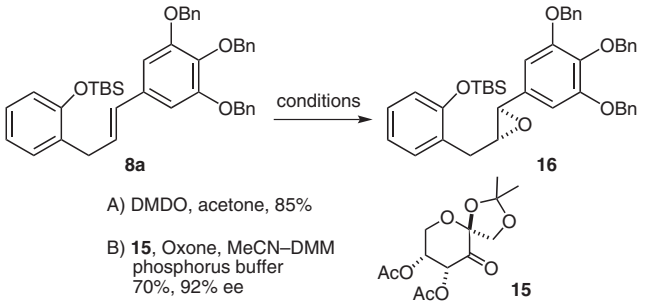
group at the B-ring of **13** as shown in Table 1. Because *E*-isomer **8a**[9] was required to synthesize **4**, the isomerization reaction was performed by treating **14a** with a catalytic amount of I_2 to predominantly afford **8a**.



Scheme 2 Stereoselective synthesis of olefin **14a** and **8a**

Table 1 Stereoselectivity of Julia–Kocienski Reaction

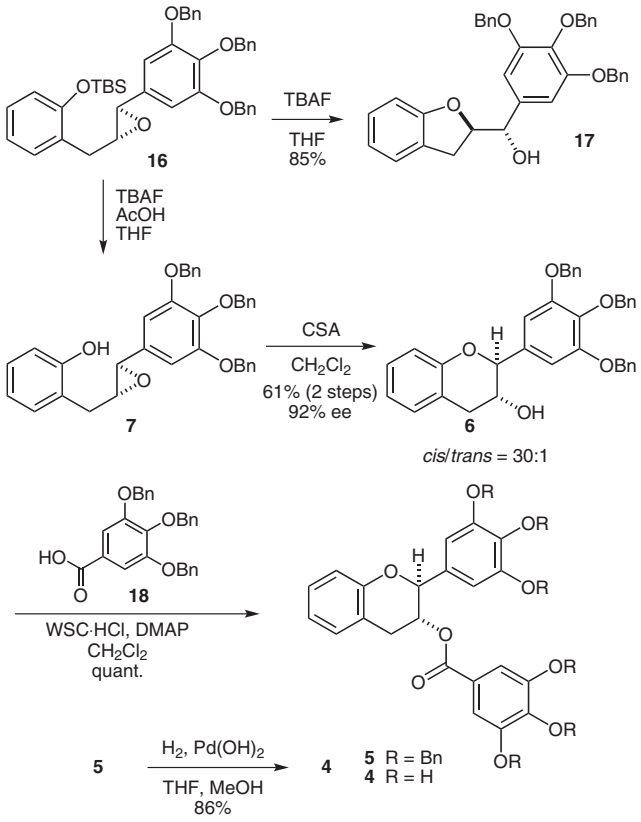
13	**14** (*cis*)	**8** (*trans*)	Yield (%)
13a R = Bn	1	0	95
13b R = TBS	10	1	75
13c R = Ms	1	1	12



Scheme 3 Conversion to epoxide**16** from **8a**

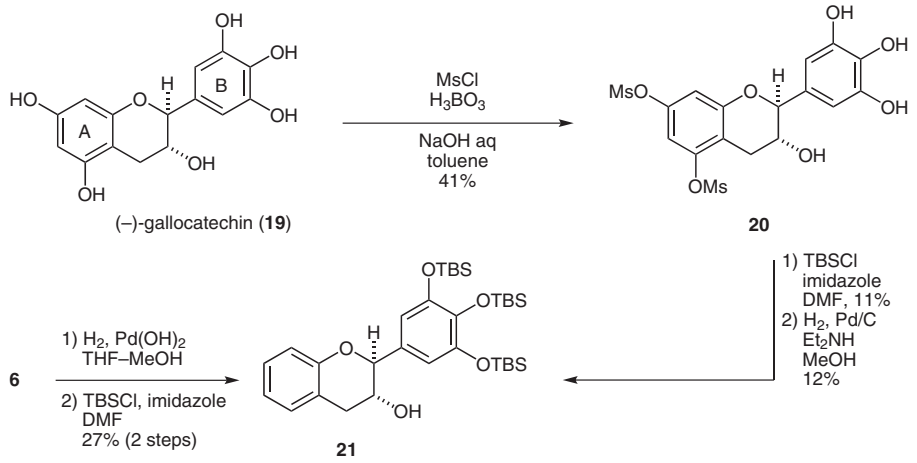
With the requisite *E*-double bond of **8a** in hand, the epoxidation and cyclization were investigated. The desired oxidation and simultaneous epoxide-opening reaction[10] occurred by treating with MCPBA under acidic conditions. However, to avoid a side reaction, neutral and non-nucleophilic DMDO was tested. As shown in Scheme 3, treating **8a** with DMDO caused the oxidation to proceed smoothly to provide **16** in high yield (conditions A). For an optically active compound, oxidation was performed by Shi's conditions[11] in the presence of fructose derivative **15** (conditions B).

As shown in Schemes 4, 2, 3-*trans*-dihydrobenzopyran **6** was constructed by a regio- and stereoselective 6-*endo*-cyclization. Because treating **16** with TBAF, a basic 5-*exo*-cyclization (Baldwin's rule), gave dihydrobenzofuran **17**, the TBS group was deprotected in the presence of AcOH to provide **7**. Upon treating **7** with CSA, the desired 6-*endo*-cyclization reaction[12] proceeded smoothly with a high diastereoselectivity, and subsequent recrystallization gave optically pure **6**. Conversion from **6** to (–)-5,7-dideoxy-gallocatechin gallate (**4**) was achieved in two steps and involved the incorporation of gallic acid **18** and the deprotection of benzyl groups under hydrogenation conditions. An efficient synthesis of (–)-5,7-dideoxy-gallocatechin gallate (**4**)[13] was accomplished in nine steps from **9**.



Scheme 4 Synthesis of (–)-5,7-dideoxy-gallocatechin gallate (**4**)

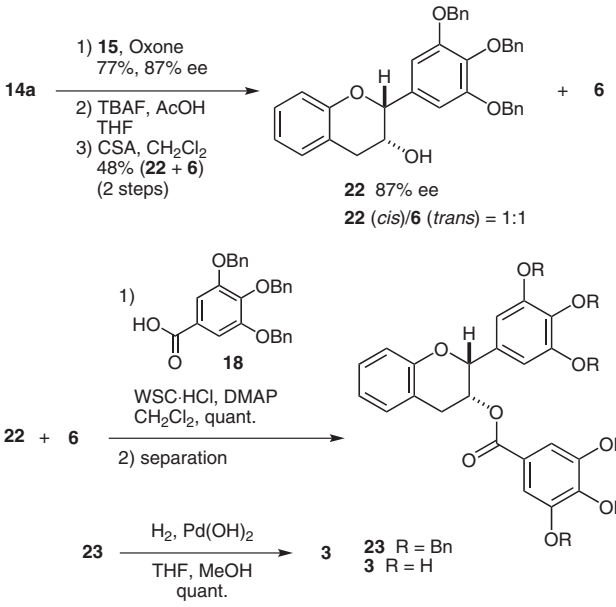
The absolute configuration of synthetic **4** was confirmed by comparing to natural (–)-gallocatechin (**19**) as shown in Scheme 5. Selective mesylation of the phenols at the A-ring of **19**, which should occur through the corresponding borate intermediate,[14] was performed in the presence of boric acid to provide **20**. After protecting **20** with a TBS group, the mesyloxy group was removed using Sajiki's protocol.[15] Upon treating the mesylate under hydrogenolysis conditions in the presence of diethylamine, the mesyloxy group was smoothly removed to afford **21**. On the other hand, synthetic intermediate **6** was also convert-



Scheme 5 Confirmation of absolute configuration of **4**

ed into **21** through the deprotection of the benzyl groups and subsequent introduction of TBS groups. All spectral data, including retention time on a chiral column, were identical regardless of how **21** was synthesized.[16]

As shown in Scheme 6, (–)-5,7-dideoxy-epigallocatechin gallate (**3**) was synthesized by employing **14a** using a similar reaction procedure as that to prepare **4**. After Shi epoxidation of **14a** and the removal of TBS ether, treating the corresponding epoxy phenol with CSA enabled 6-*endo*-cyclization to proceed smoothly to provide **22** and **6** as a 1:1 mixture. Formation of **6** might be explained by a cyclization reaction, which proceeds through quinone methide intermediate **25**.[10,17] Compared to **7**, the steric hindrance of the *cis*-epoxide would make a direct inversion reaction difficult and would readily lead to quinone methide formation by a self-opening reaction of the epoxide. After incorporating **18**, separation of **5** and **23** was readily carried out by silica gel column chromatography.[18] Finally, deprotection of the benzyl ether by hydrogenolysis



Scheme 6 Synthesis of (–)-5,7-dideoxy-epigallocatechin gallate (**3**)

conditions afforded (–)-5,7-dideoxy-epigallocatechin gallate (**3**).

In conclusion, the enantioselective syntheses of (–)-5,7-dideoxy-epigallocatechin gallate (**3**) and (–)-5,7-dideoxy-gallocatechin gallate (**4**) were achieved using regioselective 6-*endo*-cyclization of optically active epoxides. Our synthesis features *E*- and *Z*-selective olefination and subsequent enantioselective Shi epoxidation protocol. Considering the mildness of our reaction conditions, the present synthesis should be compatible with a variety of functional groups. Furthermore, substituted 2-allylphenol derivatives are also readily available. Hence, applying our method should provide various gallocatechin derivatives, including **1** and **2**. Further synthetic investigation and the biologically evaluation of **3** and **4** are currently under investigation in our laboratory.

Acknowledgment

The authors thank Mr. Masayuki Suzuki (Mitsui Norin Co., Ltd) for kindly providing a sample of **19**. The authors also acknowledge Professor Hironao Sajiki (Gifu Pharmaceutical University) for his kind suggestion about the reduction conditions. This work was financially supported by a Grant from the Novartis Foundation (Japan) for Promotion of Science (2008), Takeda Science Foundation, and a Grant-in-Aid for Scientific Research on Priority Areas 12045232 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

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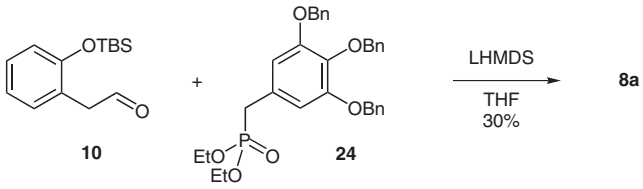
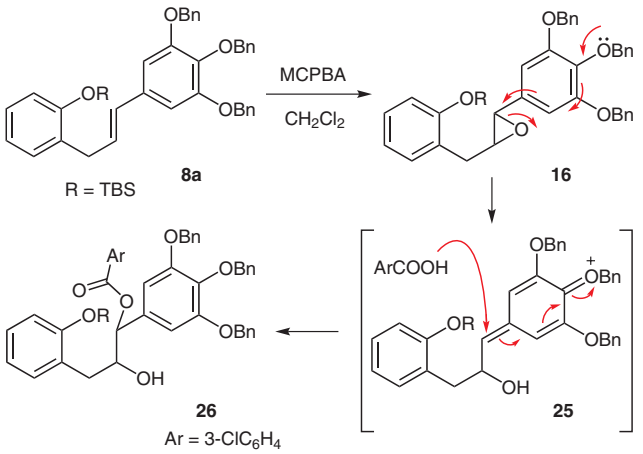
(9) Although HWE reaction of **10** and phosphonate **24** provided **8a** in good stereoselectivity, it resulted in a low yield (Scheme 7).



Scheme 7

(10) In acidic conditions, epoxide **16** was readily converted into quinone methide intermediate **25**, and sequential attack by MCBA to benzyl position of **25** afforded **26** (Scheme 8).



Scheme 8

(11) **Experimental Procedure for Shi Epoxidation**
To a solution of **15** (77.0 mg, 0.255 mmol) in MeCN–DMM (dimethyl methylether) (1:2, 2.7 mL) were successively added **8a** (100 mg, 0.156 mmol), $Bu_4N^+HSO_4^-$ (2.4 mg, 7.0 μmol), phosphorus buffer (pH 9.18, 4 mL), Oxone (376 mg, 0.611 mmol), and K_2CO_3 (125 mg, 0.90 mmol) at 0 °C. After being stirred for 25 min at 0 °C, H_2O was added to the reaction mixture, extracted with EtOAc, dried over anhyd $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel column (*n*-hexane–EtOAc, 10:1) to afford **16** (71.5 mg, 70%) as a yellow oil. The ee of **16** was determined by HPLC analysis on a chiral stationary phase under the conditions described below.
Spectral Data for 16
$[\alpha]_D^{20}$ +14.1 (*c* 1.0, $CHCl_3$). IR (neat): 1116, 1253, 1591, 2927, 3030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 6 H), 1.01 (s, 9 H), 2.93 (dd, *J* = 14.3, 5.2 Hz, 1 H), 3.04 (dd, *J* = 14.3, 5.2 Hz, 1 H), 3.15 (td, *J* = 5.2, 2.0 Hz, 1 H), 3.58 (d, *J* = 2.0 Hz, 1 H), 5.02 (s, 2 H), 5.07 (s, 4 H), 6.57 (s, 2 H), 6.82 (dd, *J* = 7.9, 1.2 Hz, 1 H), 6.92 (td, *J* = 7.9, 1.2 Hz, 1 H), 7.13 (td, *J* = 7.9, 1.2 Hz, 1 H), 7.31–7.42 (m, 15 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ = –4.0, 18.3, 25.8, 33.0, 58.6, 62.2, 71.2, 75.2, 105.0, 118.4, 121.2, 127.4, 127.7, 127.8, 128.1, 128.5, 128.6, 130.7, 133.3, 137.0, 137.8, 153.0, 153.7. MS–FAB: *m/z* = 659 $[M + H]^+$. HRMS: *m/z* calcd for $C_{42}H_{47}O_5Si$ $[M + H]^+$: 659.3193; found: 659.3167. HPLC analysis: Daicel Chiralpak AD-H 0.46 cm ø x 25 cm, eluent: 7% IPA–hexane, flow rate: 0.5 mL/min, t_R = 98.7 min (96.2%), 109.7 min (3.7%).

(12) **Experimental Procedure for 6-*endo* Cyclization**
To a solution of **16** (127 mg, 0.193 mmol) in THF (4.5 mL) were successively added AcOH (33 μL, 0.578 mmol) and TBAF (1 M in THF, 231 μL, 0.231 mmol) at 0 °C under an Ar atmosphere. After being stirred for 10 min at 0 °C, H_2O was added to the mixture and extracted with EtOAc, dried over anhyd $MgSO_4$, and evaporated to the crude product (major constituent: **7**; 185 mg) as a yellow oil. The crude **7** (185 mg) and CSA (45.4 mg, 0.193 mmol) were dissolved in CH_2Cl_2 (4.5 mL) under an Ar atmosphere. After being stirred for 30 min at 0 °C, H_2O was added to the mixture and extracted with CH_2Cl_2, dried over anhyd $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel column (*n*-hexane–EtOAc, 3:1) to afford **6** (63.7 mg, 61%, 2 steps), containing a small amount of the corresponding *cis*-isomer, as a yellow oil. The product (20.3 mg) was recrystallized from EtOAc–hexane to afford optically pure *trans*-isomer **6** (13.7 mg, 67%). The ee of **6** was determined by HPLC analysis on a chiral stationary phase under the conditions described below. Spectral date for **6**: $[\alpha]_D$ +1.7 (*c* 0.84, $CHCl_3$). IR (neat): 1132, 1246, 1597, 3032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 3.8 Hz, 1 H), 2.89 (dd, *J* = 15.8, 9.1 Hz, 1 H), 3.07 (dd, *J* = 15.8, 5.5 Hz, 1 H), 3.99 (dq, *J* = 15.8, 3.8 Hz, 1 H), 4.65 (d, *J* = 7.9 Hz, 1 H), 5.11–5.16 (m, 6 H), 6.73 (s, 2 H), 6.91–6.95 (m, 1 H), 7.11 (d, *J* = 7.3 Hz, 1 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 7.25–7.44 (m, 16 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 32.9, 68.1, 71.2, 75.2, 81.9, 106.7, 116.4, 120.2, 121.1, 127.5, 127.7, 127.8, 127.9, 128.2, 128.47, 128.53, 130.0, 133.3, 136.8, 137.7, 138.7, 153.0, 153.9. MS.FAB: *m/z* = 544 $[M]^+$. HRMS: *m/z* calcd for $C_{36}H_{32}O_5$ $[M]^+$: 544.2250; found: 544.2264. HPLC analysis: Daicel Chiralcel OD 0.46 cm ø x 25 cm, eluent: 10% IPA–hexane, flow rate: 0.5 mL/min, t_R: 77.8 min (>99%).

(13) **Spectral Data for 4**
$[\alpha]_D^{20}$ –73.5 (*c* 1.1, 50% acetone–H_2O). IR (neat): 1230, 1336, 1693, 3287 cm^{-1}. ^1H NMR (270 MHz, acetone-d_6): δ = 2.79 (dd, *J* = 16.2, 5.6 Hz, 1 H), 2.93 (dd, *J* = 16.2, 4.6

Hz, 1 H), 5.11 (d, *J* = 5.3 Hz, 1 H), 5.30 (q, *J* = 5.3 Hz, 1 H), 6.34 (s, 2 H), 6.76 (t, *J* = 7.9 Hz, 2 H), 6.97 (d, *J* = 6.6 Hz, 1 H), 6.98 (s, 2 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 7.93 (br s, 6 H). ^{13}C NMR (68 MHz, acetone-d_6): δ = 52,1, 70.5, 79.0, 106.3, 110.1, 110.2, 117.1, 120.4, 121.7, 121.8, 128.8, 131.0, 131.1, 133.6, 139.2, 146.2, 146.9, 155.0, 166.3. MS–FAB: *m/z* = 427 $[M + H]^+$. HRMS: *m/z* calcd for $C_{22}H_{19}O_9$ $[M + H]^+$: 427.1029; found: 427.1049.

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(16) **Spectral Data for 21**
$[\alpha]_D^{20}$ –16.7 (*c* 0.075, $CHCl_3$). IR (neat): 837, 1255, 1608, 3543 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.30 (s, 3 H), –0.08 (s, 3 H), 0.17 (m, 9 H), 0,78–0.98 (m, 30 H), 2.90 (dd, *J* = 15.8, 5.5 Hz, 1 H), 3.08 (dd, *J* = 15.8, 5.5 Hz, 1 H), 3.93 (tt, *J* = 10.7, 3.1 Hz, 1 H), 4.57 (t, *J* = 8.5 Hz, 1 H), 5.23 (s, 1 H), 6.55 (s, 2 H), 6.87–6.90 (m, 2 H), 7.07 (d, *J* = 2.0 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.2, –4.8, –4.5, –4.3, –0.01, 1.0, 17.9, 18.3, 25.7, 25.9, 26.2, 35.4, 69.2, 82.0, 107.5, 112.0, 112.3, 116.4, 120.6, 120.7, 127.5, 129.6, 129.8, 138.6, 142.9, 154.3. MS–FAB: *m/z* = 617 $[M + H]^+$. HRMS: *m/z* calcd for $C_{33}H_{57}O_5Si_3$ $[M + H]^+$: 617.3514; found: 617.3516. HPLC analysis: Daicel Chiralpak AD-H 0.46 cm ø x 25 cm, eluent: hexane, flow rate: 0.7 mL/min, t_R: 30.5 min.

(17) A similar pyran ring construction through the quinone methide intermediate has been reported, see: Noda, I.; Horita, K.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 1917; although many 6-*endo* cyclizations of epoxyalchol have been reported, *cis*-disubstituted epoxide has yet to be reported.

(18) **Experimental Procedure and Separation of Diasteromers**
Compounds **22** and **6** (33.5 mg, 61.5 mmol), **18** (81.3 mg, 184 mmol), WSC (29 mg, 154 mmol), and DMAP (0.8 mg, 6.2 mmol) were dissolved in CH_2Cl_2 (3 mL) under an Ar atmosphere. After being stirred for 3 h at r.t., sat. NH_4Cl aq was added to the reaction mixture, extracted with CH_2Cl_2, dried over anhyd $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel column (*n*-hexane–EtOAc, 6:1) to afford **23** (33.3 mg, 56%, R_f = 0.42, *n*-hexane–EtOAc, 3:1) and **5** (26.2 mg, 44%, R_f = 0.49, *n*-hexane–EtOAc, 3:1).