Synthetic Studies on Bilobalide

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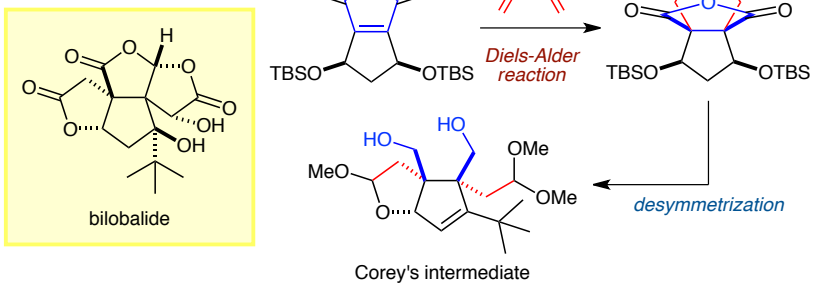

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Abstract We disclose our synthetic studies on bilobalide, which features a Diels-Alder reaction of a cyclic anhydride to from two contiguous quaternary carbons, desymmetrization of a symmetric diol, and construction of a cyclic acetal under acidic conditions with inversion of configuration at an allylic position.

Key words desymmetrization, Diels-Alder reaction, Mukaiyama hydration, quaternary carbon, tertiary alcohol

Bilobalide is a sesquiterpene, whose isolation from leaves of the ginkgo tree was first reported in 1967 and then in 1969.[1] Structural elucidation by Nakanishi and coworkers in 1971 showed that bilobalide has a tetracyclic skeleton composed of three lactone rings and a cyclopentane ring, on which two hydroxy groups and a *tert*-butyl group are substituted (Figure 1).[2] The substituents and the complicated connection of the rings form six contiguous stereogenic centers, which contain two quaternary carbons and a tertiary alcohol moiety. These intriguing structural features, as well as its biological activities such as neuroprotective activity,[3] antagonism against GABA receptor,[4] and others, have attracted much attention in chemistry, and the total syntheses of bilobalide have been reported by three research groups.[5] Herein we disclose our synthetic studies on bilobalide.

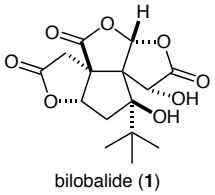
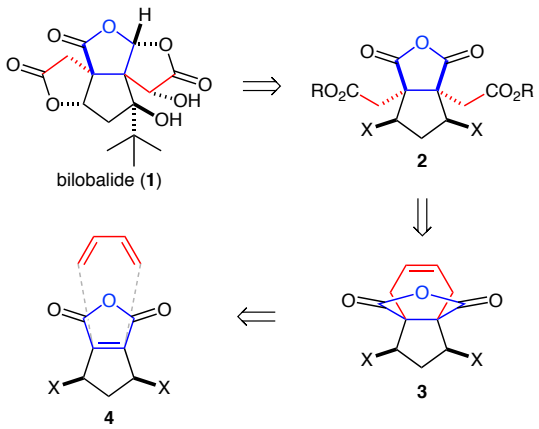
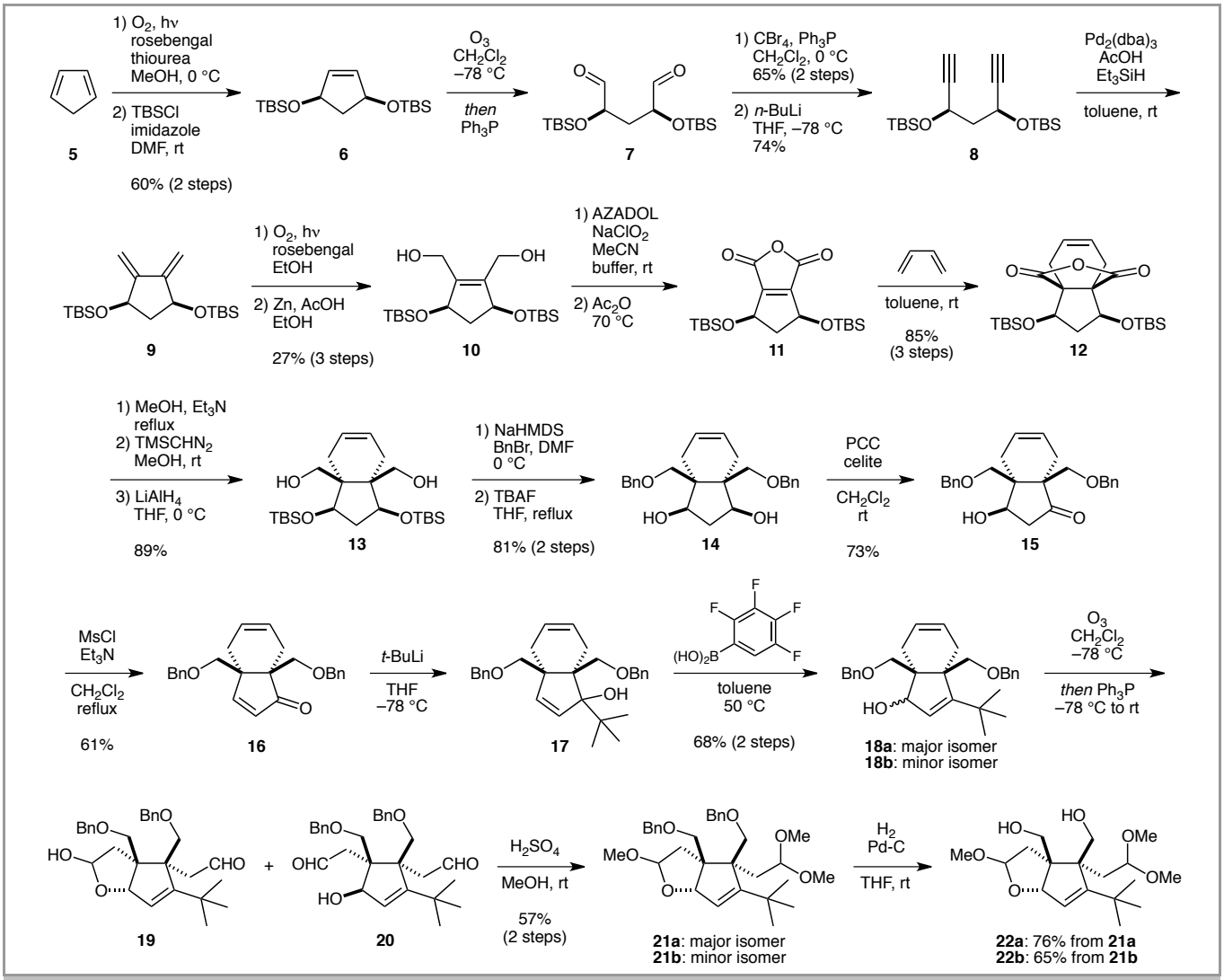


Figure 1 Structure of Bilobalide.

Our retrosynthetic analysis is shown in Scheme 1. We paid attention to the symmetrical component in the structure of bilobalide (**1**). Thus, removal of the hydroxy groups and the *tert*-butyl group, as well as cleavage of the lactone rings would generate symmetrical compound **2**. Connection of the two carbonyl groups in ester moieties would form cyclohexene **3**, which could be constructed via a Diels-Alder reaction of cyclic anhydride **4**. The Diels-Alder reaction is a reliable tool that constructs contiguous quaternary carbons,[6] and therefore we commenced our synthesis with preparation of the requisite cyclic anhydride.



Scheme 1 Retrosynthesis of Bilobalide.



Scheme 2 Synthetic Studies toward Bilobalide.

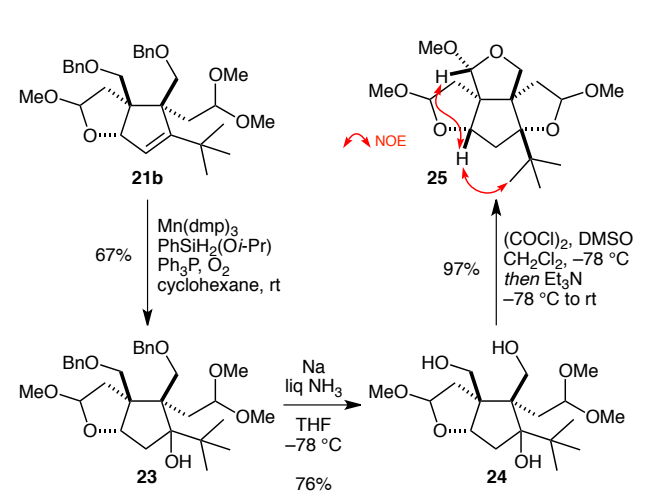
A reaction of cyclopentadiene (**5**) with singlet oxygen in the presence of thiourea afforded a diol,[7] which was protected with TBS groups (Scheme 2). Ozonolysis of the resulting cyclopentene **6** produced dialdehyde **7**, which was subjected to the Corey-Fuchs alkyne synthesis with a 2-step conversion,[8] giving diyne **8**. A palladium-mediated reductive cyclization converted the diyne into diene **9**,[9] which was immediately reacted with singlet oxygen. Reduction of the resulting endoperoxide with zinc and acetic acid afforded diol **10**. AZADO oxidation of the diol furnished dicarboxylic acid,[10,11] which was converted into cyclic anhydride **11** by heating in acetic anhydride.

The Diels-Alder reaction of the cyclic anhydride with butadiene proceeded smoothly at room temperature. The reaction occurred stereoselectively from the less substituted face, giving a tricyclic compound having two quaternary carbons. Reduction of the anhydride moiety in **12** via formation of a diester was followed by protection of the resulting diol **13** with benzyl groups. Deprotection with TBAF afforded diol **14**.

Desymmetrization of the molecule could be achieved at this stage. PCC oxidation afforded β-hydroxyketone **15** in good yield. A slightly excess amount of PCC did not affect the results. This indicates that the reactivity of the remaining hydroxy group in **15** was significantly reduced by the electron withdrawing nature of the ketone moiety. Elimination of the hydroxy group via formation of a mesylate produced enone **16**. Addition of *tert*-butyllithium to the enone moiety occurred smoothly at –78 °C to give alcohol **17** as a sole isomer, although the stereochemsitry could not be determined. 1,3-Isomerization of the tertiary alcohol moiety in **17** was mediated by 2,3,4,5-tetrafluorophenylboronic acid to give a 2:1 inseparable mixture of **18a** and **18b**.[12,13] Selective ozonolysis of the less hindered C-C double bond on the cyclohexene ring furnished a mixture of aldehydes including **19** and **20**. Upon treatment with sulfuric acid in methanol, inversion of configuration at the allylic position in **20** occurred, and both **19** and **20** could be converted into acetal **21a** and **21b**.[14,15,16] After separation of the diastereomer, removal of the benzyl groups of both isomers **21a** and **21b** could be carried out under usual conditions in the presence of the trisubstituted C-C double bond, giving diol **22a** and **22b**, the latter of which was identical to the intermediate in the Corey's synthesis.[5a,17,18]

On the other hand, we tried to form the tertiary alcohol moiety of bilobalide, starting from **21b**.[19] Mukaiyama hydration with

Shenvi's modification could convert **21b** into tertiary alcohol **23** in 67% yield.[20,21] Although the stereochemistry of the reaction could not be confirmed at this stage, we conducted further transformation of tertiary alcohol **23**. Thus, Birch reduction removed the benzyl groups to give triol **24**, which was subjected to Swern oxidation. In the latter transformation we attempted to simultaneously oxidize the two primary alcohol moieties to obtain the corresponding dialdehyde. The reaction of **24**, however, afforded tetracyclic compound **25** in 97% yield.[22] The bulky *tert*-butyl group might hamper the Swern oxidation of the adjacent primary alcohol moiety, and the resulting mono-aldehyde underwent formation of cyclic acetals via an unusual transposition of a methoxy group in the dimethyl acetal, leading to **25**. The structure of compound **25** was confirmed by using 2D NMR techniques, including H-H COSY, HMQC, HMBC and NOESY, which revealed that the Mukaiyama hydration afforded the product with the stereochemistry opposite to that of bilobalide.



Scheme 3 Formation of the Tertiary Alcohol Moiety via Mukaiyama Hydration.

In conclusion, through our synthetic studies on bilobalide, we achieved construction of the two contiguous quaternary carbons and introduction of the *tert*-butyl group, resulting in establishing another synthetic route toward the Corey's intermediate.

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Supporting Information

YES

Primary Data

NO

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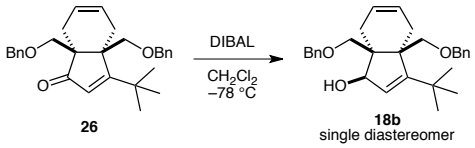
(13) **3a,7a-bis((benzyloxy)methyl)-3-(*tert*-butyl)-3a,4,7,7a-tetrahydro-1*H*-inden-1-ol (18a and 18b)** To a solution of enone **16** (23 mg, 0.061 mmol) in THF (1.0 ml) was added *tert*-butyllithium (1.53 M solution in hexane, 0.048 ml, 0.073 mmol) at –78 °C, and the mixture was stirred for 15 min. The reaction was then quenched with water, and the resulting mixture was extracted three times with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residual oil containing **17** was used for the next step without further purification. To a stirred solution of the above crude material in toluene (1.0 ml) was added 2,3,4,5-tetrafluorophenylboronic acid

(2 mg, 0.01 mmol) at room temperature. The mixture was heated at 50 °C with stirring for 2 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (EtOAc-hexane = 1:3) to give a 2:1 mixture of **18a** and **18b** (18 mg, 0.042 mmol, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 10H), 5.75 (d, *J* = 2.8 Hz, (1/3)1H), 5.73 (m, (2/3)1H), 5.68-5.60 (m, (1/3)2H+(2/3)1H), 5.57 (d, *J* = 1.6 Hz, (2/3)1H), 4.98 (d, *J* = 1.6 Hz, (2/3)1H), 4.52-4.28 (m, (1/3)4H+(2/3)44H), 4.03 (d, *J* = 11.2 Hz, (1/3)1H), 3.81-3.75 (m, (1/3)1H+(2/3)1H), 3.53-3.47 (m, (1/3)2H+(2/3)1H), 2.48-2.14 (m, (1/3)2H+(2/3)4H), 2.03 (d, *J* = 18.0 Hz, (1/3)1H), 1.76 (d, *J* = 18.8 Hz, (1/3)1H), 1.10 (s, (1/3)9H), 1.09 (s, (2/3)9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.7 (C), 139.0, 138.5 (C), 138.4, 136.8 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.6, (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 126.3, 125.7 (CH), 124.7, 123.5 (CH), 81.0, 80.3 (CH), 74.1 (CH_2), 73.5 (CH_2), 73.5 (CH_2), 73.3 (CH_2), 73.0 (CH_2), 72.8 (CH_2), 72.7 (CH_2), 72.6 (CH_2), 54.6, 53.9 (C), 52.3, 48.4 (C), 34.5, 34.3 (C), 34.1 (CH_2), 30.8, 30.8 (CH_3), 29.4 (CH_2), 28.3 (CH_2), 25.7 (CH_2); HRMS (ESI+) 455.2549 (calcd for $C_{29}H_{36}NaO_3$: 455.2562).

(14) **3a,4-bis((benzyloxy)methyl)-5-(*tert*-butyl)-4-(2,2-dimethoxyethyl)-2-methoxy-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan (21a and 21b)** To a stirred solution of allyl alcohol **18a** and **18b** (mixture of diastereomers, 4 mg, 0.01 mmol) in dichloromethane (1.0 ml) was added a solution of ozone in dichloromethane at −78 °C. The reaction was quenched with triphenylphosphine (6 mg, 0.02 mmol) and removal of the solvent under reduced pressure gave a crude material containing **19** and **20**, which was used in the next step without further purification. To a solution of the crude material in MeOH (1.0 ml) was added concentrated sulfuric acid (0.004 ml, 0.08 mmol) at room temparature. After stirring for 30 min, the reaction was then quenched with solid $NaHCO_3$ and the mixture was concentrated *in vacuo*. To the residue was added water, and the mixture was extracted three times with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by preparative TLC (EtOAc-hexane, 1:6) to give a 3:2 mixture of **21a** and **21b** (3 mg, 0.006 mmol, 57%) as a colorless oil. **21a** (major isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 10H), 5.56 (d, *J* = 1.6 Hz, 1H), 4.98 (d, *J* = 7.6 Hz, 1H), 4.94 (d, *J* = 5.6 Hz, 1H), 4.59 (d, *J* = 1.6 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 3.65 (d, *J* = 10.4 Hz, 1H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.48 (d, *J* = 10.4 Hz, 1H), 3.29 (s, 3H), 3.19 (s, 3H), 3.14 (s, 3H), 2.34 (d, *J* = 12.8 Hz, 1H), 2.18 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.02 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.80 (d, *J* = 14.8 Hz, 1H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5 (C), 138.7 (C), 138.3 (C), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.6 (CH), 105.5 (CH), 103.4 (CH), 90.1 (CH), 73.4 (CH_2), 72.0 (CH_2), 71.9 (CH_2), 71.6 (CH_2), 59.3 (C), 58.6 (C), 54.7 (CH_3), 53.6 (CH_3), 52.4 (CH_3), 39.0 (CH_2), 37.6 (CH_2), 34.6 (C), 31.3 (CH_3); HRMS (ESI+) 547.3021 (calcd for $C_{32}H_{44}NaO_6$ 547.3036). **21b** (minor isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 10H), 5.68 (d, *J* = 2.0 Hz, 1H), 5.06 (dd, *J* = 5.6, 5.2 Hz, 1H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.60 (d, *J* = 2.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.8 Hz, 1H), 4.33 (d, *J* = 12.8 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 3.62 (d, *J* = 10.0 Hz, 1H), 3.57 (d, *J* = 9.6 Hz, 1H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.34 (s, 3H), 3.31 (d, *J* = 9.6 Hz, 1H), 3.20 (s, 3H), 3.12 (s, 3H), 2.39 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.16 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.00 (dd, *J* = 13.2, 5.2 Hz, 1H), 1.95 (d, *J* = 14.8 Hz, 1H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (C), 138.7 (C), 138.2 (C), 128.7 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 106.5 (CH), 103.1 (CH), 89.9 (CH), 73.4 (CH_2), 72.7 (CH_2), 72.2 (CH_2), 72.2 (CH_2), 59.8 (C), 58.5 (C), 55.2 (CH_3), 53.4 (CH_3), 52.2 (CH_3), 39.2 (CH_2), 39.0 (CH_2), 34.5 (C), 31.3 (CH_3); HRMS (ESI+) 547.3038 (calcd for $C_{32}H_{44}NaO_6$ 547.3036).

(15) Oxidative rearrangement of **17** with PCC, followed by reduction of the resulting enone **26** with DIBAL, afforded one of the isomers of alcohol **18b**, ozonolysis of which furnished **20**. Acetal formation from **20** under the same conditions afforded **21a** and **21b** in 60% yield. For details, see ref 16.



26 **18b** single diastereomer

(16) **3a,7a-bis((benzyloxy)methyl)-3-(*tert*-butyl)-3a,4,7,7a-tetrahydro-1*H*-inden-1-ol (18b)** Enone **16** (30 mg, 0.081 mmol) was converted into 17 according to the procedure provided in ref 13. The crude was **17** was dissolved in dichloromethane (5.0 ml), and to the resulting solution were added Celite (64 mg) and pyridinium chlorochromate (33 mg, 0.16 mmol) at room temperature. After stirring for 30 minutes, the solution was filtered through a pad of silica gel and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc-hexane, 1:3) to give enone **26** (30 mg, 0.069 mmol, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (m, 10H), 6.07 (s, 1H), 5.80-5.75 (m, 1H), 5.73-5.65 (m, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.28 (s, 2H), 4.35 (d, *J* = 16.2 Hz, 1H), 4.28 (s, 1H), 3.93 (d, *J* = 9.2 Hz, 1H), 3.75 (d, *J* = 9.2 Hz, 1H), 3.73 (d, *J* = 9.6 Hz 1H), 3.59 (d, *J* = 9.6 Hz, 1H), 2.47-2.36 (m, 2H), 2.25-2.20 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (C), 189.5 (C), 138.3 (C), 138.0 (C), 131.2 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 125.4 (C), 73.3 (CH_2), 73.1 (CH_2), 72.6 (CH_2), 72.3 (CH_2), 57.2 (C), 56.8 (C), 36.8 (C), 31.1 (CH_3), 30.6 (CH_2), 30.4 (CH_2). Three CH peaks of phenyl groups were not observed perhaps due to overlapping. To a solution of enone **26** (30 mg, 0.069 mmol) in dichloromethane (1.2 ml) was added diisobutylaluminiun hydride (1.0 M solution in hexane, 0.14 ml, 0.14 mmol) at −78 °C, and the mixture was stirred for 15 min. The reaction was then quenched with saturated aqueous potassium sodium tartrate. The mixture was extracted three times with dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified preparative TLC (EtOAc-hexane, 1:3) to give **18b** (29 mg, 0.067 mmol, 97%) as a single diastereomer and as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (m, 10H), 5.76 (d, *J* = 2.4 Hz, 1H), 5.67-5.57 (m, 2H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.79 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.52 (d, *J* = 9.2 Hz, 1H), 3.48 (d, *J* = 9.2 Hz, 1H), 3.31 (d, *J* = 10.4 Hz, 1H), 3.26 (d, *J* = 10.4 Hz, 1H), 2.44 (d, *J* = 18.0 Hz, 1H), 2.38 (d, *J* = 18.8 Hz, 1H), 2.03 (d, *J* = 18.0 Hz, 1H), 1.76 (d, *J* = 18.8 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (C), 139.0 (C), 136.8 (C), 138.0 (C), 128.4 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 126.3 (CH), 123.5 (CH), 80.3 (CH), 73.3 (CH_2), 73.0 (CH_2), 72.8 (CH_2), 72.6 (CH_2), 54.0 (C), 48,4 (C), 34.5 (C), 34.1 (CH_2), 30.8 (CH_3), 29.4 (CH_2); One CH peak of a phenyl group was not observed perhaps due to overlapping; HRMS (ESI+) 455.2560 (calcd for $C_{29}H_{36}NaO_3$ 455.2562).

(17) NMR data for one of the epimers are available in the literature of the Corey's synthesis.

(18) **5-(*tert*-butyl)-4-(2,2-dimethoxyethyl)-2-methoxy-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-3a,4-diyl)dimethanol (22b)** A mixture of **21b** (3 mg, 0.005 mmol) and 10% Pd/C (56 mg, 0.053 mmol) in THF (0.5 ml) was stirred for 6 h at room temperature under H_2 (1 atm), before the mixture was filtered though a pad of Celite. The filtrate was concentrated to afford a crude material, which was purified by preparative TLC (EtOAc) to give **22b** (1 mg, 0.003 mmol, 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, *J* = 2.0 Hz, 1H), 5.09 (dd, *J* = 6.0, 4.4 Hz, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.69 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.99 (dd, *J* = 12.0, 6.8 Hz, 1H), 3.76 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.68 (dd, 11.6, 7.2 Hz, 1H), 3.46 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.34 (s, 9H), 3.30 (m, 1H), 2.91 (m, 1H), 2.23-2.17 (m, 3H), 1.97 (dd, *J* = 14.0, 4.4 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5 (CH), 105.9 (CH), 102.4 (CH), 86.9 (CH), 65.6 (CH_2), 65.1 (CH_2), 61.9 (C), 60.1 (C),

55.3 (CH_3), 53.1 (CH_3), 52.6 (CH_3), 40.4 (CH_2), 38.2 (CH_2), 34.6 (C), 31.4 (CH_3); HRMS (ESI+) 367.2101 (calcd for $C_{18}H_{32}NaO_6$: 367.2097).

(19) The isomers **21a** and **21b** showed different reactivity in the Mukaiyama hydration. The reaction of the major isomer **21a** proceeded sluggishly under the same conditions to produce the corresponding tertiary alcohol in 16% yield even after 5 h.

(20) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *18*, 1071. (b) Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962.

(21) **3a,4-bis((benzyloxy)methyl)-5-(*tert*-butyl)-4-(2,2-dimethoxyethyl)-2-methoxyhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (23)** A solution of **21b** (6 mg, 0.01 mmol), $Mn(dpm)_3$ (7 mg, 0.01 mmol) and triphenylphosphine (4 mg, 0.02 mmol) in cyclohexane (0.5 ml) was prepared in a test tube, which was charged with O_2. To this mixture was added monoisopropoxy(phenyl)silane (6 µl, 0.03 mmol), and the resulting mixture was stirred at room temperature for 20 min before it was concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc-hexane, 1:3) to give **23** (4 mg, 0.008 mmol, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 10H), 5.13 (dd, *J* = 6.4, 2.8 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.44 (dd, *J* = 8.8, 1.6 Hz, 1H), 4.41 (d, *J* = 9.2 Hz, 1H), 4.35 (d, *J* = 12.0 Hz), 4.28 (d, *J* = 11.6, 1H), 4.26 (s, 1H), 4.06 (d, *J* = 11.6 Hz, 1H), 3.58 (d, *J* = 10.8, 1H), 3.43 (d, *J* = 10.8 Hz, 1H), 3.40 (s, 3H), 3.37 (s, 2H), 3.22 (s, 3H), 3.11 (s, 3H), 2.80 (dd, *J* = 15.2, 9.2 Hz, 1H), 2.65 (dd, *J* = 15.6, 1.6 Hz, 1H), 2.60 (dd, *J* = 13.6, 2.8 Hz, 1H), 2.47 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.84 (dd, *J* = 15.6 Hz, 8.8 Hz, 1H), 1.60 (d, *J* = 15.2 Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ138.4 (C), 137.8 (C), 128.3 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.5 (CH), 107.9 (CH), 103.7 (CH), 88.9 (C), 88.2 (CH), 74.5 (CH_2), 73.4 (CH_2), 72.3 (CH_2), 71.9 (CH_2), 59.5 (C), 58.4 (C), 55.1 (CH_3), 53.1 (CH_3), 51.9 (CH_3), 43.6 (CH_2), 40.8 (CH_2), 39.8 (C), 35,7 (CH_2), 28.3 (CH_3); HRMS (ESI+) 565.3158 (calcd for $C_{32}H_{46}NaO_7$ 565.3141).

(22) **3a-(*tert*-butyl)-2,6,8-trimethoxyoctahydro-1*H*-cyclopenta[1,2-*b*:4,3-*b*′:2,3-*c*′′]trifuran (25)** To a stirred solution of dimethyl sulfoxide (19 µl, 0.27 mmol) in dichloromethane (0.5 ml) was added dropwise oxalyl chloride (16 µl, 0.18 mmol) at –78 °C. After stirring for 10 min at –78 °C, to the mixture was added dropwise a solution of triol **24** (1 mg, 0.003 mmol) in dichloromethane (0.5 ml), and the resulting mixture was stirred for another 40 min at –78 °C. To the mixture was added triethylamine (62 µl, 0.45 mmol) before it was allowed to warm to room temperature. After stirring for another 20 min at room temperature, the mixture was quenched with water, and extracted three times with dichloromethane. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by preparative TLC (EtOAc-hexane = 1:3) to give **25** (1 mg, 0.003 mmol, 97%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (dd, *J* = 6.4, 6.0 Hz, 1H), 5.06 (dd, *J* = 6.4, 4.8 Hz, 1H), 4.65 (s, 1H), 4.53 (d, *J* = 10.0 Hz, 1H), 4.16 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.64 (d, *J* =10.0 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.31 (s, 3H), 2.62 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.39 (dd *J* = 14.4, 6.0 Hz, 1H), 2.35 (dd, *J* = 14.8, 7.2, 1H), 2.16 (dd, *J* = 14.8, 5.6 Hz, 1H), 1.94 (dd, *J* = 15.2, 4.8 Hz, 1H), 1.85 (dd, *J* = 14.4, 6.4 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.8 (CH), 107.3 (CH), 103.6 (CH), 100.8 (C), 87.4 (CH), 70.3 (CH_2), 68.8 (C), 63.2 (C), 56.2 (CH_3), 56.1 (CH_3), 54.7 (CH_3), 43.1 (CH_2), 41.3 (CH_2), 37.8 (C), 35.8 (CH_2) 27.2 (CH_3; detected as a cross peak in the HMQC spectrum); HRMS (ESI+) 365.1940 (calcd for $C_{18}H_{30}NaO_6$ 365.1940).