Pergamon

Tetrahedron 56 (2000) 10141–10151

TETRAHEDRON

Asymmetric Desymmetrization of Saturated and Unsaturated *meso*-1,2-Diols

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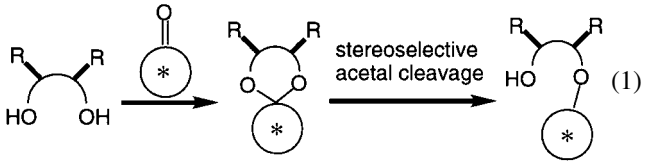
Received 27 November 1999; accepted 27 January 2000

Abstract—An asymmetric desymmetrization of saturated and unsaturated cyclic and acyclic *meso*-1,2-diols has been developed from the ene acetals, prepared from the norbornene carboxyaldehyde and *meso*-1,2-diols. The intramolecular haloetherification of the ene acetals as a key step afforded 8-membered acetals in a stereoselective manner just by the reaction of norbornene olefin even when the ene acetals from unsaturated *meso*-1,2-diols having olefins in the same molecule were used. Subsequent reductive elimination, followed by protecting the hydroxy group and transacetalization, gave optically active 1,2-diol derivatives and the starting ene acetals in good yields.

Introduction

Enantiodifferentiation of the σ-symmetric diols (including *meso*-diols) is an important area in organic synthesis. Many methodologies have been developed so far. They are widely divided into two groups. One is the group using enzymes as a tool.[1] The other is the group using chemical methods.[2] The chemical enantiodifferentiation of diols is also divided into three categories: (1) desymmetrization by the stereoselective cleavage of the acetals derived from σ-symmetric diols and chiral carbonyl compounds,[2a–i] (2) direct desymmetrization of σ-symmetric diols with a chiral reagent,[2j–n] and (3) direct desymmetrization of σ-symmetric diols in the presence of chiral sources.[2o–s] Among these three methodologies, method (1) using chiral carbonyl compounds seems to be most reliable at this time, because the products obtained by cleavage of the acetal still have chiral unit and this chiral unit can help to purify the product in an optically pure state, when they are obtained in highly optically active but not optically pure forms (Eq. (1)).

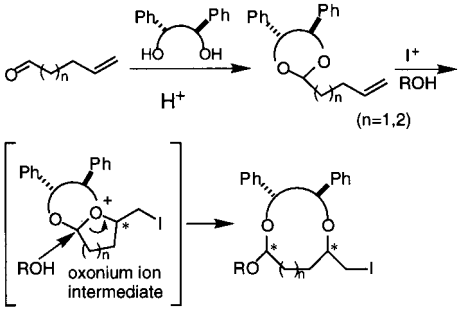


(1)

Several methodologies using chiral carbonyl compounds such as menthon, β-ketosulfoxide compounds, and so on have been developed so far. However, the desymmetrization of acyclic *meso*-1,2-diols still remains a problem. We chose to use a chiral aldehyde, chiral methyl norbornene aldehyde, as a chiral carbonyl compound and succeeded in discrimination of saturated and unsaturated not only cyclic *meso*-1,2-diols but also acyclic ones.[3,4] We present here the details of these studies.

Concept

Recently, we have developed a new asymmetric synthesis of optically active 1,4- and 1,5-diols, where intramolecular haloetherification of chiral ene acetals, prepared from C_2-symmetric optically active diols and optically nonactive ene aldehydes, is characterized as a crucial step. The reactions of the ene acetals proceed via oxonium ion intermediates (Eq. (2)).[5] This finding suggested us that if a large energy difference existed among the possible intermediates formed from the ene acetal derived from the proper chiral non-racemic ene aldehyde and symmetric *meso*-diol, the reaction may proceed through the most stable intermediate, resulting in the discrimination of the two oxygen atoms of the *meso*-diol (Eq. (3)).



(2)

Keywords: asymmetric desymmetrization; *meso*-1,2-diol; norbornene aldehyde; intramolecular haloetherification; ene acetal.

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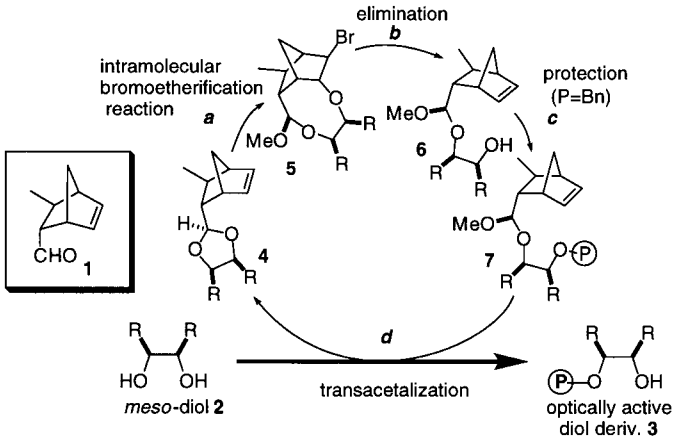
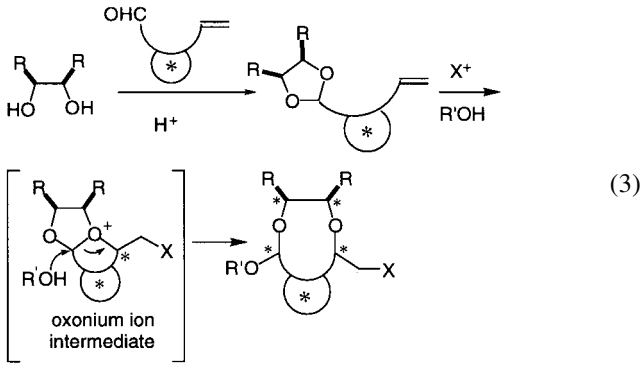
PII: S0040-4020(00)00859-0



Scheme 1.



(3)

Result and Discussion

As a chiral non-racemic auxiliary, we chose methyl norbornene aldehyde **1**. Our desymmetrization reaction cycle is depicted in Scheme 1. The cycle consists of four steps: (1) intramolecular haloetherification of the ene acetal (step ***a***), (2) dehaloetherification (step ***b***), (3) protection of the alcohol (step ***c***), then (4) transacetalization with *meso*-1,2-diol (step ***d***). This is very useful because transacetalization gives the optically active *meso*-1,2-diol derivatives with the starting ene acetals. This means the cycle works repeatedly once after obtaining the starting ene acetals. We selected (1*R*,2*R*,3*S*,4*S*)-3-methyl-5-norbornene-2-carboxaldehyde **1** as a chiral norbornene aldehyde for the following four reasons: (1) **1** is easily prepared by asymmetric Diels–Alder reaction,[6] (2) acetalization would proceed stereoselectively to give the *cis*-isomer,[7] (3) a newly produced chiral center (correspond to * center in oxonium ion intermediate of Eq. (3)) would be formed stereospecifically in the haloetherification because both of the aldehyde and the double bond are fixed, and most importantly (4) sterically rigid forms of the oxonium ion intermediates would be expected to create a large energy difference. We chose methyl norbornene aldehyde instead of norbornene aldehyde itself. One reason is point 1 above and another reason is to avoid the possibility of epimerization of the aldehyde during the reactions.

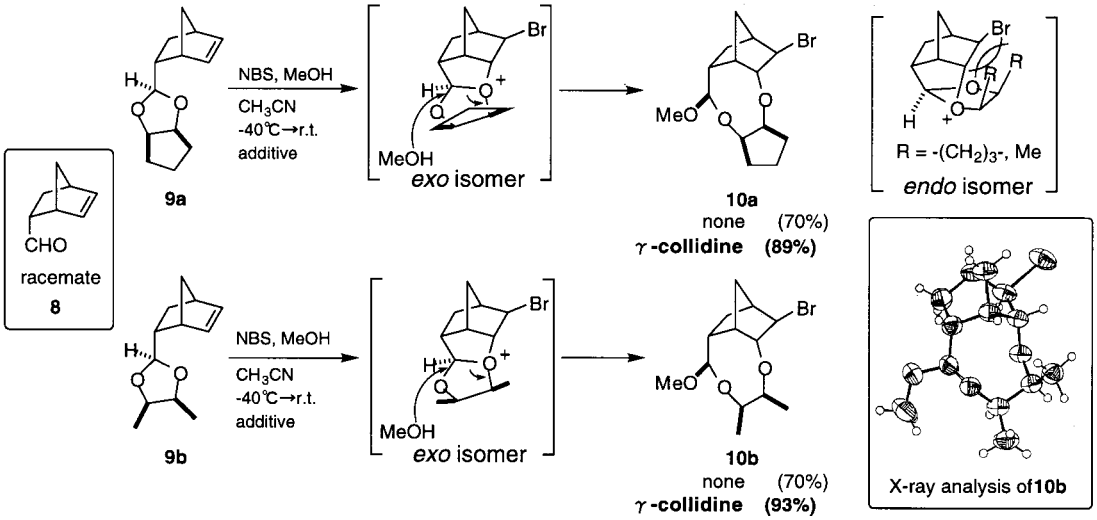
Preparation of ene acetals from *meso*-1,2-diols

Ene acetals were prepared stereospecifically in good yields in every case from *meso*-1,2-diols **2** and **1** in the presence of a catalytic amount of prydinium *p*-toluenesulfonate (PPTS). *p*-TsOH or *d*-camphorsulfonic acid as an acid catalyst in place of PPTS decreased the stereoselectivity of acetalization. The stereochemistries of the acetals were determined by NOE experiments. It has been reported that five-membered acetalization tends to give the acetals with *cis*-orientation via *anti*-transoid oxonium ion intermediates.[7] In our cases, the bulkiness of the norbornene aldehyde skeleton realized such high stereospecificity. It is worthy noting that even the reaction of acyclic 2,5-dimethyl-3,4-hexanediol **2h**, which is supposed to be disadvantageous in the formation of the acetal structure because of the repulsion between the two substituents, proceeds without any problem (Table 1).

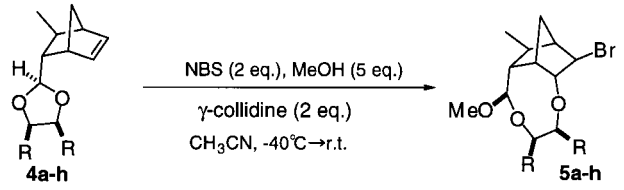
Intramolecular bromoetherification in Scheme 1 (step *a*)

This step is the most crucial step in our desymmetrization reaction cycle. We then investigated the reactivity and stereochemistry of this reaction using two acetals **9a**,**b** derived from *meso*-1,2-cyclopentanediol or *meso*-2,3-butanediol and commercially available racemic norbornene aldehyde **8**. Intramolecular haloetherification with 2 equiv. of NBS in the presence of 5 equiv. of MeOH proceeded in good yields in the presence of 2 equiv. of γ-collidine to give the products **10a** and **10b** as a single isomer, respectively. As shown from the conformations of the intermediates, a large steric repulsion not only between the substituents and the bicyclo[2.2.1]heptane skeleton but also between the 1,3-dioxolane skeleton and the bicyclo[2.2.1]heptane skeleton is observed in *endo* isomer whereas such repulsion is not observed in *exo* isomer. X-Ray analysis of compound **10b** revealed its structure, and the reaction proceeded via the expected preferable *exo*-intermediates followed by S_N2 attack of MeOH (Scheme 2).

We then examined the intramolecular haloetherification of optically pure ene acetals **4a**–**h** from saturated *meso*-1,2-diols under the same reaction condition as described



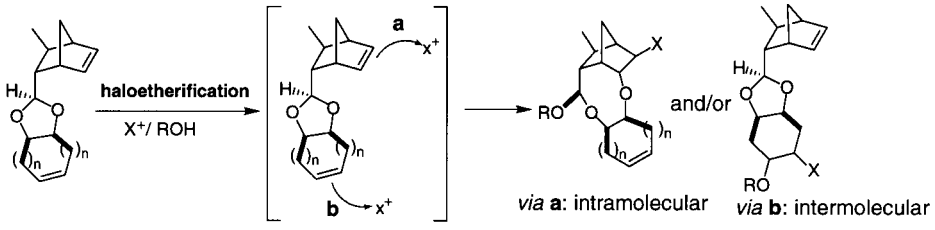
Scheme 2.



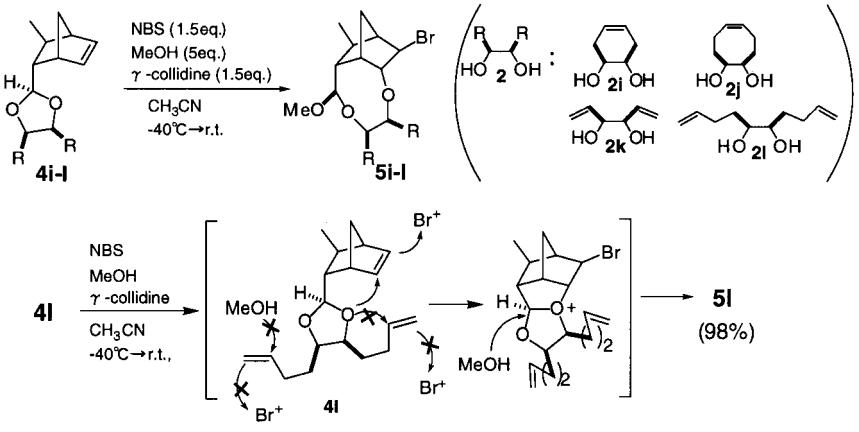
Scheme 3.

above. Reactions for all ene acetals **4a**–**h** proceeded smoothly and gave 8-membered acetals **5a**–**h**. Yields of all 8-membered acetals **5a**–**h** are shown in Table 2. The absolute stereochemistry of **5a** was determined by conversion to the optically active **3a** described below and comparison of its specific rotation [+16.6° (*c* 1.03, $CHCl_3$)] with the reported value [+16.5° (*c* 1.10, $CHCl_3$)][8] and the X-ray crystallographic structure of **10b**. The absolute stereochemistries of other compounds **5b**–**h** were tentatively determined by assuming the same sense of diastereoselection as observed in **5a** and also by mechanistic consideration (Scheme 3).

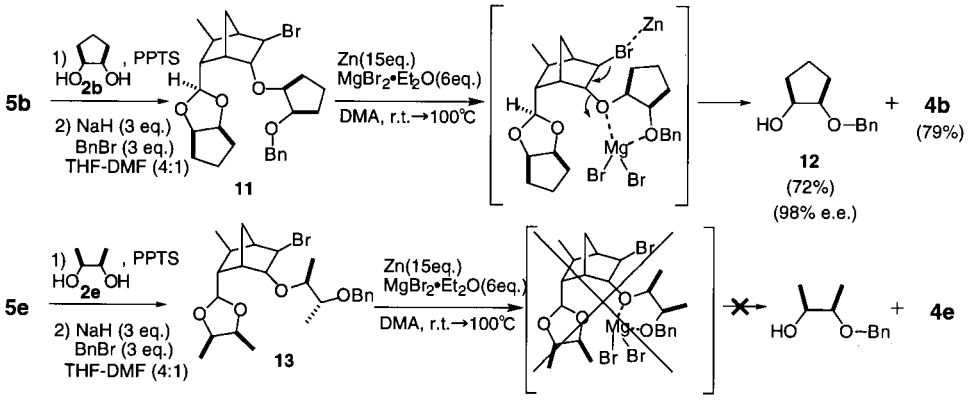
As mentioned above, our asymmetric desymmetrization was based on an intramolecular haloetherification reaction and worked very well. We next examined to apply this method to the ene acetals **4i**–**l** from unsaturated *meso*-1,2-diols **2i**–**l** having olefins in the same molecule, although the bromoetherification reaction of the ene acetals from



Scheme 4.



Scheme 5.



Scheme 6.

unsaturated diols is anticipated to cause competition between the intra- vs intermolecular route (Scheme 4).

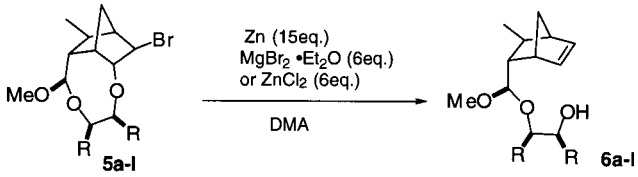
In every case, strong kinetic control was observed, and the desired products **5i–l** by intramolecular reaction were obtained in extremely high yields. High selectivity in these bromoetherification reactions must be due to preference for the intramolecular reaction vs the intermolecular one in addition to the high reactivity of norbornene olefin to the bromonium ion. It is noteworthy that high selectivity was observed even in compound **4l**. In this case, because the distance between the norbornene olefin and the acetal oxygen is the same as that between the diol olefin and the acetal oxygen and both olefins are under same situation for the intramolecular version, in other words each reaction proceeds via a 5-membered transition state, compound **4l** was expected to proceed by two types of intramolecular haloetherification reaction, one with a norbornene olefin and the other with a diol olefin. This high reactivity of the olefin of the norbornene skeleton toward the bromonium ion is suited to our desymmerization method (Scheme 5).

Reductive debromoetherification

This step was examined in two ways, (1) debromoetherification of bromobenzyl ether, and (2) debromoetherification of an 8-membered mixed acetal. Method (2) was found to be effective for our purpose.

(1) Debromoetherification of bromobenzyl ether. For reductive debromoetherification, we first examined the reductive debromination of bromobenzyl ether **11**, prepared from 8-membered acetal **5b** by transacetalization with *meso*-1,2-cyclopentanediol **2b** and protection of the hydroxy group as a benzyl ether. After several disappointing trials, we succeeded in reductive debromoetherification of **11** using 15 equiv. of Zn and 6 equiv. of $MgBr_2{\cdot}Et_2O$ in DMA to give the optically pure benzyl ether **12** along with the ene acetal **4b**. However, this condition failed in the debromoetherification of the corresponding compound **13** from **5e**. The differences between the two reactions might be rationalized by the coordination of $MgBr_2$, which aids the debromoetherification. That is, $MgBr_2$ can coordinate with two oxygen atoms in **11**, because two oxygen atoms are fixed *cis*-orientation in **11**. However, in acyclic case **13**, the most preferable conformation of the two oxygen atoms is *trans*-orientation because of repulsion between the bulky norbornane skeleton and the benzyl ether. $MgBr_2$ cannot then coordinate with two oxygen atoms in **13** (Scheme 6).

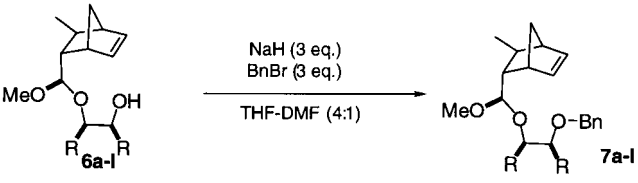
(2) Debromoetherification of 8-membered acetal in Scheme 1 (step *b*). The above results suggested that the coordination of $MgBr_2$ to two oxygen atoms, one of which is the debromoetherified oxygen, is essential for the success of debromoetherification. We then studied reductive debromoetherification of 8-membered acetals **5a–l** using 15 equiv. of Zn in the presence of additive, 6 equiv. of $MgBr_2{\cdot}Et_2O$ for **5a–h** or 6 equiv. of $ZnCl_2$ for **5i–l**, in DMA (Scheme 7). The effects of the additives on the saturated diols ($MgBr_2$) and the unsaturated ones ($ZnCl_2$) are different to each other. The reason for this result is not clear at this time. Anyway, debromoetherification of every 8-membered acetals proceeded smoothly to give the corresponding acetal alcohols **6a–l** in high yields. It is noteworthy that the debromoetherification reaction works well even towards acetal **5k** which has two acid labile allylic ether moieties. Yields are shown in Table 2.



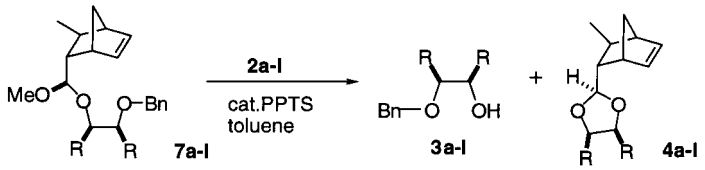
Scheme 7.

Protection of alcohol in Scheme 1 (step *c*)

Protection of the hydroxy group of **6a–l** as a benzyl ether by



Scheme 8.



Scheme 9.

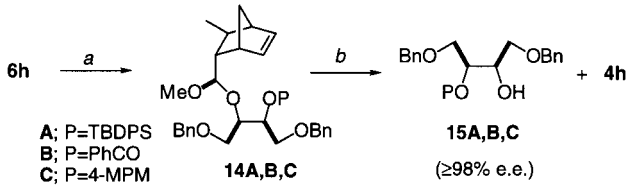
usual way proceeded well to give benzyl ether **7a–l** (Scheme 8). Yields are shown in Table 2.

Transacetalization with *meso*-1,2-diols in Scheme 1 (step *d*)

Transacetalization with one equiv. of *meso*-diols **2a–l** in the presence of a catalytic amount of PPTS afforded the optically active **3a–l** in good yields. At the same time, the ene acetals **4a–l** (Scheme 9) were produced stereospecifically in good yields. Yields are shown in Table 2.

Use of other protecting groups except benzyl ether

The advantage of this method was also proved by the proper choice of a protective group. For example, in the case of the diol **2g** having a benzyl group, a silyl or acyl group can also be used as a protective group. Thus **6h** was converted to silyl, acyl and *para*-methoxybenzyl compounds **15A**[9],**B**,**C** in good yields without any problem (Scheme 10).



Scheme 10. *a* For **14A**: TBDPSCl, imidazole, DMF (86%); For **14B**: $(PhCO)_2O$, pyr (99%); For **14C**: *p*-$MeOC_6H_4CH_2Br$, NaH, DMF (86%). *b* **2h** (1 eq.), cat. PPTS, C_6H_6, rt {**15A** (91%), **4h** (96%); **15B** (89%), **4h** (87%); **15C** (97%), **4h** (90%)}.

Conclusion

We have developed a new asymmetrization method for saturated and unsaturated *meso*-1,2-diols. Characteristic points of the method are (i) asymmetrization with extremely highly enantiomeric excess, (ii) wide applicability not only to cyclic saturated and unsaturated *meso*-1,2-diols but also to acyclic saturated and unsaturated ones, and (iii) high efficiency through out the asymmetrization reaction cycle.

Experimental

NMR spectra were measured on 270 MHz and 500 MHz spectrometers with $CDCl_3$ as a solvent and with $SiMe_4$ as an internal standard. All solvents were dried and distilled according to standard procedure.

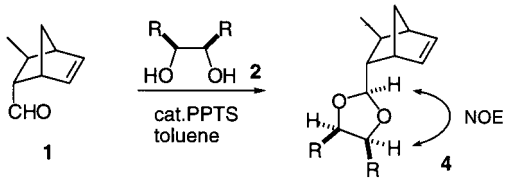
Procedure for the preparation of aldehyde 1

To a solution of $LiAlH_4$ (1.73 g, 6.6 mmol) in THF (10.0 mL) was added (4*S*)-3-((3′*R*,4′*R*,5′*S*,6′*S*)-5′-methylbicyclo[2.2.1]heptene-4′-carbonyl)-4-(1-methylethyl)-2-oxazolidinone (499 mg, 13.1 mmol) in THF (3.0 mL) at 0°C under a nitrogen atmosphere. After stirring at 0°C for 1 h, AcOEt, MeOH, and aqueous NH_4Cl were successively added to the reaction mixture. The resulting solution was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane-AcOEt (5/1) as an eluent to give (1*R*,2*R*,3*S*,4*S*)-3-methyl-5-norbornene-2-methanol (875 mg, 97%) in a pure state, whose structure was determined by the ^1H NMR spectrum: ^1H NMR δ 6.22 (dd, 1H, *J*=3.3, 5.6 Hz), 5.98 (dd, 1H, *J*=2.8, 5.6 Hz), 3.45–3.27 (m, 2H), 2.86 (brs, 1H), 2.38 (brs, 1H), 2.46–2.25 (m, 1H), 1.52–1.42 (m, 2H), 1.12 (d, 3H, *J*=6.6 Hz). Thus obtained (1*R*,2*R*,3*S*,4*S*)-3-methyl-5-norbornene-2-methanol (101 mg, 0.7 mmol) in CH_2Cl_2 (3.6 mL) was added to a solution of oxalyl chloride (0.14 mL, 1.6 mmol) and DMSO (0.23 mL, 3.2 mmol) in CH_2Cl_2 (3.6 mL) at −78°C under a nitrogen atmosphere. After stirring at −78°C for 1 h, Et_3N (0.50 mL, 3.5 mmol) was added to the solution, and the temperature was allowed to rise to rt, then aqueous NH_4Cl was added to the reaction mixture. The resulting solution was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with pentane-Et_2O (25/1) as an eluent to give (1*R*,2*R*,3*S*,4*S*)-3-methyl-5-norbornene-2-carboxaldehyde **1** (73 mg, 73%). Compound **1** is fairly volatile and its structure was determined by ^1H NMR and IR spectra:[10] ^1H NMR δ 9.37 (d, 1H, *J*=3.3 Hz), 6.29 (dd, 1H, *J*=3.1, 5.6 Hz), 6.05 (dd, 1H, *J*=2.6, 5.6 Hz), 3.13 (brs, 1H), 2.56 (brs, 1H), 2.35–2.30 (m, 1H), 1.85–1.79 (m, 1H), 1.59–1.45 (m, 2H), 1.17 (d, 3H, *J*=6.9 Hz); IR (KBr) 1721, 720 cm^{-1}.

General procedure for the acetalization of 1 with *meso*-diol 2 in Table 1

To a solution of *meso*-diol **2** (1 mmol) and norbornene aldehyde **1** (1 mmol) in toluene (10 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate at rt under a nitrogen atmosphere. After being stirred for over 12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane-AcOEt as an eluent to give **4** in yields shown in Table 1.

Table 1. Acetalization of **1** with *meso*-diol (**2**)



Entry		*meso*-Diol **2**	Product	Yield of **4** (%)
1		**2a**: R=–$(CH_2)_4$–	**4a**	93
2		**2b**: R=–$(CH_2)_3$–	**4b**	99
3		**2c**: R=–$(CH_2)_6$–	**4c**	96
4		**2d**: R=–CH_2OCH_2–	**4d**	99
5		**2e**: R=CH_3	**4e**	99
6		**2f**: R=*n*-Pr	**4f**	99
7		**2g**: R=CH_2OBn	**4g**	91
8		**2h**: R=*i*-Pr	**4h**	83
9		**2i**: R=–CH_2CH=$CHCH_2$–	**4i**	86
10		**2j**: R=–$(CH_2)_2CH$=$CH(CH_2)_2$–	**4j**	86
11		**2k**: R=–CH=CH_2	**4k**	84
12		**2l**: R=–$(CH_2)_2CH$=CH_2	**4l**	81

General procedure for the intramolecular haloetherification reaction of 4 (from 4 to 5)

To a solution of **4** (1 mmol), γ-collidine (2 equiv.) and MeOH (5 equiv.) in CH_3CN (10 mL) was added *N*-bromosuccinimide (2 equiv.) at −40°C under a nitrogen atmosphere. The mixture was allowed to warm to rt under stirring. Completion of the reaction was examined by TLC. The solution was quenched with saturated aqueous $NaHCO_3$, then extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane-AcOEt as an eluent to give **5** in yields shown in Table 2.

5a. ^{1}H NMR δ 4.72 (d, 1H, *J*=7.9 Hz), 4.42–4.39 (m, 1H), 3.81–3.70 (m, 3H), 3.34 (s, 3H), 2.69 (brs, 1H), 2.11 (brs, 1H), 2.11–1.42 (m, 12H), 1.03 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 111.93, 85.90, 59.71, 53.69, 52.36, 48.97, 42.07, 32.74, 30.42, 25.05, 24.85, 21.19, 20.63; Anal. Calcd for $C_{16}H_{25}BrO_3$: C, 55.66; H, 7.03; Br, 23.14. Found: C, 55.25; H, 7.01; Br, 23.40.

5b. ^{1}H NMR δ 4.86 (d, 1H, *J*=7.9 Hz), 4.35 (m, 1H), 4.02 (m, 2H), 3.75 (m, 1H), 3.35 (s, 3H), 2.61 (brs, 1H), 2.12 (brs, 1H), 1.95–1.45 (m, 10H), 1.03 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 108.48, 86.94, 59.50, 53.87, 52.92, 48.48, 41.08, 32.80, 31.59, 28.48, 23.74, 22.66, 19.97, 14.18, 14.09; Anal. Calcd for $C_{15}H_{23}BrO_3$: C, 54.38; H, 7.00; Br, 24.12. Found: C, 54.18; H, 6.72; Br, 24.01.

5c. ^{1}H NMR δ 4.67 (d, 1H, *J*=7.9 Hz), 4.44 (brs, 1H), 4.19–4.10 (m, 1H), 3.74–3.67 (m, 1H), 3.33 (s, 3H), 2.39 (brs, 1H), 2.13 (brs, 1H), 2.03–1.22 (m, 16H), 1.00 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 111.57, 85.73, 84.33, 80.00, 58.96, 54.90, 54.07, 51.84, 47.32, 42.19, 32.13, 27.91, 27.28, 26.65, 24.51, 23.22, 21.93, 21.12; HRMS *m/z* Calcd for $C_{18}H_{29}BrO_3$: 372.1301 (M^+), 374.1294 (M^++2). Found: 372.1300 (M^+), 374.1280 (M^++2).

5d. ^{1}H NMR δ 4.91 (d, 1H, *J*=7.9 Hz), 4.36–3.70 (m, 8H), 3.35 (s, 3H), 2.68–2.65 (m, 1H), 2.11 (brs, 1H), 1.92–1.46 (m, 4H), 1.03 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 107.84, 87.73, 79.08, 78.80, 71.84, 63.45, 59.00, 55.15, 53.71, 52.78, 48.20, 40.70, 32.81, 21.15; Anal. Calcd for $C_{14}H_{21}BrO_4$: C, 50.46; H, 6.35; Br, 23.98. Found: C, 50.39; H, 6.23; Br, 23.73.

5e. ^{1}H NMR δ 4.72 (d, 1H, *J*=7.6 Hz), 4.43–4.37 (m, 1H), 4.00–3.80 (m, 2H), 3.71 (t, 1H, *J*=2.8 Hz), 3.34 (s, 3H), 2.60–2.50 (m, 1H), 2.12 (brs, 1H), 1.90–1.40 (m, 4H), 1.25 (d, 3H, *J*=6.9 Hz), 1.12 (d, 3H, *J*=6.6 Hz,), 1.02 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 111.61, 85.77, 79.84, 76.44, 59.28, 54.79, 53.75, 52.27, 48.57, 42.03, 32.56, 21.15, 15.96, 10.16; HRMS *m/z* Calcd for $C_{14}H_{23}BrO_3$: 319.0868 (M^+), 321.0867 (M^++2). Found: 319.0864 (M^+), 321.0844 (M^++2)

5f. ^{1}H NMR δ 4.74 (d, 1H, *J*=8.3 Hz), 4.37 (brs, 1H), 3.71–3.69 (m, 3H), 3.39 (s, 3H), 2.55 (brs, 1H), 2.13 (brs, 1H), 1.91–1.29 (m, 12H), 1.02 (d, 3H, *J*=6.9 Hz), 0.98 (d, 3H, *J*=6.3 Hz), 0.93 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 111.91, 85.82, 84.22, 80.41, 59.12, 55.53, 53.77, 52.15, 48.16, 42.12, 34.13, 32.47, 26.65, 21.42, 21.13, 20.04, 14.18, 14.13; Anal. Calcd for $C_{18}H_{31}BrO_3$: C, 57.60; H, 8.32; Br, 21.29. Found: C, 57.41; H, 8.08; Br, 21.28.

5g. ^{1}H NMR δ 7.36–7.28 (m, 10H), 4.71 (d, 1H, *J*=7.9 Hz), 4.63–4.37 (m, 6H), 4.20–4.03 (m, 2H), 3.89–3.42 (m, 4H), 3.40 (s, 3H), 2.35 (2.36–2.33, 1H), 2.09 (brs, 1H), 1.78–1.26 (m, 4H), 1.00 (d, 3H, *J*=6.9 Hz); ^{13}C NMR δ 137.90, 137.38, 128.48, 128.39, 128.18, 127.92, 127.67, 127.57, 111.97, 85.86, 82.14, 76.44, 73.48, 73.12, 69.38, 65.59, 59.09, 55.22, 53.68, 52.31, 48.27, 41.91, 32.53, 21.15;

Anal. Calcd for $C_{28}H_{35}BrO_5$: C, 63.28; H, 6.64; Br, 15.03. Found: C, 63.07; H, 6.51; Br, 14.88.

5h. ^{1}H NMR δ 4.67 (d, 1H, J=7.9 Hz), 4.39 (brs, 1H), 3.85–3.60 (m, 2H), 3.36 (s, 3H), 3.19 (brs, 1H), 2.60 (brs, 1H), 2.18 (brs, 1H), 2.01–1.45 (m, 8H), 1.17–0.81 (m, 15H); ^{13}C NMR δ 107.15, 82.98, 80.41, 77.20, 55.20, 54.79, 53.71, 52.53, 47.26, 42.93, 32.02, 28.18, 27.66, 22.18, 21.33, 21.03, 19.36, 14.81; FAB-HRMS *m/z* Calcd for $C_{18}H_{31}BrO_3$: 374.1497 (M^+). Found 374.1486 (M^+).

5i. ^{1}H NMR δ 5.62–5.51 (m, 2H), 4.70 (d, 1H, J=7.6 Hz), 4.43 (m, 1H), 4.09 (m, 1H), 3.91 (m, 1H), 3.73 (t, 1H, J=2.8 Hz), 3.35 (s, 3H), 2.71–2.30 (m, 5H), 2.21 (brs, 1H), 1.93–1.47 (m, 4H), 1.04 (d, 3H, J=6.9 Hz); ^{13}C NMR δ 123.32, 122.91, 112.74, 86.20, 78.51, 74.59, 59.39, 54.83, 53.59, 52.02, 49.18, 42.34, 32.81, 31.04, 23.29, 21.17; Anal. Calcd for $C_{16}H_{23}BrO_3$: C, 55.99; H, 6.75; Br, 23.28. Found: C, 55.78; H, 6.59; Br, 23.16.

5j. ^{1}H NMR δ 5.49 (m, 2H), 4.69 (d, 1H, J=8.1 Hz), 4.41 (brs, 1H), 4.25 (m, 1H), 3.77 (m, 1H), 3.69 (m, 1H), 3.35 (s, 3H), 2.78–2.42 (m, 4H), 2.22–1.85 (m, 7H), 1.72 (m, 1H), 1.57–1.45 (m, 2H), 1.03 (d, 3H, J=8.9 Hz); ^{13}C NMR δ 130.82, 124.13, 112.78, 86.49, 86.38, 77.65, 59.46, 54.95, 53.75, 52.08, 48.34, 42.28, 32.46, 28.81, 27.46, 22.93, 22.63, 21.13; Anal. Calcd for $C_{18}H_{27}BrO_3$: C, 58.22; H, 7.33; Br, 21.52. Found: C, 58.02; H, 7.13; Br, 21.71.

5k. ^{1}H NMR δ 6.00–5.86 (m, 1H), 5.60–5.07 (m, 5H), 4.74 (d, 1H, J=7.9 Hz), 4.26–4.17 (m, 3H), 3.66 (t, 1H, J=2.8 Hz), 3.27 (s, 3H), 2.40 (brs, 1H), 2.06 (brs, 1H), 1.83–1.40 (m, 4H), 0.97 (d, 3H, J=7.3 Hz); ^{13}C NMR δ 133.5, 130.9, 124.9, 116.4, 111.7, 86.1, 84.2, 82.1, 58.9, 54.8, 54.0, 52.3, 48.2, 42.0, 32.6, 21.2; Anal. Calcd for $C_{16}H_{23}BrO_3$: C, 55.99; H, 6.75; Br, 23.28. Found: C, 55.90; H, 6.65; Br, 22.89.

5l. ^{1}H NMR δ 5.86– 5.75 (m, 2H), 5.13– 4.98 (m, 4H), 4.74 (d, 1H, J=8.1 Hz), 4.39 (brs, 1H), 3.79– 3.70 (m, 3H), 3.40 (s, 3H), 2.55 (brs, 1H), 2.30– 1.43 (m, 13H), 1.03 (d, 3H, J=6.8 Hz); ^{13}C NMR δ 137.7, 137.3, 115.7, 115.2, 111.9, 86.0, 83.5, 79.4, 58.9, 55.6, 53.7, 52.1, 48.1, 42.1, 32.5, 31.9, 31.1, 30.8, 23.7, 21.1; FAB-MS *m/z* 399 (M^+); FAB-HRMS Calcd for $C_{20}H_{32}O_3Br$: 399.1495 (M^+). Found: 399.1523 (M^+).

General procedure for the elimination reaction of 5 (from 5 to 6)

To a solution of **5** (1 mmol) in *N*,*N*-dimethylacetamide (10 mL) was added $MgBr_2{\cdot}Et_2O$ (6 equiv.) for **5a–h** and $ZnCl_2$ (6 equiv.) for **5i–l** under a nitrogen atmosphere. After stirring for 30 min at 60°C, Zn powder (15 equiv.) was added to the reaction mixture. The resulting mixture was stirred at 75°C for about 12 h. After completion of the reaction checked by TLC, AcOEt was added to the solution, then filtered with celite for removal of precipitate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane-AcOEt as an eluent to give **6** in yields shown in Table 2. Compounds **6** are rather labile and tend to give **4**. Then their structures were ascertained by ^{1}H NMR, ^{13}C NMR, and IR.

Table 2. Reaction cycle for asymmetrization. Yields of the products **5**, **6**, **7**, **3**, and **4** in every step of our asymmetric desymmerization, whose procedures were mentioned previously, are summarized. The optical purity of **3a–l** was determined by HPLC analysis (Chiralpak AD)

Entry	Substr	Yield (%)					ee of **3**[a] (%)
		5	**6**	**7**	**3**	**4**	
1	**4a**	99	83	95	90	99	97
2	**4b**	86	86	93	90	93	98
3	**4c**	95	89	98	95	99	≥99
4	**4d**	95	96	99	94	96	≥99
5	**4e**	89	93	96	99	95	97
6	**4f**	87	89	98	97	94	≥99
7	**4g**	90	86	91	91	96	98
8	**4h**	87	81	90	90	93	≥99
9	**4i**	97	85	99	90	83	≥99
10	**4j**	92	84	98	89	89	≥99
11	**4k**	91	85	79	97	83	≥99
12	**4l**	98	84	91	97	84	≥99

[a] Determined by HPLC analysis (Chiralpak AD).

6a. ^{1}H NMR δ 6.24 (dd, 1H, J=3.1, 5.8 Hz), 6.00 (dd, 1H, J=2.8, 5.8 Hz), 3.99 (d, 1H, J=8.4 Hz), 3.84–3.58 (m, 2H), 3.32 (s, 3H), 2.80 (brs, 1H), 2.39 (brs, 1H), 2.29 (brs, 1H), 1.94–1.19 (m, 12H), 1.14 (d, 3H, J=6.2 Hz); ^{13}C NMR δ 138.74, 132.83, 106.58, 76.12, 68.43, 52.17, 50.82, 48.90, 46.11, 44.85, 36.50, 30.44, 27.87, 23.24, 21.13, 20.29.

6b. ^{1}H NMR δ 6.24 (dd, 1H, J=3.1, 5.8 Hz), 6.00 (dd, 1H, J=2.8, 5.8 Hz), 4.03–3.91 (m, 3H), 3.34 (s, 3H), 2.81 (brs, 1H), 2.51 (brs, 1H), 2.50 (brs, 1H), 1.91–1.18 (m, 10H), 1.13 (d, 3H, J=5.9 Hz).

6c. ^{1}H NMR δ 6.24 (dd, 1H, J=3.1, 5.6 Hz), 6.00 (dd, 1H, J=2.6, 5.6 Hz), 3.97 (d, 1H, J=9.2 Hz), 3.84–3.76 (m, 2H), 3.33 (s, 3H), 2.70 (brs, 1H), 2.65 (d, 1H, J=2.6 Hz), 2.39 (brs, 1H), 1.91–1.20 (m, 16H), 1.14 (d, 3H, J =6.3 Hz); ^{13}C NMR δ 138.81, 132.83, 106.68, 77.97, 71.18, 52.18, 50.82, 48.91, 44.83, 36.60, 29.18, 28.55, 26.99, 26.13, 25.30, 21.99, 21.17.

6d. ^{1}H NMR δ 6.25 (dd, 1H, J=3.1, 6.1 Hz), 5.99 (dd, 1H, J=2.7, 6.1 Hz), 4.27–3.75 (m, 6H), 3.97 (d, 1H, J=9.16 Hz), 3.34 (s, 3H), 2.79 (d, 1H, J=3.05 Hz), 2.76 (brs, 1H), 2.41 (brs, 1H), 1.87–1.83 (m, 1H), 1.53–1.41 (m, 2H), 1.26–1.19 (m, 1H), 1.14 (d, 3H, J=6.7 Hz); ^{13}C NMR δ 138.83, 132.78, 108.57, 74.25, 73.55, 70.53, 70.17, 53.86, 51.14, 48.68, 46.02, 44.62, 36.62, 21.15.

6e. ^{1}H NMR δ 6.24 (dd, 1H, J=3.1, 5.6 Hz), 5.99 (dd, 1H, J=2.6, 5.6 Hz), 3.98 (d, 1H, J=9.2 Hz), 3.87–3.82 (m, 1H), 3.70–3.66 (m, 1H), 3.33 (s, 3H), 2.80 (brs, 1H), 2.39 (brs, 1H), 2.29 (d, 1H, J=2.3 Hz), 1.94–1.20 (m, 4H), 1.19–1.11 (m, 9H); ^{13}C NMR δ 138.80, 132.83, 106.94, 75.87, 69.04, 52.33, 50.84, 48.91, 46.09, 44.82, 36.53, 21.15, 17.45, 14.68.

6f. ^{1}H NMR δ 6.25 (dd, 1H, J=3.3, 5.6 Hz), 6.00 (dd, 1H, J=2.6, 5.6 Hz), 3.99 (d, 1H, J=9.2 Hz), 3.70–3.66 (m, 1H), 3.62–3.56 (m, 1H), 3.36 (s, 3H), 2.80 (brs, 1H), 2.39 (brs,

1H), 2.31 (d, 1H, *J*=4.3 Hz), 1.95–1.20 (m, 12H), 1.14 (d, 3H, *J*=6.3 Hz), 0.95 (t, 3H, *J*=6.9 Hz), 0.94 (t, 3H, *J*=7.1 Hz).

6g. ^{1}H NMR 7.27–7.18 (m, 10H), 6.12 (dd, 1H, *J*=3.1, 5.8 Hz), 5.88 (dd, 1H, *J*=2.8, 5.8 Hz), 4.54–4.40 (m, 4H), 4.03–3.98 (m, 1H), 3.92 (d, 1H, *J*=9.2 Hz), 3.73–3.54 (m, 5H), 3.22 (s, 3H), 2.75 (d, 1H, *J*=4.6), 2.70 (brs, 1H), 2.29 (brs, 1H), 1.80–1.77 (m, 1H), 1.41–1.11 (m, 3H), 1.04 (d, 3H, *J*=6.3 Hz); ^{13}C NMR δ 138.42, 137.99, 137.92, 133.33, 128.39, 128.34, 127.80, 127.73, 127.66, 108.19, 76.05, 73.46, 73.42, 71.00, 70.96, 70.12, 52.67, 51.04, 48.91, 45.88, 44.76, 36.28, 21.13.

6h. ^{1}H NMR δ 6.26 (dd, 1H, *J*=3.0, 5.6 Hz), 6.00 (dd, 1H, *J*=2.6, 5.6 Hz), 3.99 (d, 1H, *J*=8.6 Hz), 3.48 (dd, 1H, *J*=2.6, 3.6 Hz), 3.38 (s, 3H), 3.35 (dd, 1H, *J*=1.7, 3.6 Hz), 2.81 (brs, 1H), 2.39 (brs, 1H), 2.23 (d, 1H, *J*=2.0 Hz), 2.02–1.20 (m, 8H), 1.17–0.78 (m, 15H); ^{13}C NMR δ 138.78, 132.92, 105.32, 79.21, 76.82, 53.73, 51.45, 49.06, 46.22, 45.00, 36.41, 30.10, 27.73, 21.71, 21.22, 19.95, 18.83, 17.74.

6i. ^{1}H NMR δ 6.25 (dd, 1H, *J*=5.8, 3.1 Hz), 6.01 (dd, 1H, *J*=5.6, 2.6 Hz), 5.60 (m, 2H), 3.94 (m, 3H), 3.33 (s, 3H), 2.81 (brs, 1H), 2.36 (m, 6H), 1.92 (m, 1H), 1.44 (m, 2H), 1.22 (m, 1H), 1.13 (d, 3H, *J*=5.9 Hz); ^{13}C NMR δ 138.78, 132.85, 124.04, 123.70, 106.78, 73.19, 67.17, 52.63, 50.66, 48.90, 46.04, 44.78, 36.66, 31.66, 28.75, 21.13.

6j. ^{1}H NMR δ 6.24 (dd, 1H, *J*=5.8, 3.1 Hz), 6.00 (dd, 1H, *J*=5.6, 2.6 Hz), 5.63 (m, 2H), 3.96–3.85 (m, 3H), 3.33 (s, 3H), 2.82 (brs, 1H), 2.58 (m, 2H), 2.38 (brs, 1H), 2.20 (d, 1H, *J*=4.6 Hz), 2.10–1.37 (m, 9H), 1.20 (m, 1H), 1.13 (d, 3H, *J*=6.3 Hz); ^{13}C NMR δ 138.69, 132.99, 130.01, 128.99, 107.67, 79.48, 73.78, 52.54, 50.95, 48.95, 46.04, 44.85, 36.48, 32.17, 30.19, 23.24, 22.61, 21.15.

6k. ^{1}H NMR δ 6.24 (dd, 1H, *J*=3.1, 5.6 Hz), 5.99 (dd, 1H, *J*=3.0, 5.6 Hz), 5.93–5.82 (m, 2H), 5.39–5.21 (m, 4H), 4.23–4.10 (m, 2H), 3.97 (d, 1H, *J*=9.2 Hz), 3.30 (s, 3H), 2.82 (brs, 1H), 2.57 (d, 1H, *J*=5.0 Hz), 2.39 (brs, 1H), 1.95–1.86 (m, 1H), 1.53–1.17 (m, 3H), 1.13 (d, 1H, *J*=5.6 Hz); ^{13}C NMR δ 138.71, 136.17, 135.08, 132.94, 118.08, 116.73, 107.64, 80.29, 74.41, 54.00, 51.25, 48.74, 45.99, 44.55, 36.68, 21.19.

6l. ^{1}H NMR δ 6.26 (dd, 1H, *J*=3.1, 5.8 Hz), 5.99 (dd, 1H, *J*=2.8, 5.8 Hz), 5.89– 5.77 (m, 2H), 5.10–4.96 (m, 4H), 3.98 (d, 1H, *J*=9.0 Hz), 3.71–3.59 (m, 2H), 3.36 (s, 3H), 2.80 (brs, 1H), 2.38–2.09 (m, 6H), 1.93 (m, 1H), 1.73–1.22 (m, 7H), 1.15 (d, 3H, *J*=6.3 Hz); ^{13}C NMR δ 138.68, 138.22, 138.08, 132.48, 114.79, 114.53, 106.28, 78.07, 70.99, 53.46, 50.88, 48.87, 46.05, 44.75, 36.50, 30.72, 30.36, 30.10, 28.58, 21.16.

General procedure for the benzylation reaction of 6 (from 6 to 7)

A solution of **6** (1 mmol) and NaH (60% oil suspension, 3 equiv.) in THF-DMF (v/v=4/1, 10 mL) was stirred for 30 min at rt under a nitrogen atmosphere. BnBr (3 equiv.) was added to the solution. The reaction mixture was stirred for 24 h at rt, then quenched with MeOH and H_2O. The resulting solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane-AcOEt as an eluent to give **7** in yields shown in Table 2.

7a. ^{1}H NMR δ 7.29–7.18 (m, 5H), 6.02 (brs, 1H), 5.92 (brs, 1H), 4.52 (s, 2H), 4.05 (d, 1H, *J*=9.1 Hz), 3.73 (brs, 1H), 3.42 (brs, 1H), 3.23 (s, 3H), 2.81 (brs, 1H), 2.27 (brs, 1H), 1.86–1.08 (m, 12H,), 1.06 (d, 3H, *J*=6.7 Hz); ^{13}C NMR δ 137.63, 134.12, 128.37, 128.16, 127.75, 127.60, 127.42, 127.19, 106.99, 78.19, 73.86, 72.09, 70.33, 51.30, 50.68, 49.11, 45.73, 45.02, 36.26, 29.71, 27.41, 22.21, 21.15; FAB-HRMS *m/z* Calcd for $C_{23}H_{32}O_3$: 356.2351 (M^+). Found: 356.2315 (M^+).

7b. ^{1}H NMR δ 7.38–7.31 (m, 5H), 6.12 (dd, 1H, *J*=2.9, 5.1 Hz), 5.98 (dd, 1H, *J*=2.6, 5.1 Hz), 4.61 (s, 2H), 4.05 (d, 1H, *J*=9.4 Hz), 4.00–3.99 (m, 1H), 3.78–3.77 (m, 1H), 3.29 (s, 3H), 2.86 (brs, 1H), 2.35 (brs, 1H), 1.86–1.19 (m, 10H)1.12 (d, 3H, *J*=6.6 Hz); ^{13}C NMR δ 137.81, 134.00, 128.21, 127.66, 127.33, 107.31, 80.58, 76.41, 71.14, 52.08, 50.71, 48.99, 45.77, 44.87, 36.46, 28.99, 27.32, 21.21, 18.92; HRMS *m/z* Calcd for $C_{22}H_{30}O_3$: 342.2190 (M^+), 343.2240 (M^++1). Found 342.2195 (M^+), 343.2228 (M^++1).

7c. ^{1}H NMR δ 7.37–7.26 (m, 5H), 6.11 (dd, 1H, *J*=3.0, 5.6 Hz), 6.00 (dd, 1H, *J*=2.6, 5.6 Hz), 4.59–4.56 (m, 2H), 4.10 (d, 1H, *J*=9.2 Hz), 3.95–3.91 (m, 1H), 3.64–3.61 (m, 1H), 3.31 (s, 3H), 2.86 (brs, 1H), 2.34 (brs, 1H), 2.11–1.18 (m, 16H), 1.13 (d, 3H, *J*=6.6 Hz); ^{13}C NMR δ 137.77, 134.05, 128.40, 128.18, 127.78, 127.62, 127.49, 127.19, 107.46, 80.67, 77.00, 71.02, 51.38, 50.84, 49.13, 45.77, 45.00, 36.23, 30.75, 29.13, 27.24, 26.72, 23.33, 22.68, 21.15; FAB-HRMS *m/z* Calcd for $C_{25}H_{36}O_3$: 384.2720 (M^+). Found 384.2728 (M^+).

7d. ^{1}H NMR δ 7.39–7.27 (m, 5H), 6.16 (dd, 1H, *J*=3.3, 5.6 Hz), 5.96 (dd, 1H, *J*=2.6, 5.6 Hz), 4.67 (d, 2H, *J*=6.6 Hz), 4.25–3.83 (m, 7H), 3.29 (s, 3H), 2.82 (brs, 1H), 2.37 (brs, 1H), 1.89–1.18 (m, 4H), 1.13 (d, 3H, *J*=5.9 Hz); ^{13}C NMR δ 138.11, 137.93, 133.60, 128.37, 127.84, 127.75, 107.75, 77.77, 73.60, 72.04, 70.41, 70.10, 52.65, 50.62, 48.90, 45.75, 44.71, 36.46, 21.15; HRMS *m/z* Calcd for $C_{21}H_{28}O_4$: 344.1991 (M^+), 345.2038 (M^++1). Found: 344.1987 (M^+), 345.2021 (M^++1).

7e. ^{1}H NMR δ 7.34–7.31 (m, 5H), 6.20–6.10 (m, 1H), 6.03–5.95 (m, 1H), 4.60 (s, 2H), 4.05 (d, 1H, *J*=9.2 Hz), 3.77–3.74 (m, 1H), 3.50–3.47 (m, 1H), 3.32 (s, 3H), 2.86 (brs, 1H), 2.35 (brs, 1H), 1.23 (d, 3H, *J*=6.1 Hz), 1.22 (d, 3H, *J*=6.1 Hz), 1.13 (d, 3H, *J*=6.7 Hz); ^{13}C NMR δ 138.06, 133.76, 128.27, 127.53, 127.35, 107.85, 78.42, 75.53, 71.02, 51.68, 51.09, 49.08, 45.86, 44.96, 36.23, 21.17, 17.33, 15.29; FAB-HRMS *m/z* Calcd for $C_{21}H_{30}O_3$: 330.2195 (M^+). Found: 330.2182 (M^+).

7f. ^{1}H NMR δ 7.38–7.29 (m, 5H), 6.12 (dd, 1H, *J*=3.0, 5.8 Hz), 6.06 (dd, 1H, *J*=2.6, 5.8 Hz), 4.57 (s, 2H), 4.11 (d, 1H, *J*=9.2 Hz), 3.81–3.73 (m, 1H), 3.43–3.35 (m, 1H), 3.35 (s, 3H), 2.87 (brs, 1H), 2.34 (brs, 1H), 1.95–

1.10 (m, 12H), 1.14 (d, 3H, *J*=6.3 Hz), 1.00–0.80 (m, 6H); ^{13}C NMR δ137.90, 128.21, 127.78, 127.67, 127.64, 124.26, 109.87, 85.72, 78.01, 77.20, 56.57, 52.90, 52.89, 51.63, 49.13, 45.05, 32.81, 29.69, 24.46, 21.08, 19.61, 14.31; FAB-HRMS *m/z* Calcd for $C_{25}H_{38}O_3$: 386.2820 (M^+). Found 386.2830 (M^+).

7g. ^{1}H NMR δ 7.34–7.23 (m, 15H), 6.13 (dd, 1H, *J*=3.0, 5.6 Hz), 5.95 (dd, 1H, *J*=2.6, 5.6 Hz), 4.73–4.50 (m, 6H), 4.05–3.65 (m, 6H), 3.29 (s, 3H), 2.76 (brs, 1H), 2.33 (brs, 1H), 1.88–1.83 (m, 1H), 1.47–1.10 (m, 8H); ^{13}C NMR δ 138.71, 138.38, 138.24, 138.06, 133.64, 128.27, 128.23, 128.16, 127.67, 127.55, 127.44, 127.33, 108.30, 78.78, 76.26, 73.24, 73.21, 72.69, 70.12, 69.87, 52.02, 51.09, 48.99, 45.81, 44.82, 36.12, 21.12; Anal. Calcd for $C_{35}H_{42}O_5$: C, 77.46; H, 7.80. Found: C, 77.64; H, 7.78.

7h. ^{1}H NMR δ 7.40–7.23 (m, 5H), 6.20 (dd, 1H, *J*=3.1, 5.8 Hz), 6.03 (dd, 1H, *J*=2.8, 5.8 Hz), 4.84 (d, 1H, *J*=11.2 Hz), 4.50 (d, 1H, *J*=11.2 Hz), 3.99 (d, 1H, *J*=8.6 Hz), 3.50–3.46 (m, 1H), 3.39 (s, 3H), 3.22–3.17 (m, 1H), 2.88 (brs, 1H), 2.36 (brs, 1H), 2.02–1.20 (m, 8H), 1.17–0.90 (m, 15H).; ^{13}C NMR δ 138.40, 133.46, 128.21, 127.57, 127.28, 107.62, 86.90, 80.74, 74.04, 55.43, 52.80, 49.06, 45.95, 44.89, 36.07, 30.37, 29.42, 21.35, 20.88, 20.76, 19.37, 18.97; Anal. Calcd for $C_{15}H_{24}O_2$: C, 77.68; H, 9.91. Found: C, 77.91; H, 9.83.

7i. ^{1}H NMR δ 7.37–7.23 (m, 5H), 6.12 (dd, 1H, *J*=5.6, 3.0 Hz), 6.00 (dd, 1H, *J*=5.5, 2.8 Hz), 5.60 (s, 2H), 4.68 (d, 1H, *J*=12.1 Hz), 4.61 (d, 1H, *J*=12.1 Hz), 4.16 (d, 1H, *J*=9.3 Hz), 4.03 (m, 1H), 3.70 (m, 1H), 3.31 (s, 3H), 2.86 (brs, 1H), 2.36 (m, 5H), 1.91 (m, 1H), 1.49–1.21 (m, 3H), 1.12 (d, 3H, *J*=6.4 Hz); ^{13}C NMR δ 137.86, 134.02, 128.23, 127.48, 127.33, 124.38, 124.28, 107.37, 76.07, 71.68, 70.68, 51.29, 50.57, 49.09, 45.77, 45.03, 36.30, 31.25, 28.84, 21.13; FAB-HRMS *m/z* Calcd for $C_{23}H_{30}O_3Na$: 377.2093 (M^++Na). Found: 377.2122.

7j. ^{1}H NMR δ 7.35–7.26 (m, 5H), 6.18 (dd, 1H, *J*=5.6, 3.2 Hz), 5.97 (brs, 1H), 5.66 (m, 2H), 4.59 (brs, 2H), 3.96 (brs, 2H), 3.72 (brs, 1H), 3.30 (s, 3H), 2.83 (brs, 1H), 2.71 (brs, 2H), 2.36 (brs, 1H), 2.11–1.21 (m, 10H), 1.13 (d, 3H, *J*=6.4 Hz); ^{13}C NMR δ 139.16, 138.13, 133.38, 130.20, 128.27, 128.10, 127.65, 127.50, 127.07, 126.98, 82.24, 79.17, 72.09, 71.50, 51.82, 51.10, 49.16, 45.95, 44.97, 36.31, 22.09, 21.47, 21.24; FAB-HRMS *m/s* Calcd for $C_{25}H_{34}O_3Na$: 405.2406 (M^++Na). Found: 405.2412.

7k. ^{1}H NMR δ 7.35–7.25 (m, 5H, Ph), 6.14 (dd, 1H, *J*=3.1, 5.4 Hz), 5.95 (dd, 1H, *J*=2.1, 6.1 Hz), 5.90–5.84 (m, 2H), 5.37–5.19 (m, 4H), 4.64 (d, 1H, *J*=11.9 Hz), 4.44 (d, 1H, *J*=12.2 Hz), 4.13–4.09 (m, 1H), 4.04 (d, 1H, *J*=9.2 Hz), 3.84–3.79 (m, 1H), 3.25 (s, 3H), 2.85 (brs, 1H), 2.34 (brs, 1H), 1.88–1.84 (m, 1H), 1.49–1.17 (m, 3H), 1.11 (d, 3H, *J*=5.9 Hz); ^{13}C NMR δ 138.04, 136.46, 135.08, 133.78, 128.21, 127.67, 127.37, 119.12, 117.17, 108.05, 83.27, 80.40, 70.33, 52.85, 51.34, 48.93, 45.81, 44.76, 36.35, 21.21.

7l. ^{1}H NMR δ 7.37–7.25 (m, 5H), 6.11–6.05 (m, 2H), 5.88–5.78 (m, 2H), 5.07– 4.95 (m, 4H), 4.70 (d, 1H, *J*=11.4 Hz), 4.44 (d, 1H, *J*=11.5 Hz), 4.09 (d, 1H, *J*=9.2 Hz), 3.79 (m, 1H), 3.43–3.35 (m, 4H), 2.86 (brs, 1H), 2.34–2.10 (m, 5H), 1.86–1.12 (m, 11H); ^{13}C NMR δ 138.7, 138.6, 138.3, 137.9, 134.0, 129.0, 128.8, 127.8, 127.46, 114.86, 114.69, 107.89, 80.91, 76.07, 71.90, 53.26, 51.73, 49.11, 45.78, 45.06, 36.1, 33.6, 30.9, 30.4, 30.4, 29.2, 21.3; FAB-MS *m/z* 433 (M^++Na); FAB-HRMS Calcd for $C_{27}H_{38}O_3Na$: 433.2697 (M^++Na). Found: 433.2708 (M^++Na).

General procedure for the transacetalization reaction of 7 (from 7 to 3 and 4)

To a solution of **7** (1 mmol) and *meso*-diol **2** (1 mmol) in toluene (10 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate at rt under a nitrogen atmosphere. After stirring for over 12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane-AcOEt as an eluent to give **3** and **4** in yields shown in Table 2. Ee values of **3** were determined by HPLC analysis (Chiralpak AD, hexane-*i*-PrOH).

3a. $[\alpha]_D^{25}$=+16.6° (*c* 1.03, $CHCl_3$); ^{1}H NMR δ 7.36–7.23 (m, 5H), 4.63 (d, 1H, *J*=11.5 Hz), 4.52 (d, 1H, *J*=11.5 Hz), 3.86 (brs, 1H), 3.52–3.51 (m, 1H), 2.26 (d, 1H, *J*=5.1 Hz), 1.83–1.26 (m, 6H); ^{13}C NMR δ 138.62, 128.43, 127.62, 127.55, 78.17, 70.15, 68.15, 30.42, 26.58, 22.10, 21.22; HRMS *m/z* Calcd for $C_{13}H_{18}O_2$: 206.1299 (M^+). Found: 206.1307 (M^+).

3b. $[\alpha]_D^{30}$=+19.6° (*c* 0.86, $CHCl_3$); ^{1}H NMR δ 7.36–7.29 (m, 5H), 4.60 (d, 1H, *J*=11.7 Hz), 4.55 (d, 1H, *J*=11.7 Hz), 4.10 (m, 1H), 3.82 (dt, 1H, *J*=4.3, 6.6 Hz), 2.49 (d, 1H, *J*=4.3 Hz), 1.88–1.47 (m, 6H); ^{13}C NMR δ 128.46, 127.78, 127.67, 81.38, 72.24, 71.56, 31.14, 27.89, 19.66; HRMS *m/z* Calcd for $C_{12}H_{16}O_2$: 192.1141 (M^+), 193.1186 (M^++1). Found: 192.1150 (M^+), 193.1184 (M^++1).

3c. $[\alpha]_D^{30}$=+49.9° (*c* 0.92, $CHCl_3$); ^{1}H NMR δ 7.39–7.27 (m, 5sH), 4.63 (d, 1H, *J*=11.9 Hz), 4.51 (d, 1H, *J*=11.5 Hz), 3.97–3.92 (m, 1H), 3.64–3.59 (m, 1H), 2.57 (d, 1H, *J*=3.6 Hz), 2.03–1.40 (m, 12H); ^{13}C NMR δ 128.43, 127.66, 127.60, 80.88, 71.52, 70.82, 29.47, 26.81, 26.63, 25.52, 22.52; Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88, H, 9.46. Found: C, 77.08; H, 9.47.

3d. $[\alpha]_D^{20}$=+16.7° (*c* 0.18, $CHCl_3$); ^{1}H NMR δ 7.38–7.25 (m, 5H), 4.60 (s, 2H), 4.26–4.22 (m, 1H), 4.06–4.03 (m, 1H), 3.89–3.86 (m, 2H), 3.79–3.72 (m, 2H), 2.85 (d, 1H, *J*=5.8 Hz); ^{13}C NMR δ 137.14, 128.61, 128.19, 127.87, 78.26, 73.44, 72.56, 70.33, 69.99; HRMS *m/z* Calcd for $C_{11}H_{14}O_3$: 194.0931 (M^+), 195.0986 (M^++1). Found: 194.0943 (M^+), 195.0976 (M^++1).

3e. $[\alpha]_D^{30}$=+23.1° (*c* 0.13, $CHCl_3$); ^{1}H NMR δ 7.36–7.25 (m, 5H), 4.63(d, 1H, *J*=11.9 Hz), 4.51(d, 1H, *J*=11.9 Hz), 3.95–3.85 (m, 1H), 3.58–3.42 (m, 1H), 2.07 (brs, 1H), 1.18–1.12 (m, 6H); ^{13}C NMR δ 128.43, 127.61, 127.58, 78.20, 70.71, 69.20, 17.65, 13.43; HRMS *m/z* Calcd for $C_{11}H_{16}O_2$: 180.1130 (M^+), 181.1158 (M^++1). Found: 180.1150 (M^+), 181.1184 (M^++1).

3f. $[\alpha]_D^{31}=-8.5°$ (*c* 0.38, $CHCl_3$); ^1H NMR δ 7.35–7.29 (m, 5H), 4.60 (d, 2H, *J*=11.6 Hz), 4.55 (d, 2H, *J*=11.6 Hz), 3.95–3.80 (m, 1H), 3.42–3.26 (m, 1H), 1.98 (s, 1H), 1.62–1.27 (m, 8H), 0.96–0.88 (m, 6H); ^{13}C NMR δ 128.43, 127.82, 127.71, 82.14, 71.92, 71.47, 34.13, 30.84, 19.41, 19.09, 14.23, 14.14; Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.41; H, 10.14.

3g. $[\alpha]_D^{31}=+17.0°$ (*c* 0.01, $CHCl_3$); ^1H NMR δ 7.35–7.25 (m, 15H), 4.72–4.52 (m, 6H), 4.00–3.86 (m, 1H), 3.78–3.75 (m, 1H), 3.71–3.59 (m, 4H), 2.59 (d, 1H, *J*=4.9 Hz), 3.28 (dd, 1H, *J*=3.3, 5.6 Hz), 2.05–1.87 (m, 3H), 1.04–0.90 (m, 12H); ^{13}C NMR δ 128.39, 128.34, 127.89, 127.82, 127.75, 127.66, 78.17, 77.22, 73.51, 73.41, 72.62, 70.98, 70.75, 70.14; Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.77; H, 7.33.

3h. $[\alpha]_D^{30}=-2.59°$ (*c* 0.54, $CHCl_3$); ^1H NMR δ 7.37–7.25 (m, 5H), 4.60 (d, 2H, *J*=4.3 Hz), 3.52 (dd, 1H, *J*=4.0, 5.6 Hz), 3.28 (dd, 1H, *J*=3.3, 5.6 Hz), 2.05–1.87 (m, 3H), 1.04–0.90 (m, 12H), ^{13}C NMR δ 128.36, 127.57, 84.44, 76.17, 73.60, 29.24, 28.92, 20.99, 19.73, 17.61, 17.25; Anal. Calcd for $C_{25}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 75.99; H, 10.05.

3i. $[\alpha]_D^{27}=+45.8°$ (*c* 0.30, $CHCl_3$); ^1H NMR δ 7.36–7.29 (m, 5H), 5.58 (m, 2H), 4.65 (d, 1H, *J*=12.1 Hz), 4.57 (d, 1H, *J*=11.9 Hz), 4.10 (brs, 1H), 3.68 (m, 1H), 2.31 (brs, 4H), 2.17 (d, 1H, *J*=4.0 Hz); ^{13}C NMR δ 138.44, 128.45, 127.69, 127.58, 123.83, 123.68, 75.89, 70.37, 66.76, 31.59, 27.21; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.31; H, 8.06.

3j. $[\alpha]_D^{20}=-5.9°$ (*c* 0.34, $CHCl_3$); ^1H NMR δ 7.35–7.25 (m, 5H), 5.63 (m, 2H), 4.61 (d, 1H, *J*=11.9 Hz), 4.52 (d, 1H, *J*=11.7 Hz), 4.06 (brs, 1H), 3.73 (dd, 1H, *J*=8.8, 4.0 Hz), 2.60 (m, 2H), 2.08–1.71 (m, 7H); ^{13}C NMR δ 130.03, 129.36, 128.36, 127.49, 127.44, 82.37, 73.69, 71.32, 32.49, 28.81, 22.82, 22.25; Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.55; H, 8.80.

3k. $[\alpha]_D^{20}=+57.6°$ (*c* 0.93, $CHCl_3$); ^1H NMR δ 7.36–7.25 (m, 5H), 5.91–5.74 (m, 2H), 5.42–5.19 (m, 4H), 4.66 (d, 1H, *J*=11.9 Hz), 4.41 (d, 1H, *J*=11.9 Hz), 4.23 (brs, 1H), 3.85 (dd, 1H, *J*=4.1, 7.8 Hz), 2.28 (d, 1H, *J*=5.3 Hz), ^{13}C NMR δ 136.24, 134.21, 128.39, 127.75, 127.67, 120.14, 116.75, 83.06, 74.50, 70.33.

3l. $[\alpha]_D^{20}=-14.2°$C (*c* 1.48, $CHCl_3$); ^1H NMR δ 7.39–7.22 (m, 5H), 5.88–5.76 (m, 2H), 5.08–4.95 (m, 4H), 4.61 (d, 1H, *J*=11.6 Hz), 4.53 (d, 1H, *J*=11.4 Hz), 3.85 (m, 1H), 3.39 (m, 1H), 2.30–2.03 (m, 5H), 1.76–1.48 (m, 4H); ^{13}C NMR δ 137.8, 138.8, 137.9, 128.8, 128.5, 128.3, 115.0, 81.0, 77.4, 71.5, 34.7, 33.5, 32.1, 29.7; MS (EI) *m*/*z* 260 (M^+); HRMS Calcd for $C_{17}H_{24}O_2$: 260.1776 (M^+). Found: 260.1776 (M^+).

Data for the compounds in Scheme 10

14A. ^1H NMR δ 7.72–7.07 (m, 20H), 6.14 (dd, 1H, *J*=3.0, 5.6 Hz), 5.93 (dd, 1H, *J*=2.6, 5.6 Hz), 4.42–3.48 (m, 11H), 3.25 (s, 3H), 2.71 (brs, 1H), 2.34 (brs, 1H), 1.84–1.19 (m, 4H, CH_2), 1.13–0.94 (m, 12H); ^{13}C NMR δ 138.47, 138.33, 137.97, 136.30, 135.98, 133.87, 133.41, 129.56, 129.38, 128.19, 128.09, 127.57, 127.51, 217.44, 127.31, 127.22, 108.21, 77.22, 76.30, 73.53, 72.99, 72.76, 71.38, 70.26, 52.22, 51.27, 49.04, 45.82, 44.82, 36.21, 27.05, 21.17, 19.39; FAB-HRMS *m*/*z* Calcd for $C_{44}H_{54}O_5Si$: 690.3734 (M^+). Found: 690.3740 (M^+).

14B. ^1H NMR δ 8.17–7.19 (m, 15H), 6.17 (dd, 1H, *J*=3.0, 5.6 Hz), 6.00 (dd, 1H, *J*=3.0, 5.6 Hz), 5.61–5.58 (m, 1H), 4.56–3.53 (m, 4H), 4.18–3.69 (m, 7H), 3.28 (s, 3H), 2.76 (brs, 1H), 2.34 (brs, 1H), 1.89–1.84 (m, 1H), 1.47–1.18 (m, 5H), 1.11 (d, 1H, *J*=6.6 Hz); ^{13}C NMR δ 165.73, 138.22, 138.04, 137.99, 134.47, 133.57, 132.90, 130.51, 130.22, 129.70, 128.82, 128.27, 127.69, 127.55, 127.51, 107.94, 74.72, 73.39, 73.39, 73.28, 73.01, 69.78, 68.16, 52.27, 50.96, 49.00, 45.90, 44.76, 36.16, 21.10, 20.97, 14.14; HRMS *m*/*z* Calcd for $C_{35}H_{40}O_6$: 556.2823 (M^+). Found: 556.2824 (M^+).

14C. ^1H NMR δ 7.34–7.20 (m, 12H), 6.85–6.80 (m, 2H), 6.13 (dd, 1H, *J*=3.3, 5.6 Hz), 5.95 (dd, 1H, *J*=2.6, 5.6 Hz), 4.61–4.45 (m, 6H), 4.03 (d, 1H, *J*=9.2, Hz), 3.92–3.80 (m, 2H), 3.79 (s, 3H), 3.74–3.65 (m, 4H), 3.29 (s, 3H), 2.76 (brs, 1H); 2.33 (brs, 1H), 1.88–1.83 (m, 1H), 1.47–1.18 (m, 5H), 1.11 (d, 1H, *J*=6.3 Hz); ^{13}C NMR δ 159.15, 138.11, 133.66, 129.34, 128.27, 127.73, 127.58, 127.49, 127.46, 113.60, 108.34, 78.31, 73.23, 72.35, 70.12, 69.87, 55.24, 51.97, 51.07, 49.02, 45.82, 44.84, 36.14, 21.15; FAB-HRMS *m*/*z* Calcd for $C_{36}H_{44}O_6$: 572.3138 (M^+). Found: 572.3136 (M^+).

15A. $[\alpha]_D^{30}=+14.4°$ (*c* 0.93, $CHCl_3$); ^1H NMR δ 7.68–7.10 (m, 20H), 4.49 (d, 1H, *J*=11.9 Hz), 4.44 (d, 1H, *J*=11.9 Hz), 4.26 (d, 1H, *J*=11.6 Hz), 4.19 (d, 1H, *J*=11.9 Hz), 4.00 (m, 1H), 3.94–3.89 (m, 1H), 3.65–3.56 (m, 2H), 3.47 (d, 2H, *J*=4.3 Hz), 2.61 (d, 1H, *J*=4.6 Hz), 1.02 (s, 9H); ^{13}C NMR δ 135.99, 135.80, 129.70, 129.54, 128.34, 128.19, 127.75, 127.60, 127.55, 127.42, 73.26, 73.01, 72.78, 72.26, 71.39, 71.12, 26.97, 19.41; Anal. Calcd for $C_{34}H_{40}O_4Si$: C, 75.52; H, 7.46. Found: C, 75.59; H, 7.54.

15B. $[\alpha]_D^{30}=+18.7°$ (*c* 1.79, $CHCl_3$); ^1H NMR δ 7.91–7.09 (m, 15H), 5.21–5.15 (m, 1H), 4.48–4.36 (m, 4H), 4.11–4.07 (m, 1H), 3.81–3.67 (m, 2H), 3.53–3.42 (m, 2H), 2.71 (brs, 1H); ^{13}C NMR δ 165.82, 137.81, 137.66, 133.10, 129.97, 129.78, 128.37, 127.76, 127.67, 127.60, 73.44, 73.33, 73.03, 70.68, 69.88, 68.88; Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.59; H, 6.59.

15C. $[\alpha]_D^{30}=+18.4°$ (*c* 0.50, $CHCl_3$); ^1H NMR δ 7.36–7.24 (m, 10H), 7.21–7.17 (m, 2H), 6.90–6.81 (m, 2H), 4.64–4.47 (m, 6H), 3.96–3.80 (m, 1H), 3.78 (s, 3H), 3.77–3.72 (m, 1H), 3.68–3.56 (m, 4H), 2.60 (d, 1H, *J*=5.5 Hz); ^{13}C NMR δ 157.50, 138.13, 138.01, 130.40, 129.52, 128.36, 127.78, 127.71, 127.64, 113.73, 77.65, 73.46, 73.35, 72.20, 70.96, 70.73, 70.14, 55.24; Anal. Calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 73.63; H, 7.25.

HPLC analysis data for 3a–h and 15B,C

Ee values of the optically active **3a–h** shown in Table 2 and **15B**,**C** in Scheme 10 were determined by comparison with their racemic ones using Daicel Chiralpak AD as a chiral

Compound	Conditions	Retention time (min)
(±) - **3a**	Hexane/*i*-PrOH=93/7, 0.5 mL/min flow rate	14.8, 16.1; (14.8)
(±) - **3b**	Hexane/*i*-PrOH=93/7, 0.5 mL/min flow rate	14.9, 16.1; (14.9)
(±) - **3c**	Hexane/*i*-PrOH=98/2, 0.4 mL/min flow rate	29.5, 33.3; (34.0)
(±) - **3d**	Hexane/*i*-PrOH=96/4, 0.8 mL/min flow rate	27.5, 29.5; (27.9)
(±) - **3e**	Hexane/*i*-PrOH=97/3, 0.5 mL/min flow rate	20.8, 22.1; (20.8)
(±) - **3f**	Hexane/*i*-PrOH=93/7, 0.5 mL/min flow rate	14.2, 15.1; (13.9)
(±) - **3g**	Hexane/*i*-PrOH=97/3, 0.9 mL/min flow rate	48.6, 53.3; (54.4)
(±) - **3h**	Hexane/*i*-PrOH=93/7, 0.35 mL/min flow rate	20.6, 22.3; (21.0)
(±) - **3I**	Hexane/*i*-PrOH=95/5, 1.0 mL/min flow rate	11.4, 12.0; (11.5)
(±) - **3j**	Hexane/*i*-PrOH=97/3, 0.8 mL/min flow rate	17.3, 18.7; (16.7)
(±) - **3k**	Hexane/*i*-PrOH=98/2, 0.8 mL/min flow rate	13.8, 15.1; (14.5)
(±) - **3l**	Hexane/*i*-PrOH=95/5, 1.0 mL/min flow rate	7.45, 8.13; (7.42)
(±) - **15B**	Hexane/*i*-PrOH=95/5, 0.8 mL/min flow rate	54.2, 63.0; (62.4)
(±) - **15C**	Hexane/*i*-PrOH=95/5, 1.0 mL/min flow rate	32.7, 41.1; (41.6)

column (UV detector: at 259 nm for benzyl compounds **3a**–**3l**, at 227 nm for benzoyl ester **15B**, and at 275 nm for 4-methoxybenzyl ether **15C**) at 24°C. Retention times shown by the optically active ones are written in the parenthesis.

X-Ray experimental data of 10b

$C_{13}H_{21}BrO_3$: M 305.20, crystal size 0.40×0.40×0.30 mm^3, monoclinic, space group $P21/n$, a=18.275 (3), **b**=9.979 (2), **c**=7.703 (2) Å, **b**=101.33 (1), **V**=1377.4 (4) $Å^3$, Z=4, D_{calc}=1.47 g/cm^3, m (Cu, K-a) 37.83 cm^{-1}, R=0.054, Reflection used 2222.

Acknowledgements

Financial support from Monbusho (Grant-in-Aid for Scientific Research on Priority Areas, No. 706: Dynamic Control of Stereochemistry) and Promotion of Science (No. 10671989) are gratefully acknowledged.

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