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Rapid atropisomerization of 1,1′:5′,1″-ternaphthalene-2,2′,6′,2″-tetrol (TERNOL) and its inhibition by tethering at positions 7 and 7″

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Abstract—Atropisomerization of 1,1′:5′,1″-ternaphthalene-2,2′,6′,2″-tetrol (TERNOL) is very fast under basic conditions. The stereochemical instability is attributed to the nature of oxide anion of the central 2,6-naphthodiol moiety. Ring-closing metathesis of 7,7″-diallyloxy TERNOL results in intramolecular tethering in a high yield, which intrinsically inhibits the rapid isomerization. Bidentate sites in the tethered TERNOL are proved to have enough structural flexibility as an axial chiral ligand.

1. Introduction

1,1′:5′,1″-Ternaphthalene-2,2′,6′,2″-tetrol (TERNOL, **1**) is one of the higher analogs of 1,1′-binaphthalene-2,2′-diol (BINOL),[1–3] and has two bidentate sites at the opposite positions (2′ and 6′), and in the chiral form, on the same face of the central naphthalene ring. An expected property of TERNOL as a chiral ligand is that two metal atoms coordinated with it are fixed in a certain distance and have electronic interaction through the central naphthodiol moiety. To supply optically active TERNOL, an asymmetric synthesis by a stereoselective coupling was developed,[4] and later on, an effective resolution of the racemic mixture was reported for a large-scale preparation.[5] TERNOL as a chiral source still has a problem due to its stereochemical instability. Especially in the presence of a base, the *rac*-isomer easily becomes a mixture with the *meso*-isomer,[5] and thus interconversion between (*R*,*R*)- and (*S*,*S*)-**1** also proceeds via (*R*,*S*)-**1** to result in racemization of the optically active compound (Fig. 1). We herein report the evaluation of the stereochemical stability of TERNOL by the kinetic study of the isomerization under weakly basic conditions. The isomerization was found to start immediately after generation of the oxide anion species at room temperature, but this stereochemical fragility of TERNOL was reinforced by introducing an intramolecular tether in keeping the flexible bis-bidentate nature.

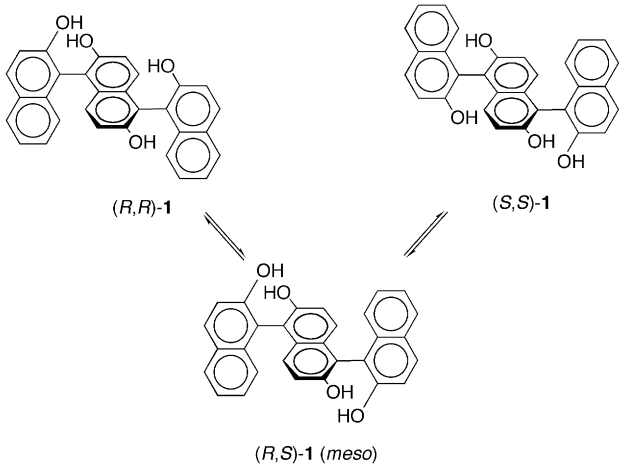

Figure 1. Interconversion of three stereoisomers of TERNOL (**1**).

2. Results and discussion

TERNOL (**1**) was known to be stereochemically less stable under basic conditions than under neutral or acidic conditions,[5] and thus the isomerization process seems to include formation of the oxide anion species. The isomerization rate was measured at pH 9.5 because a sufficient amount of the anion species should be generated from **1** at this pH. The rates were also determined for the 7,7″-disubstituted analogs **2a**–**c**, which were prepared as mixtures of *rac*- and *meso*-isomer by a similar method for the synthesis of **1**[6] via the three-component coupling of one molecule of **3**

Keywords: Axial chirality; Atropisomerization; Bidentate ligand; Metathesis.
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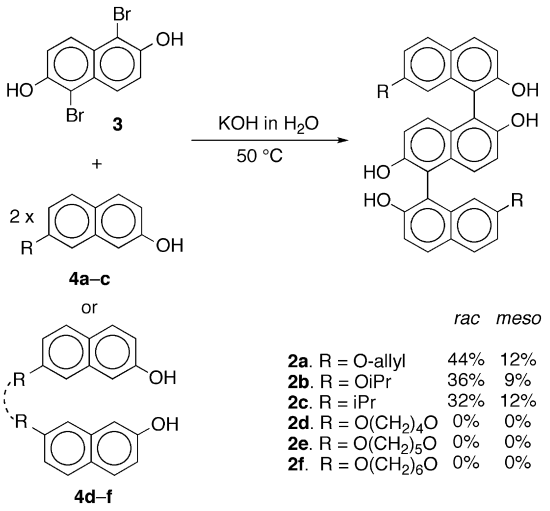


Scheme 1. Synthesis of 7,7″-disubstituted TERNOL **2**.

and two molecules of **4a–c** (Scheme 1). Separated isomers of **2a–c** were stable in a methanol solution (1.8 mM); any isomer was not changed for 8 h at 23 °C. However, it became stereochemically unstable when a small amount of an aqueous sodium carbonate buffer of pH 9.5 was added. It should be noted that such a rapid atropisomerization under the weakly basic conditions is not known for BINOLs (BINOL itself was proved to be unchanged under the same basic conditions). The isomerizations starting from both *rac*- and *meso*-**2** were monitored by the HPLC until the stationary state of the *rac*/*meso* equilibration was attained, as shown in Figure 2. The equilibrium constant K (=*meso*/*rac*) and the *pseudo*-first order rate constants k_{obs} ($=k_1+k_{-1}$, s^{-1}) calculated for the isomerization of each isomer are summarized in Table 1. The present kinetic analysis indicates that the equilibrium constant K is affected by the 7,7″-disubstitution, while the stereochemical instability (k_{obs}) is not.

The different K values depending on the 7-substituent indicate the existence of interaction between the two terminal

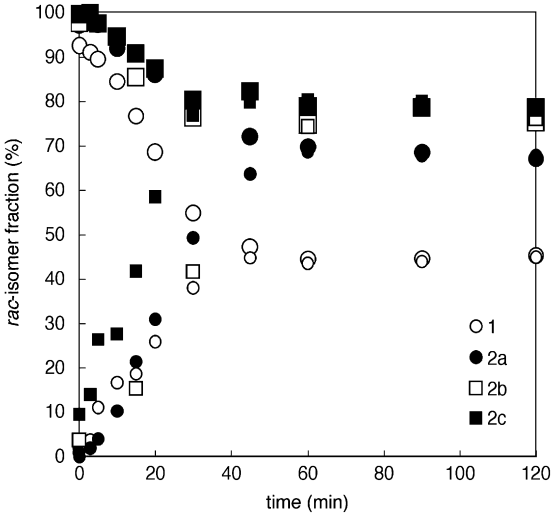


Figure 2. Isomerization starting from a *rac*- or *meso*-isomer in methanol containing 5% of an aqueous 0.5 M sodium carbonate buffer (pH 9.5) at 23 °C. The isomer fraction starting from a *rac*-isomer is given in a larger mark and that from a *meso*-isomer is a smaller one.

Table 1. Equilibrium constant K (=*meso*/*rac*) and *pseudo*-first order rate constant k_{obs} ($=k_1+k_{-1}$, s^{-1}) for isomerization of each isomer of **1** and **2a–c**[a]

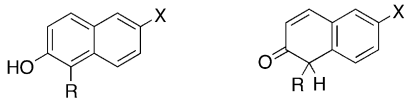
	K	k_{obs1}	k_{obs2}
1	1.22	1.4×10^{-3}	1.5×10^{-3}
2a	0.49	0.9×10^{-3}	1.0×10^{-3}
2b	0.33	—[b]	ca. 1×10^{-3}
2c	0.27	ca. 1×10^{-3}	1.5×10^{-3}

[a] k_{obs1} is obtained by the reaction with the *rac*-isomer and k_{obs2} with the *meso*-isomer.
[b] Not determined.

naphthalene moieties; probably in the *rac*-form because in the *meso*-form, the 7-position is far away from the other terminal naphthalene moiety. However, the isomerization rate itself is not affected by the substitution, and thus the stereochemical instability, which is not observed with BINOL,[7] is not attributable to the interaction between the terminal-moieties, but should be due to the nature of the central 2,6-naphthodiol moiety.

Interesting information was obtained from the computational study of 2,6-naphthodiols (Table 2). By the Gaussian calculation at the B3LYP/6-31G(d) level, 2,6-naphthodiol is 4.6 kcal mol^{-1} more stable than its keto tautomer, 6-hydroxydihydronaphthalen-2(1*H*)-one, but mono-anion of 2,6-naphthodiol (6-oxide anion in this calculation) is less stable than the corresponding keto isomer by 0.9 kcal mol^{-1}. The inversion of the enol/keto stability is also found for the 1-phenyl analog; the keto predominance in the anionic forms is 0.8 kcal mol^{-1}. The perpendicular geometry of the phenyl group to the naphthyl group in the enol form is lost in the keto form, where steric hindrance for rotation of the phenyl group is smaller than that in the enol form, and the atropisomerization in TERNOL under the basic conditions is suggested to be due to a process through the keto form.

Table 2. Heat of formation (kcal mol^{-1}) of 2,6-naphthodiols and their tautomers in neutral (X=OH) and anionic ($X=O^-$) forms obtained by the Gaussian calculations at the B3LYP/6-31G(d) level



enol form keto form

X	R	Enol form	Keto form	$\Delta E_{(enol-keto)}$
OH	H	−336,548.546	−336,543.941	−4.605
O^-	H	−336,190.557	−3361.91473	+0.880
OH	Ph	−481,535.234	−481,528.222	−7.012
O^-	Ph	−481,177.364	−481,178.149	+0.785

Rapid isomerization of TERNOL at pH 9.5 means that it is difficult to recover it in optically pure form when extraction with basic aqueous solution is necessitated after the reaction. As a chiral source, this is a fatal problem, and the atropisomerization during and after the reaction must be intrinsically suppressed. Introduction of a protection group at the phenolic OH in TERNOL is an effective way to interrupt the isomerization, but it also results in loss of the bidentate sites. Our molecular design to solve this issue is the use of an intramolecular tether at positions 7 and 7″.

Molecular model examinations of the 7,7″-tethered TERNOLs **2d–f** suggested that the tether is long enough with six atoms and the shortest tether of **2d** still keeps sufficient mobility around the chiral axis bond for use as a flexible bidentate ligand, similar to those with *rac*-**1**. However, the *meso*-forms of **2d–f** are intrinsically impossible and optically active **2d–f** can be stabilized by inhibition of the racemization through the *meso*-form. First, the precursors **4d–f** connecting two units of 2-naphthol at position 7 with a tether of different length were reacted with **3** under the coupling conditions. After several trials, it was concluded that **2d–f** were not produced by this process. The coupling reaction must necessitate a separation between the positions 7 and 7″ more than that in *rac*-**2**.

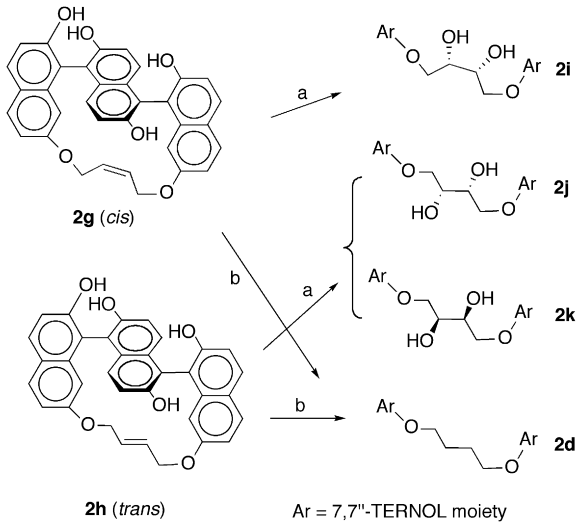
The tethered TERNOL was next planned to synthesize from *rac*-**2a** by the metathesis reaction.[8] When a benzene solution of **2a** was treated with a Grubbs' catalyst of the first generation, $(PCy_3)_2Cl_2Ru{=}CHPh$, at room temperature, **2g** was produced smoothly as a single product in a quantitative yield (Table 3, entry 1). The strong selectivity was lost when the reaction was performed in chloroform to give **2h** as a side product (entry 2). This side product became major when the second-generation catalyst, $(H_2IMes)PCy_3Cl_2Ru{=}CHPh$, was employed in benzene (entry 3). Despite expected higher reactivity of this catalyst, the reaction conversion remained only at 30%. This can be due to the deactivation of the catalyst, probably by the reductive nature of the central 2,6-naphthodiol moiety. High yield with the second-generation catalyst was achieved for the reaction of the tetraacetate analog of **2a**, in which the reductive nature was protected, to result in the acetate analogs of **2g** and **2h** in a ratio of **2g/2h**=3/7 (entry 4).

Properties of the isolated **2g** and **2h** are very similar to each other indicating that they are mutually isomers at the newly generated olefinic part. Osmium oxidation of **2g** after protection of the four phenolic hydroxy groups by acetylation gave **2i**, which has dissymmetric structure showing 42 carbon peaks in the NMR (Scheme 2). On the other hand, the same oxidation of tetraacetate analog of **2h** gave a 1/1 mixture of

Table 3. Metathesis of **2a** with Grubbs' first- and second-generation catalysts

Entry	Catalyst (mol %)	Solvent	Yield (%)	*cis*/*trans* (**2g**/**2h**)
1	First (8)	Benzene	97	>99/<1
2	First (8)	Chloroform	91	60/40
3	Second (16)	Benzene	30[a]	31/69
4[b]	Second (8)	Benzene	99	30/70

[a] Compound **2a** of 70% remained unchanged and mostly recovered.
[b] Hydroxy groups of **2a** were protected by acetylation prior to the metathesis.



Scheme 2. The metathesis products, **2g** and **2h**, and their reactions. (a) Protection of the four hydroxy groups under Ac_2O/K_2CO_3 (>95% yield), and OsO_4/NMO/THF–H_2O (87% for **2g** and 94% for **2h**). (b) H_2/Pd–C/THF (>95% yield).

isomers, **2j** and **2k**, both of which have C_2 symmetric structures giving 21 peaks in the ^{13}C NMR. Thus, **2g** is assigned as cis and **2h** as trans at the olefinic bond in the tether. Hydrogenation of both **2g** and **2h** over Pd–C in THF (room temperature/10^5 Pa of H_2) gave **2d** quantitatively.

On the basis of the common understanding of the ring-closing metathesis,[8,9] a less reactive species generated from the first-generation catalyst tends to give a kinetically controlled product from terminal olefins, while a more reactive one from the second-generation catalyst may react with an inner olefin of the initial product to give a thermodynamically more stable product. The kinetic formation of cis-isomer **2g** is reasonable if a conformationally limited structure of the substrate **2a** with the two allyloxy-groups orienting closely to each other is considered. Formation of trans-isomer **2h** must be the results of isomerization of **2g**. Indeed, when the tetraacetate analog of **2g** was treated with the second-generation catalyst in benzene-d_6, the isomerization to give the analog of **2h** was immediately observed by the ^1H NMR and finally gave a trans-rich mixture of **2g/2h**=1/4.

Separations of enantiomers of untethered **2a** and tethered **2g**, **2h**, and **2d** were effectively performed with a chiral HPLC column. Absolute stereochemistries of the separated TERNOLs were assigned on the basis of the CD spectra in comparison with **1**. The UV and CD spectra are summarized in Table 4. The tethered TERNOLs are very similar to each other, and also almost the same as the untethered **2a**. Thus,

Table 4. UV and CD spectra of TERNOLs

	UV λ_{max}, nm ($\varepsilon\times10^4$) in CH_3CN			CD λ_{ext}, nm ($\Delta\varepsilon$) in CH_3CN			
				(*R*,*R*)-form		(*S*,*S*)-form	
2a	289 (1.78)	329 (1.31)	355 (0.98)	228 (320)	242 (−348)	228 (−248)	242 (246)
2g	288 (1.84)	329 (1.30)	356 (1.01)	227 (319)	243 (−385)	229 (−321)	242 (388)
2h	288 (1.77)	329 (1.32)	356 (0.94)	230 (362)	243 (−333)	230 (−341)	243 (324)
2d	289 (1.90)	329 (1.40)	355 (1.04)	228 (321)	242 (−365)	228 (−323)	242 (410)

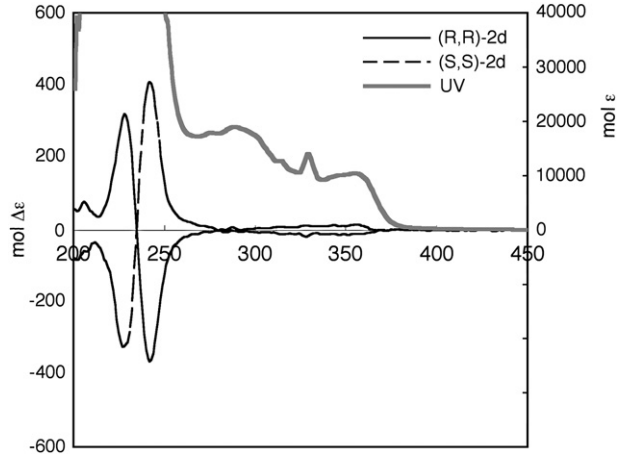
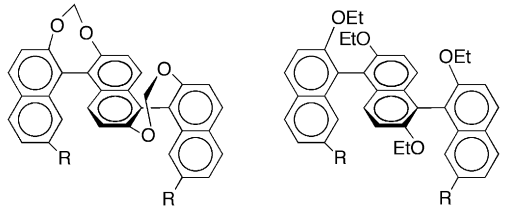


Figure 3. UV and CD spectra of **2d** in acetonitrile.

the tether in **2d** is not so tight as to affect the conformation of the TERNOL unit, or even loose because the more rigid unsaturated tethers in both cis and trans forms also did not affect the conformation of the TERNOL skeleton. The CD and UV spectra of **2d** are given in Figure 3.

Stereochemical stability of the tethered **2d** was studied for the atropisomerization between the enantiomers. When optically active (*R*,*R*)- or (*S*,*S*)-**2d** was heated to 70 °C in a diethylene glycol mono-methyl ether solution in the presence or absence of the sodium carbonate buffer, the mixture was unchanged for a week and no racemization was observed by the chiral HPLC analysis. The stability was unchanged in toluene in the presence or absence of triethylamine at 100 °C. Thus, the tether in **2d** was proved to efficiently interrupt the atropisomerization, including synchronous rotation of the two axis bonds, like pedaling, to result in direct conversion between (*R*,*R*)- and (*S*,*S*)-**2d**.

To use **2d** as a versatile chiral bidentate ligand, the structural limitation by the tether should leave some mobility at the rotation of the axis bond. As a model of metal coordination at the bidentate sites, bismethylene analogs **5** were synthesized from untethered **2a** and tethered **2d**, where angle at the bidentate sites becomes smaller.[10] Tetraethyl analogs **6** were also prepared as alkylated reference compounds (Fig. 4). Both the conversions with dibromomethylene and ethyl bromide in the presence of potassium carbonate proceeded smoothly, and no measurable difference in the reactivity between **2a** and **2d** was observed in the both alkylations. The UV spectra of the obtained compounds are shown in Figures 5 and 6. The spectra of tetraethyl analogs **6** are similar to



5a. R = O-allyl
5d. R = $O(CH_2)_4O$

6a. R = O-allyl
6d. R = $O(CH_2)_4O$

Figure 4. Structures of methylene analog **5** and ethyl analog **6**.

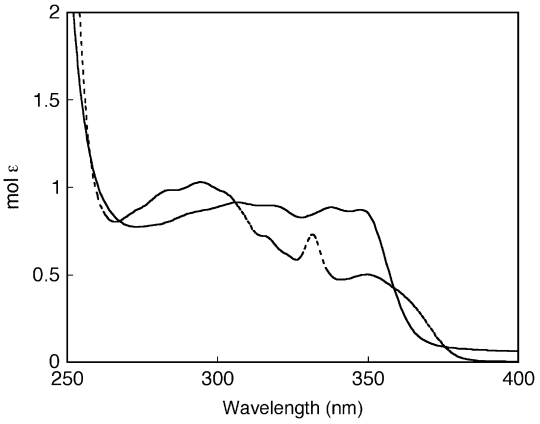


Figure 5. UV spectra of the tethered **5d** (solid line) and **6d** (broken line) in acetonitrile.

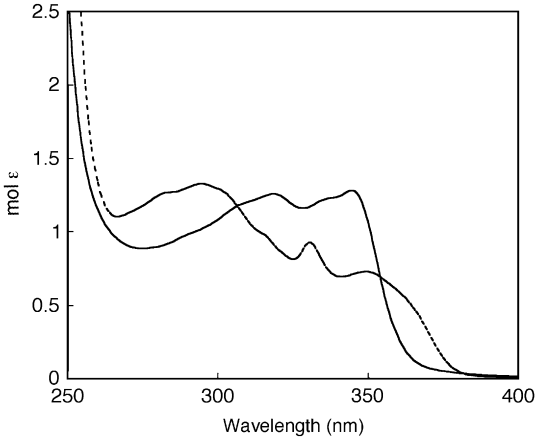


Figure 6. UV spectra of untethered **5a** (solid line) and **6a** (broken line) in acetonitrile.

those of **2** (see Fig. 3), while bismethylene analogs **5** are not. The change in spectra of **5** must indicate the change in conformation of the TERNOL skeleton by the methylene bridge. The observed change from **2d** to **5d** is almost identical to that from **2a** to **5a**, and thus the effect of the tether on the mobility around the axis bond should be enough to use as a ligand.

3. Conclusions

TERNOLs were found to be unstable at pH 9.5, and the instability is attributable to the generation of the oxide anion at the central 2,6-naphthalene moiety in the other side of the atropisomerization site. The stereochemically stable 7,7″-tethered TERNOLs were synthesized via the metathesis, and has flexibility at the bidentate sites similar to the untethered TERNOLs.

4. Experimental

4.1. General

All products were characterized by NMR spectrometry using a JEOL ECA-600 spectrometer at 600 MHz for proton

and 150 MHz for carbon, and by IR with a JASCO IR-410 spectrophotometer with a solution cell ($CHCl_3$). Optical rotations were measured with a Perkin–Elmer 241 polarimeter. UV spectra were obtained by an Agilent 8453 and CD spectra were obtained using a JASCO J-720. High-resolution MS was obtained by a JEOL JMS-T100LC with an ESI devise. Melting points were measured by a Büchi B-545. Chiral HPLC columns, Chiralpak AD and IA (4.6 mm i.d.×25 cm), were obtained from Daicel Chemicals, Co. Ltd., Japan, and used for both analysis and separation in 10–30 mg scales. All solvents were properly purified before use. All reactions were carried out under nitrogen atmosphere.

4.1.1. Preparation of 4a. A solution of 2,7-naphthodiol (1.00 g) and K_2CO_3 (0.95 g, 1.1 equiv) in acetone (12 mL) was stirred for 1 h at room temperature. To this suspension, allylbromide (0.60 mL, 1.1 equiv) was added dropwise and the mixture was allowed to stand for 8 h at the same temperature. After the addition of water, the mixture was extracted with ether, dried over Na_2SO_4, and purified by column chromatography on silica gel (30 g, elution with 30% and then 40% ethyl acetate in hexane) to give 0.55 g of **4a** (44%). Colorless needles; mp 80.5–82.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J=8.9 Hz, 2H), 7.02 (d, J=2.1 Hz, 1H), 7.00 (dd, J=8.9, 2.1 Hz, 1H), 6.97 (d, J=2.1 Hz, 1H), 6.92 (dd, J=8.9, 2.1 Hz, 1H), 6.10 (ddt, J=15.8, 10.3, 5.5 Hz, 1H), 5.45 (dd, J=15.8, 1.4 Hz, 1H), 5.30 (dd, J=10.3, 1.4 Hz, 1H), 4.92 (s, 1H), 4.62 (d, J=5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.2, 153.9, 135.9, 133.2, 129.6, 129.3, 124.5, 117.8, 116.6, 115.2, 108.8, 105.9, 68.8; IR (cm^{-1}) 3306, 1631, 1608, 1209, 1021, 930, 857, 831, 634; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{13}H_{11}O_2$ 199.0759, found 199.0767.

4.1.2. Preparation of 4b. A mixture of 2,7-naphthodiol (10.0 g), isopropylbromide (6.45 mL, 1.1 equiv), and K_2CO_3 (9.48 g, 1.1 equiv) in DMF (62.4 mL) was stirred for 12 h at 45 °C. The mixture was then cooled, treated with water, extracted with ether, dried over Na_2SO_4, and purified by column chromatography on silica gel (200 g, elution with 30% ethyl acetate in hexane) to give 5.46 g of **4b** (43%). The spectral data of the obtained **4b** were identical with those of the reported ones.[11]

4.1.3. Preparation of 4c. To a solution of **4b** (2.0 g) in pyridine (10 mL) was added trifluoromethanesulfonic anhydride (1.8 mL, 1.0 equiv) dropwise in 15 min. After 30 min, the mixture was treated with 2 M HCl, extracted with ether, dried over Na_2SO_4, and purified by column chromatography on silica gel (60 g, elution with 20% ethyl acetate in hexane) to give 3.24 g of a triflate derivative of **4b** (98%). Light yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J=8.9 Hz, 1H), 7.75 (d, J=8.9 Hz, 1H), 7.58 (dd, J=2.8 Hz, 1H), 7.15–7.18 (m, 2H), 7.11 (d, J=2.1 Hz, 1H), 4.69 (sept, J=6.2 Hz, 1H), 1.40 (d, J=6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 157.13, 147.71, 134.94, 130.08, 129.32, 127.59, 121.10, 117.79, 116.63, 107.86, 69.94, 21.674; IR (cm^{-1}) 1633, 1511, 1423, 1243, 1212, 1141, 987, 957, 887, 836, 597; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{14}H_{13}F_3O_4S$ 333.0408, found 333.0412. To a solution of the triflate derivative (0.71 g) and a catalytic amount of $NiCl_2$(dppe) in ether (11 mL) was added a solution of isopropyl magnesium bromide (ca. 2 equiv), and the mixture was allowed to stand for 22 h at 40 °C. After cooling, the mixture was treated with aqueous NH_3, extracted with ether, dried over $MgSO_4$, and purified by column chromatography on silica gel (20 g, elution with 6% ethyl acetate in hexane) to give 0.40 g of 2-isopropyloxy-7-isopropylnaphthalene (73%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J=8.3 Hz, 2H), 7.49 (d, J=1.5 Hz, 1H), 7.23 (dd, J=8.3, 1.5 Hz, 1H), 7.10 (d, J=2.4 Hz, 1H), 7.04 (dd, J=8.3, 2.4 Hz, 1H), 4.68 (sept, J=6.4 Hz, 1H), 3.03 (sept, J=6.8 Hz, 1H), 1.38 (d, J=6.4 Hz, 6H), 1.31 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 156.0, 146.7, 135.0, 128.9, 127.7, 127.5, 123.3, 123.0, 119.0, 118.9, 108.9, 70.1, 38.35, 34.35, 24.0, 22.2; IR (cm^{-1}) 2960, 1630, 1512, 1460, 1384, 1210, 1115, 983, 837. To a solution of the obtained compound (502.5 mg) in CH_2Cl_2 (5.4 mL), BBr_3 (0.5 mL) was added at −78 °C and the mixture was stirred for 30 min at the same temperature. The mixture was treated with 2 M HCl, warmed to room temperature, extracted with ether, dried over Na_2SO_4, and purified by column chromatography on silica gel (15 g, elution with 30% ethyl acetate in hexane) to give 386.5 mg of **4c** (81%). Spectral data of the obtained compound were identical with those of reported **4c**.[12]

4.1.4. Preparation of 4d–f. A mixture of 2,7-naphthalenediol (8.0 g), 1,4-dibromobutane (1.96 mL, 1.0 equiv), and K_2CO_3 (2.5 g, 1.1 equiv) in DMF (35 mL) was stirred for 2 days at 40 °C. The mixture was cooled to room temperature, treated with water, extracted with ethyl acetate, dried over Na_2SO_4, and purified by column chromatography on silica gel (200 g, elution with 30% ethyl acetate in hexane) to give 766 mg of **4d** (12%). By the same procedure except for the use of 1,5-dibromopentane or 1,6-dibromohexane, **4e** (12%) and **4g** (11%) were obtained. These three compounds were only identified by ^{1}H NMR and ESI-MS. Compound **4d**: ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J=8.9 Hz, 2H), 7.61 (d, J=8.9 Hz, 2H), 7.23–6.91 (m, 8H), 4.09–4.03 (m, 4H), 1.94–1.89 (m, 4H); HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{24}H_{21}F_3O_4$ 374.1518, found 374.1550. Compound **4e**: ^{1}H NMR ($CDCl_3$) δ 7.64–7.62 (m, 4H), 7.02–6.90 (m, 4H), 4.93 (s, 2H), 4.05 (t, J=6.2 Hz, 2H), 3.44 (t, J=6.2 Hz, 2H), 1.97–1.90 (m, 4H), 1.89–1.83 (m, 4H); HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{25}H_{23}O_4$ 388.1675, found 388.1647. Compound **4f**: ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J=8.9 Hz, 2H), 7.62 (d, J=8.9 Hz, 2H), 7.02–6.90 (m, 8H), 4.83 (s, 2H), 4.06 (t, J=6.2 Hz, 4H), 1.90–1.85 (m, 4H), 1.60–1.58 (m, 4H); HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{26}H_{25}O_4$ 401.1758, found 401.1789.

4.1.5. Synthesis of 2a–c (direct process intended to obtain 2d–f). A solution of **3** (3.85 g), **4a** (5.0 g, 2.1 equiv), and KOH (2.0 g, 2.5 equiv) in water (30 mL) was stirred for 3 days at 50 °C. The mixture was treated with 2 M HCl, extracted with ether, dried over Na_2CO_3, and purified by column chromatography on silica gel (240 g, elution with 30% and then 40% ethyl acetate in hexane) to give 2.97 g of *rac*-**2a** and 0.78 g of *meso*-**2a**. The reactions with **4b–f** were performed by following this process. The yields of **2** are given in Scheme 1. *rac*-**2a**: brown solid; mp 127.1–132.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J=8.9 Hz, 2H), 7.79 (d, J=8.9 Hz, 2H), 7.28 (d, J=8.9 Hz, 2H), 7.19 (d, J=8.9 Hz, 2H), 7.16 (d, J=8.9 Hz, 2H), 7.06 (dd, J=8.9, 2.1 Hz, 2H), 6.51 (d, J=2.1 Hz, 2H), 5.85 (ddt, J=17.2, 10.3, 5.5 Hz, 2H), 5.14 (dd, J=17.2, 1.4 Hz, 2H), 5.13 (dd, J=10.3, 1.4 Hz, 2H), 5.10 (s, 2H), 5.00 (d, J=9.6 Hz, 2H),

4.31 (d, J=5.5 Hz, 2H), 4.28 (d, J=5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 158.03, 153.36, 151.32, 134.82, 132.72, 131.23, 130.10, 129.11, 127.60, 124.86, 119.04, 118.27, 116.20, 115.31, 112.14, 110.00, 104.92, 68.70; IR (cm^{-1}) 3478, 1621, 1512, 1445, 1374, 1335, 1209, 1161, 1016, 991, 834; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{36}H_{28}O_6$ 555.1808, found 555.1773; Anal. Calcd for $C_{44}H_{36}O_{10}$ (tetraacetate analog of **2a**) C: 72.92, H: 5.01; obsd C: 72.38, H: 5.01. HPLC (Chiralpak AD, elution with IPA/Hex=3/7, 1.00 mL/min, 230 nm) 8.88 and 14.22 min. (*R*,*R*)-**2a**: $[\alpha]_D^{20}$ +33.0 (*c* 0.02, THF), (*S*,*S*)-**2a**: $[\alpha]_D^{20}$ −30.0 (*c* 0.02, THF), *meso*-**2a**: pale red solid; mp>300 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J=8.9 Hz, 2H), 7.81 (d, J=8.9 Hz, 2H), 7.31 (d, J=8.9 Hz, 2H), 7.25 (d, J=8.9 Hz, 2H), 7.21 (d, J=8.9 Hz, 2H), 7.08 (dd, J=8.9, 2.1 Hz, 2H), 6.53 (d, J=2.1 Hz, 2H), 5.89 (ddt, J=17.2, 10.3, 5.5 Hz, 2H), 5.19 (dd, J=17.2, 1.4 Hz, 2H), 5.14 (dd, J=10.3, 1.4 Hz, 2H), 5.09 (s, 2H), 4.98 (s, 2H), 4.38 (d, J=5.5 Hz, 2H), 4.34 (d, J=5.5 Hz, 2H); IR (cm^{-1}) 3347, 1620, 1513, 1445, 1328, 1211, 1166, 1046, 1021, 991, 935, 873, 834; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{36}H_{28}O_6$ 555.1808, found 555.1852; HPLC (Chiralpak AD, elution with IPA/Hex=3/7, 1.00 mL/min, 230 nm) 22.4 min. *rac*-**2b**: pale brown solid; mp 143.2–146.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J=8.9 Hz, 2H), 7.79 (d, J=8.9 Hz, 2H), 7.30 (d, J=8.9 Hz, 2H), 7.19 (d, J=8.9 Hz, 2H), 7.18 (d, J=8.9 Hz, 2H), 7.03 (dd, J=8.9, 2.1 Hz, 2H), 6.47 (d, J=2.1 Hz, 2H), 5.16 (s, 2H), 5.01 (s, 2H), 4.32 (sept, J=6.2 Hz, 2H), 1.21 (d, J=6.2 Hz, 6H), 1.14 (d, J=6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 157.2, 153.2, 151.2, 134.9, 131.1, 130.0, 129.1, 127.5, 124.6, 118.9, 116.6, 115.1, 112.3, 109.9, 106.1, 69.6, 21.8, 21.6; IR (cm^{-1}) 3484, 2976, 1620, 1512, 1445, 1375, 1334, 1269, 1221, 1160, 1138, 1115, 1039, 955, 860, 833; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{36}H_{32}O_6$ 559.2121, found 559.2113; HPLC (Chiralpak AD, elution with IPA/Hex=3/7, 1.00 mL/min, 230 nm) 7.04 and 10.94 min. *meso*-**2b**: pale red solid; mp 274.8–281.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J=8.9 Hz, 2H), 7.81 (d, J=8.9 Hz, 2H), 7.31 (d, J=8.9 Hz, 2H), 7.24 (d, J=8.9 Hz, 2H), 7.20 (d, J=8.9 Hz, 2H), 7.04 (dd, J=8.9, 2.1 Hz, 2H), 6.50 (d, J=2.1 Hz, 2H), 5.08 (s, 2H), 4.99 (s, 2H), 4.37 (sept, J=6.2 Hz, 2H), 1.22 (d, J=6.2 Hz, 6H), 1.15 (d, J=6.2 Hz, 6H); IR (cm^{-1}) 3442, 2976, 1738, 1620, 1511, 1446, 1375, 1339, 1216, 1166, 940, 875, 825, 664; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{36}H_{32}O_6$ 559.2121, found 559.2146; HPLC (Chiralpak AD, elution with IPA/Hex=3/7, 1.00 mL/min, 230 nm) 14.4 min. *rac*-**2c**: pale brown solid; mp 151.2–159.2 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J=8.9 Hz, 2H), 7.83 (d, J=8.9 Hz, 2H), 7.25–7.31 (m, 6H), 7.14 (d, J=8.9 Hz, 2H), 6.93 (s, 2H), 5.26 (s, 2H), 5.01 (s, 2H), 2.84 (sept, J=6.9 Hz, 2H), 1.12 (d, J=6.9 Hz, 6H), 1.11 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 152.73, 151.21, 148.14, 133.68, 131.15, 129.27, 128.31, 128.09, 127.72, 123.78, 120.66, 118.84, 116.87, 112.15, 110.74, 34.15, 23.84, 23.49; IR (cm^{-1}) 3408, 2959, 1624, 1598, 1510, 1195, 1160, 836; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{36}H_{32}O_4$ 527.2222, found 527.2212; HPLC (Chiralpak AD, elution with IPA/Hex=3/7, 1.00 mL/min, 230 nm) 8.25 and 9.12 min. *meso*-**2c**: colorless solid; mp 230.0–233.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J=8.9 Hz, 2H), 7.86 (d, J=8.9 Hz, 2H), 7.21–7.35 (m, 8H), 6.99 (s, 2H), 5.09 (s, 2H), 4.94 (s, 2H), 2.86 (sept, J=6.9 Hz, 2H), 1.15–1.20 (m, 12H); IR (cm^{-1}) 3486, 2959, 2360, 1623, 1598, 1509, 1457, 1201, 1173, 1125, 838; HRMS (ESI) m/z ($M-H^+$) calcd for $C_{36}H_{32}O_4$ 527.2222, found 527.2242; HPLC (Chiralpak AD, elution with IPA/Hex=3/7, 1.00 mL/min, 230 nm) 9.86 min.

4.1.6. Isomerization kinetics of 1 and 2a–c. To a methanol solution (1.8 mM) of *rac*- or *meso*-isomer of TERNOL, **1** or **2**, was added 5% of an aqueous 0.5 M sodium carbonate buffer (pH 9.5) at 23 °C. The isomerization was monitored by taking out a part, acidified with acetic acid, and charged to HPLC with an ODS column (4.6 mm i.d.×25 cm, elution with 20% water in methanol, monitored at 254 nm). The results are shown in Figure 2. To verify the identity of the isomerization conditions for each substrate, a mixture of **1** and **2** (**2a** or **2c**) was also treated under the same basic conditions. This mixed experiments gave the rates almost identical with the independent experiments.

4.1.7. Metathesis of 2a to give 2g (Table 2, entry 1). A solution of **2a** (401.7 mg) and $(PCy_3)_2Cl_2Ru$=CHPh (48.6 mg, 8 mol %) in benzene (48 mL) was stirred for 5 h at room temperature. The mixture was concentrated and purified by column chromatography on silica gel (40 g, elution with 50%, then 100% ethyl acetate in hexane) to give 369 mg of **2g** (97%). Colorless solid; mp>300 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J=8.9 Hz, 2H), 7.78 (d, J=8.9 Hz, 2H), 7.27 (d, J=8.9 Hz, 2H), 7.25 (d, J=8.9 Hz, 2H), 7.18 (d, J=8.9 Hz, 2H), 7.01 (dd, J=8.9, 2.1 Hz, 2H), 6.10 (d, J=2.1 Hz, 2H), 5.45 (s, 2H), 5.31 (s, 2H), 4.98 (s, 2H), 4.42 (d, J=13.8 Hz, 2H), 4.31 (d, J=13.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.72, 153.09, 151.14, 135.29, 131.08, 129.96, 129.47, 127.93, 126.99, 124.90, 118.84, 116.93, 115.20, 112.17, 110.27, 104.17, 65.15; IR (cm^{-1}) 3419, 3063, 2926, 2855, 1074, 1621, 1512, 1444, 1376, 1337, 1270, 1207, 1159, 1032, 994, 969, 948, 833, 774, 703, 659, 632; HRMS (ESI^-) m/z ($M-H^+$) calcd for $C_{34}H_{23}O_6$ 527.1495, found 527.1535; Anal. Calcd for $C_{42}H_{32}O_{10}$ (tetraacetate analog of **2g**) C: 72.41, H: 4.63; obsd C: 71.95, H: 5.13. HPLC (Chiralpak IA, elution with IPA/Hex=4/6, 1.00 mL/min, 250 nm) 11.1 and 22.3 min. (*R*,*R*)-**2g**: $[\alpha]_D^{20}$ +47.5 (*c* 0.11, THF), (*S*,*S*)-**2g**: $[\alpha]_D^{20}$ −44.7 (*c* 0.09, THF).

4.1.8. Acetylation and deacetylation of 2. Typical procedure is as follows: a solution of **2a** (500 mg), acetic anhydride (5 mL), and pyridine (5 mL) was stirred over night at room temperature. After the addition of H_2O, the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and purified by column chromatography on silica gel (20 g, elution with 40% ethyl acetate in hexane) to give 596 mg of tetraacetate analog of **2a** (96%). Deacetylation was carried out in methanol in the presence of K_2CO_3 followed by extraction. Usually the purification was not necessary.

4.1.9. Metathesis of acetate analog of 2a to give 2h (Table 2, entry 4). A solution of tetraacetate analog of **2a** (91.3 mg) and $(H_2IMes)PCy_3Cl_2Ru$=CHPh (9.4 mg, 8 mol %) in benzene (9 mL) was stirred for 2 h at room temperature. The mixture was concentrated to give 106 mg of **2g/2h** (30/70, >99%). A mixture of isomers was recrystallized from ethyl acetate followed by the deacetylation to give 69.1 mg of **2h** (98% pure). Colorless solid; mp>300 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J=8.9 Hz, 2H), 7.72 (d, J=8.9 Hz, 2H), 7.27 (d, J=8.9 Hz, 2H), 7.21 (d, J=8.9 Hz, 2H), 7.18 (d, J=8.9 Hz,

2H), 6.93 (dd, *J*=8.9, 2.7 Hz, 2H), 6.04 (d, *J*=2.7 Hz, 2H), 5.38 (s, 4H), 5.04 (s, 2H), 4.39 (d, *J*=13.8 Hz, 2H), 4.28 (d, *J*=13.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.82, 153.27, 151.43, 135.00, 131.06, 130.07, 129.23, 128.40, 127.68, 124.75, 118.95, 117.47, 114.99, 112.34, 110.22, 102.05, 67.59; IR (cm^{-1}) 3410, 1620, 1509, 1445, 1375, 1335, 1267, 1195, 985, 835, 754; HRMS (ESI^-) *m/z* ($M-H^+$) calcd for $C_{34}H_{23}O_6$ 527.1495, found 527.1493.

4.1.10. Osmium oxidation of acetate analog of 2g to give 2i. A solution of *N*-methylmorpholine-*N*-oxide (16 mg) in a mixture of THF and H_2O (1/1, 6 mL) was mixed with a solution of OsO_4 in *tert*-butanol (20 mM, 0.2 mL) at 0 °C. To this solution, tetraacetate analog of **2g** (50 mg) in THF (2 mL) was added dropwise. The mixture was stirred for 3 days at room temperature. After the addition of 2 M HCl, the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and purified by recrystallization from a mixture of CH_2Cl_2 and hexane to give 46 mg of **2i** (87%). Colorless solid; mp 276.6–279.2 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J*=8.9 Hz, 1H), 7.92 (d, *J*=8.9 Hz, 1H), 7.82 (d, *J*=8.9 Hz, 1H), 7.81 (d, *J*=8.9 Hz, 1H), 7.32 (dd, *J*=8.9, 2.1 Hz, 2H), 7.31 (d, *J*=8.9 Hz, 1H), 7.27 (d, *J*=8.9 Hz, 1H), 7.20 (d, *J*=8.9 Hz, 1H), 7.15 (d, *J*=8.9 Hz, 2H), 7.14 (d, *J*=8.9 Hz, 1H), 6.34 (d, *J*=2.1 Hz, 1H), 6.30 (d, *J*=2.1 Hz, 1H), 4.09 (dt, *J*=9.6, 2.7 Hz, 1H), 3.95 (dt, *J*=9.6, 2.7 Hz, 1H), 3.78–3.63 (m, 4H), 1.98–1.82 (m, 2H), 1.98 (s, 3H), 1.97 (s, 3H), 1.90 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.43, 157.27, 157.03, 147.55, 146.90, 146.79, 134.65, 134.55, 131.41, 131.37, 129.74, 129.69, 129.44, 129.40, 128.05, 127.90, 127.19, 127.15, 124.11, 123.87, 123.17, 122.91, 122.15, 122.01, 119.62, 119.14, 118.86, 105.29, 105.08, 70.16, 70.04, 68.51, 67.93, 20.66, 20.62, 20.46; IR (cm^{-1}) 3493, 3020, 2934, 1759, 1625, 1507, 1437, 1369, 1322, 1210, 1020, 906, 838, 754, 666; HRMS (ESI^+) *m/z* ($M+Na^+$) calcd for $C_{42}H_{34}NaO_{12}$ 753.1948, found 753.1921.

4.1.11. Osmium oxidation of acetate analog of 2h to give 2j and 2k. Oxidation of tetraacetate analog of **2h** was performed the same as that for **2g**. The obtained mixture of **2j** and **2k** was partially separated by a silica gel column eluted with 25% CH_2Cl_2 in ether. Total yields are ca. 90% of a 1/1 mixture, but the isomers were isolated in 20–25% by a single column. Compound **2j**: Colorless solid; 256.5–259.8 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J*=8.9 Hz, 2H), 7.82 (d, *J*=8.9 Hz, 2H), 7.32 (d, *J*=8.9 Hz, 2H), 7.32 (d, *J*=8.9 Hz, 2H), 7.20 (d, *J*=8.9 Hz, 2H), 7.13 (dd, *J*=8.9, 2.7 Hz, 2H), 6.19 (d, *J*=2.7 Hz, 2H), 3.93–3.85 (m, 4H), 3.67–3.63 (m, 2H), 3.15–3.07 (m, 2H), 1.93 (s, 6H), 1.83 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.30, 156.54, 147.51, 146.86, 134.60, 131.19, 129.92, 129.39, 127.62, 127.14, 123.97, 123.20, 122.10, 119.61, 119.20, 104.18, 69.60, 69.16, 20.54, 20.52; IR (cm^{-1}) 3503, 2925, 1760, 1625, 1508, 1439, 1369, 1204, 1137, 1022, 974, 901, 838, 756; HRMS (ESI) *m/z* ($M+Na^+$) calcd for $C_{42}H_{34}NaO_{12}$ 753.1948, found 753.1929. Compound **2k**: colorless solid; 271.7–273.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.9 Hz, 2H), 7.81 (d, *J*=8.9 Hz, 2H), 7.31 (d, *J*=8.9 Hz, 2H), 7.29 (d, *J*=8.9 Hz, 2H), 7.15 (d, *J*=8.9 Hz, 2H), 7.13 (dd, *J*=8.9, 2.7 Hz, 2H), 6.55 (d, *J*=2.7 Hz, 2H), 3.93–3.89 (m, 4H), 3.67–3.64 (m, 2H), 2.67–2.45 (m, 2H), 2.01 (s, 6H), 1.87 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.82, 169.43, 157.31, 147.56, 146.76, 134.67, 131.66, 129.55, 129.44, 128.46, 127.14, 124.18, 122.78, 121.95, 119.53, 119.25, 106.08, 71.90, 68.48, 20.79, 20.59; IR (cm^{-1}) 3505, 2933, 1756, 1626, 1509, 1439, 1368, 1198, 1138, 1085, 1025, 974, 904, 837, 756; HRMS (ESI^+) *m/z* ($M+Na^+$) calcd for $C_{42}H_{34}NaO_{12}$ 753.1948, found 753.1979.

4.1.12. Hydrogenation of 2g and 2h to give 2d. A solution of **2g** (34 mg) and 5% Pd–C (30 mg) in THF (2 mL) was stirred for 1 day at room temperature under hydrogen atmosphere. The mixture was filtrated and purified by column chromatography on silica gel (5 g, elution with 50% ethyl acetate in hexane) to give 36 mg of **2d** (100%). The reaction of **2h** to give **2d** was also performed under the same conditions. Colorless solid; mp 188–195 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J*=8.9 Hz, 2H), 7.77 (d, *J*=8.9 Hz, 2H), 7.27 (d, *J*=8.9 Hz, 2H), 7.25 (d, *J*=8.9 Hz, 2H), 7.21 (d, *J*=8.9 Hz, 2H), 6.96 (dd, *J*=8.9, 2.7 Hz, 2H), 6.13 (d, *J*=2.7 Hz, 2H), 5.21 (s, 2H), 4.97 (s, 2H), 3.80–3.62 (m, 4H), 1.48–1.41 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 157.8, 151.4, 135.2, 131.2, 130.0, 129.3, 127.8, 125.0, 124.7, 119.0, 117.4, 115.0, 112.2, 110.0, 102.1, 66.6, 23.3; IR (cm^{-1}) 3434, 3063, 2956, 2359, 1621, 1511, 1445, 1376, 1335, 1268, 1201, 1159, 1340, 1026, 969, 834, 774, 703, 667; HRMS (ESI^-) *m/z* ($M-H^+$) calcd for $C_{34}H_{25}O_6$ 529.1651, found 529.1657; Anal. Calcd for $C_{42}H_{34}O_{10}$ (tetraacetate analog of **2d**) C: 72.20, H: 4.90; obsd C: 71.49, H: 5.58. HPLC (Chiralpak IA, elution with IPA/Hex=4/6, 1.00 mL/min, 250 nm), 8.7, 17.8 min. (*R*,*R*)-**2d**: $[\alpha]_D^{20}$ +30.9 (*c* 0.14, THF), (*S*,*S*)-**2d**: $[\alpha]_D^{20}$ −34.9 (*c* 0.12, THF). Optically active (*R*,*R*)- or (*S*,*S*)-**2d** was stable under following conditions for 5–6 days: diethylene glycol mono-methyl ether at 150 °C, diethylene glycol mono-methyl ether containing 5% of an aqueous 0.5 M sodium carbonate buffer (pH 9.5) at 70 °C, *p*-xylene at 100 °C, diethylene glycol mono-methyl ether containing 1% of Et_3N at 150 °C, *p*-xylene containing 1% of Et_3N at 100 °C.

4.1.13. Preparation of 5a and 5d. A solution of **2a** (101 mg), ethyl bromide (0.2 mL, 15 equiv), K_2CO_3 (317 mg, 13 equiv), and a catalytic amount of NaI in acetone (5 mL) was refluxed for 1 day. After cooling, the mixture was poured into water, extracted with ethyl acetate, dried over Na_2SO_4 and purified by column chromatography on silica gel (14 g, elution with 20% ethyl acetate in hexane) to give 108 mg of **5a** (89%). Colorless solid; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.9 Hz, 2H), 7.85 (d, *J*=8.9 Hz, 2H), 7.65 (d, *J*=8.9 Hz, 2H), 7.34 (d, *J*=8.9 Hz, 2H), 7.29 (d, *J*=8.9 Hz, 2H), 7.15 (dd, *J*=8.9, 2.4 Hz, 2H), 6.93 (d, *J*=2.4 Hz, 2H), 5.77 (ddt, *J*=17.2, 10.3, 5.5 Hz, 2H), 5.66 (d, *J*=3.4 Hz, 2H), 5.62 (d, *J*=3.4 Hz, 2H), 5.08 (dd, *J*=17.2, 1.4 Hz, 2H), 5.03 (dd, *J*=10.3, 1.4 Hz, 2H), 4.19 (d, *J*=5.5 Hz, 2H), 4.17 (d, *J*=5.5 Hz, 2H); HRMS (ESI^+) *m/z* ($M+Na^+$) calcd for $C_{38}H_{28}NaO_6$ 603.1784, found 603.1734.

By the same procedure, **2d** (71 mg) was converted into 71 mg of **5d** (96%). Colorless solid; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J*=8.9 Hz, 2H), 7.81 (d, *J*=8.9 Hz, 2H), 7.66 (d, *J*=8.9 Hz, 2H), 7.35 (d, *J*=8.9 Hz, 2H), 7.31 (d, *J*=8.9 Hz, 2H), 7.01 (dd, *J*=8.9, 2.4 Hz, 2H), 6.74 (d, *J*=2.4 Hz, 2H), 5.67 (d, *J*=3.4 Hz, 2H), 5.64 (d, *J*=3.4 Hz, 2H), 3.88 (dt, *J*=11.7, 4.7 Hz, 2H), 3.40 (dt, *J*=11.7, 4.7 Hz, 2H), 1.40–1.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.22, 152.19, 150.07, 133.43, 130.45, 130.21, 130.06, 128.91, 127.03, 126.12, 124.88, 121.50, 118.79, 118.25, 104.53, 103.02,

67.25, 21.36; IR (cm^{-1}) 2962, 1623, 1508, 1441, 1326, 1237, 1202, 1136, 1073, 841, 756; HRMS (ESI^+) *m/z* ($M+Na^+$) calcd for $C_{36}H_{26}O_6Na$ 557.1627, found 557.1609.

4.1.14. Preparation of 6a and 6d. A solution of **2a** (100 mg), dibromomethane (0.1 mL, 8 equiv), K_2CO_3 (303 mg, 13 equiv), and a catalytic amount of NaI in acetone (4 mL) was refluxed for 3 days. After cooling, the mixture was poured into water, extracted with ethyl acetate, dried over Na_2SO_4, and purified by column chromatography on silica gel (30 g, elution with 20% then 100% ethyl acetate in hexane) to give 69 mg of **6a** (66%). Colorless solid; ^1H NMR ($CDCl_3$) δ 7.84 (d, J=8.9 Hz, 2H), 7.76 (d, J=8.9 Hz, 2H), 7.26 (d, J=8.9 Hz, 2H), 7.22 (d, J=8.9 Hz, 2H), 7.13 (d, J=8.9 Hz, 2H), 7.02 (dd, J=8.9, 2.4 Hz, 2H), 6.61 (d, J=2.4 Hz, 2H), 5.84 (ddt, J=17.2, 10.7, 5.5 Hz, 2H), 5.12 (dd, J=17.2, 1.4 Hz, 2H), 5.08 (dd, J=10.7, 1.4 Hz, 2H), 4.25 (d, J=5.5 Hz, 2H), 4.24 (d, J=5.5 Hz, 2H), 4.00 (q, J=6.9 Hz, 2H), 3.97 (q, J=6.9 Hz, 2H), 3.94 (q, J=6.9 Hz, 2H), 3.91 (q, J=6.9 Hz, 2H), 1.00 (t, J=6.9 Hz, 2H), 0.99 (t, J=6.9 Hz, 2H); HRMS (ESI^+) *m/z* ($M+Na^+$) calcd for $C_{44}H_{44}NaO_6$ 691.3036, found 691.3045.

By the same procedure, **2d** (51 mg) was converted into 48 mg of **6d** (90%). Colorless solid; ^1H NMR ($CDCl_3$) δ 7.84 (d, J=8.9 Hz, 2H), 7.72 (d, J=8.9 Hz, 2H), 7.29 (d, J=8.9 Hz, 2H), 7.20 (d, J=8.9 Hz, 2H), 7.13 (d, J=8.9 Hz, 2H), 6.91 (dd, J=8.9, 2.4 Hz, 2H), 6.23 (d, J=2.4 Hz, 2H), 4.14 (q, J=6.9 Hz, 4H), 3.94 (q, J=6.9 Hz, 2H), 3.92 (q, J=6.9 Hz, 2H), 3.73–3.60 (m, 4H), 1.53–1.47 (m, 4H), 1.17 (t, J= 6.9 Hz, 6H), 1.01 (t, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 156.85, 155.36, 152.93, 135.95, 130.03, 129.62, 128.80, 126.88, 124.96, 121.25, 117.03, 113.61, 103.77, 66.79, 65.55, 65.49, 24.02, 15.33; IR (cm^{-1}) 2930, 1623, 1508, 1319, 1234, 1113, 1058, 828; HRMS (ESI^+) *m/z* ($M+Na^+$) calcd for $C_{42}H_{42}O_6Na$ 665.2879, found 665.2875.

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References and notes

1. For a recent review of BINOL, see: Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.
2. For a higher analog of TERNOL, see: Sugimura, T.; Kurita, S.; Inoue, S.; Fujita, M.; Okuyama, T.; Tai, A. *Enantiomer* **2001**, *6*, 35.
3. For other higher analogs of 2,3-naphthodiol connected at 1,4-poisons, see: Fuji, K.; Furuta, T.; Tanaka, K. *Org. Lett.* **2001**, *3*, 169 (correction 961); Belohradsky, M.; Budesinsky, M.; Gunterova, J.; Hodacova, J.; Holy, P.; Zavada, J.; Cisarova, I.; Podlaha, J. *J. Org. Chem.* **1996**, *61*, 1205.
4. Sugimura, T.; Inoue, S.; Tai, A. *Tetrahedron Lett.* **1998**, *39*, 6487.
5. Sugimura, T.; Wada, M.; Tai, A. *Enantiomer* **2000**, *5*, 23.
6. Belohradsky, M.; Budesinsky, M.; Hodacova, J.; Holy, P.; Zavada, J.; Cisarova, I.; Podlaha, J. *Tetrahedron* **1996**, *52*, 11013.
7. For a recent computational study for the isomerization mechanism of BINOL, see: Meca, L.; Reha, D.; Havlas, Z. *J. Org. Chem.* **2003**, *68*, 5677.
8. For general reviews, see: Grubbs, R. H.; Trnka, T. M. *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; pp 153–177; Schmidt, B.; Hermanns, J. *Metal Carbenes in Organic Synthesis*; Dötz, K. H., Ed.; Springer: Berlin, 2004; pp 223–267.
9. Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145; Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826.
10. Deussen, H. J.; Hendrickx, E.; Boutton, C.; Krog, D.; Clays, K.; Bechgaard, K.; Persoons, A.; Bjornholm, T. *J. Am. Chem. Soc.* **1996**, *118*, 6841.
11. Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Thomas, N. R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510.
12. Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2004**, *346*, 199.