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SELECTIVE FORMATION OF *TRANS/THREO/CIS* AND *CIS/THREO/CIS* BIS-TETRAHYDROFURANS FROM THE SAME DIENE DIOLS

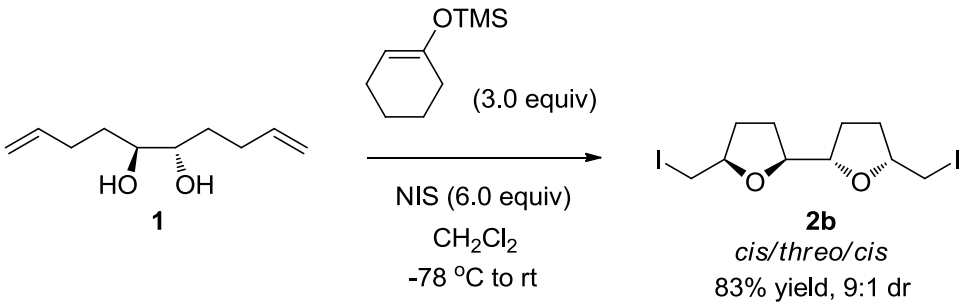
Hiromichi Fujioka,* Tomohiro Oki, Tatsuya Hayashi, Maki Yamakawa, Takeshi Kurachi, Kenji Nakahara, Ryota Maehata, Tomohito Hamada, Kenichi Murai, and Yasuyuki Kita

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan; E-mail: fujioka@phs.osaka-u.ac.jp

Abstract – Double intramolecular iodoetherification reactions of cyclic acetals and ketals, prepared from the same C_2-symmetric diene diol with aldehydes or ketones, stereoselectively afford *trans/threo/cis* or *cis/threo/cis* bis-THF ring systems.

INTRODUCTION

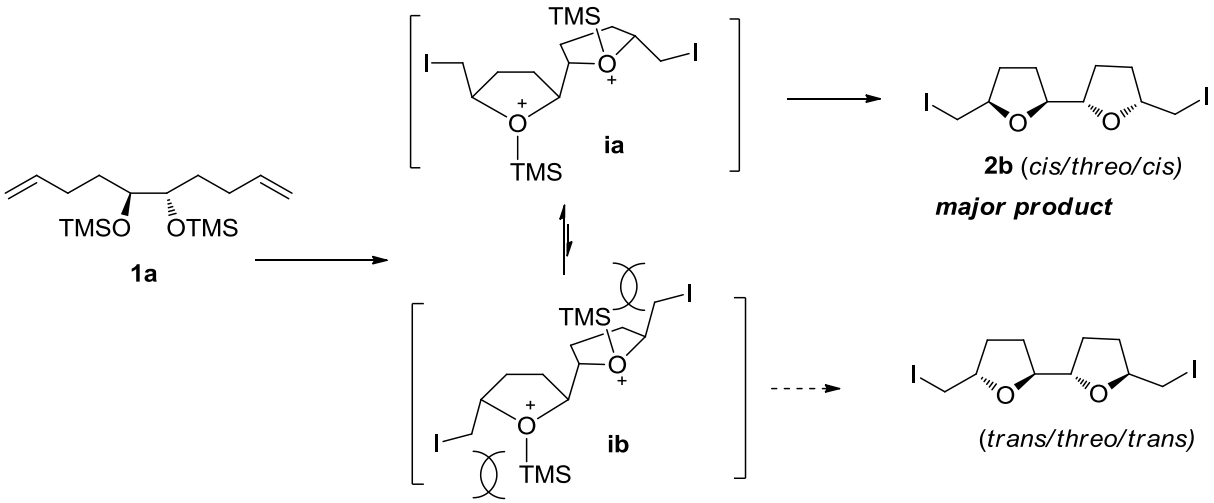
Substituted tetrahydrofuran (THF) ring systems are found in many biologically active natural products.[1-3] Moreover, bis-THF moieties, existing with different substitution patterns and stereochemistry (eg., *trans/threo/trans, cis/threo/cis, and trans/threo/cis*) are essential components of the structures of important naturally occurring substances including the Annonaceous acetogenins.[1] In a recent investigation, we developed a method for the efficient one-pot synthesis of the *cis/threo/cis* bis-THF **2b** that relies on the use of a double iodocyclization reaction of the C_2-symmetric diene diol **1** (Scheme 1), which is readily obtained from *trans*-1,5,9-decatriene by utilizing a regioselective Sharpless asymmetric dihydroxylation.[4] In that effort, we employed this method to prepare several members of the acetogenin family.[5,6]



Scheme 1

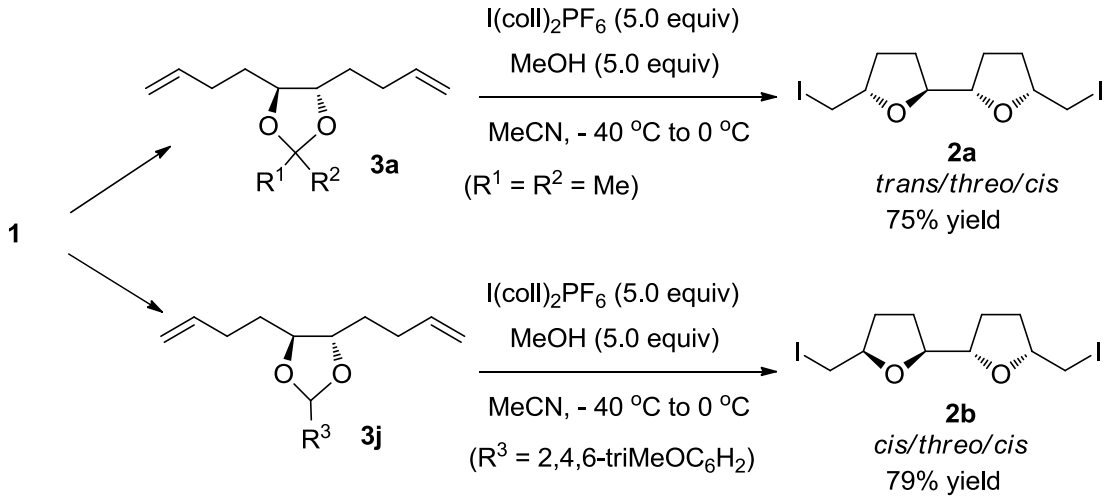
† *This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.*

An NMR investigation showed that in the route for generation of *cis/threo/cis* bis-THF **2b**, the diol **1** is first transformed to the bis-silyl ether **1a** by reaction with cyclohexanone silyl enol ether (Scheme 2). This substance then undergoes selective intramolecular iodoetherification to form **2b** via oxonium ion intermediate **ia**, which is of lower energy than its analog **ib** owing to steric repulsion between the *cis*-disposed silyl and iodomethyl groups in the latter one (Scheme 2).



Scheme 2. Plausible mechanism for stereoselective formation of *cis/threo/cis* bis-THF **2b**

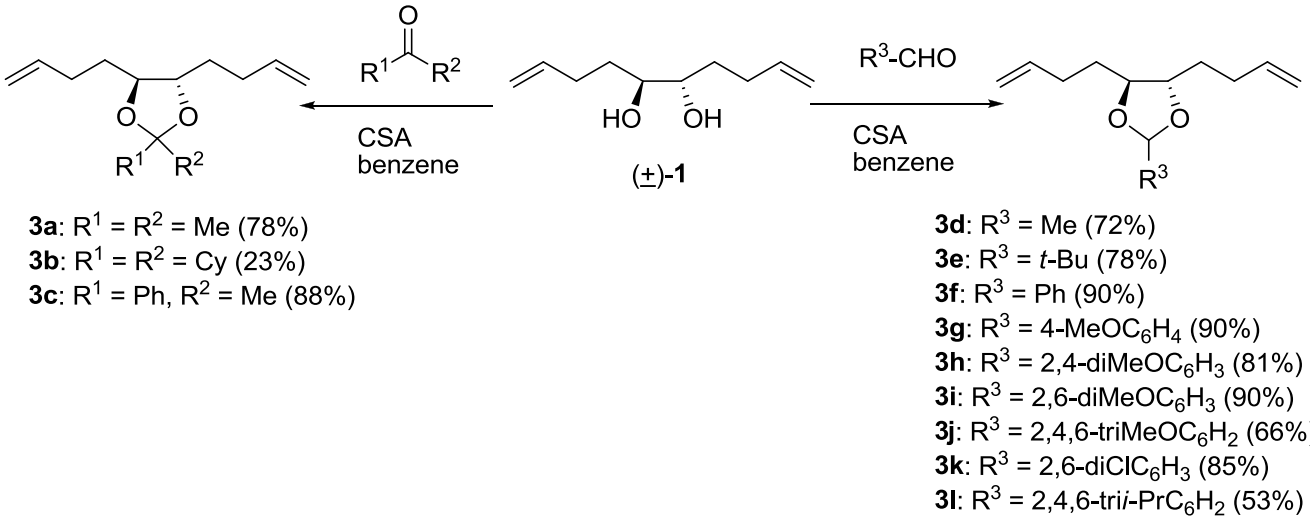
During the course of these studies, we also investigated intramolecular iodoetherification reactions of diene diol **1** derived cyclic acetals in the presence of MeOH.[7] In the current investigation described below, we discovered that the acetonide **3a** and 2,4,6-trimethoxybenzylidene acetal **3j** undergo efficient iodoetherification reactions to produce the respective *trans/threo/cis* and *cis/threo/cis* bis-THFs **2a** and **2b** (Scheme 3) with high degrees of stereoselectivity.



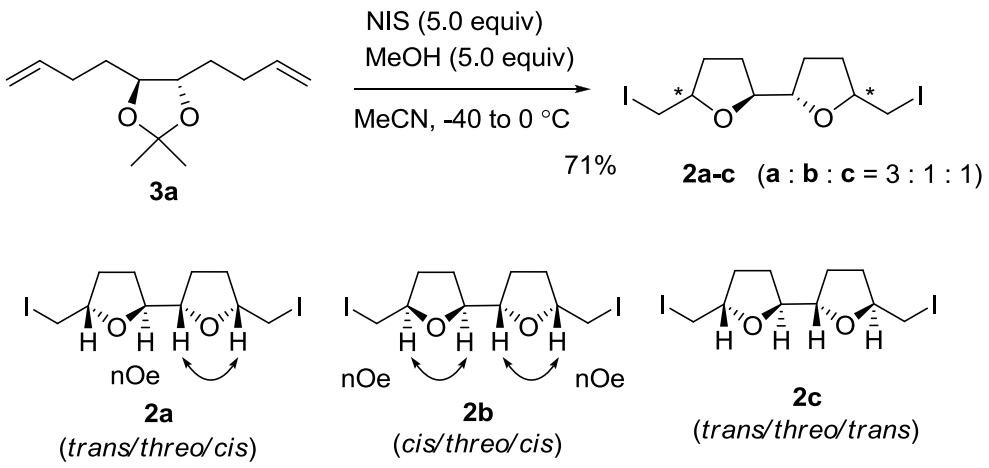
Scheme 3. Stereoselective formation of *trans/threo/cis* and *cic/threo/cis* bis-THFs

RESULTS AND DISCUSSION

Diene ketals **3a-c** and acetals **3d-l** were prepared by condensation reactions of the known C_2-symmetric diol **1**[8] with appropriate ketones and aldehydes. In the initial phase of the study, ketal **3a** was subjected to reaction with NIS in MeCN in the presence of MeOH. The ensuing tandem double intramolecular iodoetherification reaction took place to give the three, separable, diastereomeric bis-THFs **2a**, **2b** and **2c** in a total yield of 71% and a ratio of 3:1:1 (Scheme 5). Inspection of their ^{1}H NMR spectra showed that **2a** contains four different protons on oxygen-bonded carbons, whereas **2b** and **2c** each possess only two different protons of this type. These observations demonstrate that **2b** and **2c** possess C_2-symmetry while **2a** is non-symmetric. The results of ^{13}C NMR analysis support this conclusion. Furthermore, strong NOE effects are observed for protons on oxygen-bonded carbons in both **2a** and **2b**. Based on the combined findings, the structures of the bis-THFs were assigned to be *trans/threo/cis* for **2a**, *cis/threo/cis* for **2b**, and *trans/threo/trans* for **2c** (Scheme 5). Finally, the structures of **2b** and **2c** were unambiguously



Scheme 4. Syntheses of diene ketals and acetals

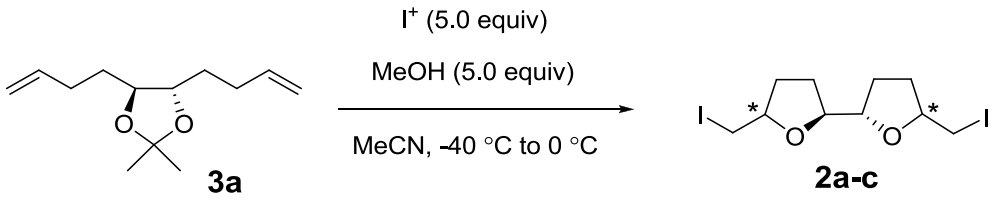


Scheme 5. NIS promoted intramolecular iodoetherification of **3a**

determined based on the observation that these substances have spectroscopic properties that are identical to those of bis-THFs prepared earlier.[5,9]

Although the intramolecular iodoetherification of **3a** takes place efficiently, the diastereoselctivity of the process is low. In order to improve the stereoselctivity, different iodonium ion sources were examined (Table 1). Inspection of the results of this effort, displayed in Table 1, shows that the use of $I(coll)_2ClO_4$[10] or $I(coll)_2PF_6$[11] in place of NIS leads to increased amounts of **2a**, with $I(coll)_2PF_6$ giving this *trans/threo/cis* isomer as the major product (90% yield, **2a**:**2b**:**2c** 10:1:1, Table 1, entry 3).

Table 1. Intramolecular iodoetherification reaction of **3a** using various iodonium ion sources

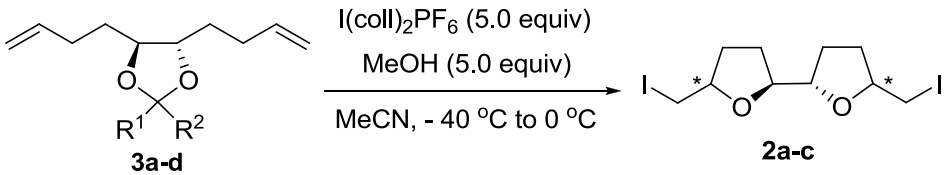


entry	I^+	yield (%)	dr (**2a** : **2b** : **2c**) [a]
1	NIS	71	3 : 1 : 1
2	$I(coll)_2ClO_4$	91	8 : 1 : 1
3	$I(coll)_2PF_6$	90	10 : 1 : 1

[a] Dr was determined by using ^{1}H NMR.

In Table 2 are displayed the results of intramolecular iodoetherification reactions of selected diene ketals and acetals **3a-d** derived from diene diol **1** (entry 1 is the same as entry 3 in Table 1). Dicyclohexylidene diene acetal **3b**, which contains more bulky cyclohexyl groups than **3a**, reacts to form bis-THFs **2a**, **2b** and

Table 2. Intramolecular iodoetherification reactions of diene cyclic acetals

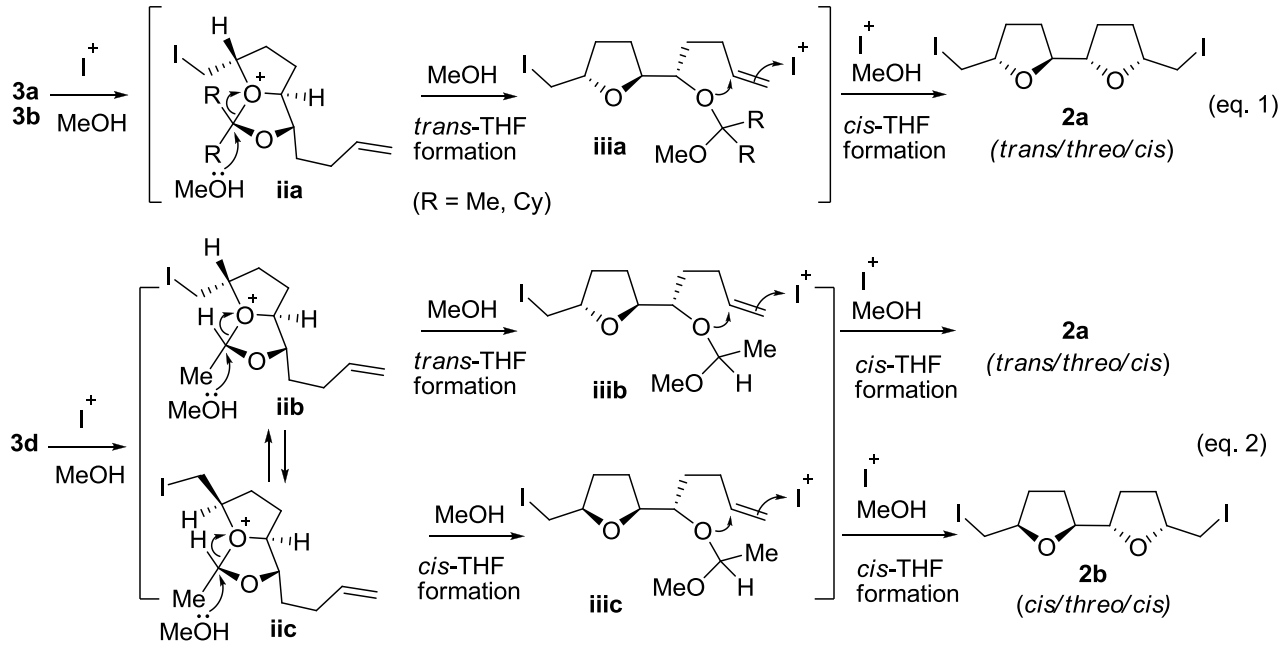


entry	substrate	R^1	R^2	yield (%)	dr (**2a** : **2b** : **2c**) [a]
1	**3a**	Me	Me	90	10 : 1 :1
2	**3b**	Cy	Cy	54	10 : 1 :1
3	**3c**	Ph	Me	95	6 : 1 : 1
4	**3d**	Me	H	95	6 : 5 : 2

[a] Dr was determined by using ^{1}H NMR.

2c in a lower yield (54%) but with a high level of diatereoselectivity (10:1:1, entry 2). On the other hand, reaction of the acetophenone derived ketal **3c**, possessing two different substituents on the acetal carbon, takes place with a decreased level of diastereoselectivity (**2a**:**2b**:**2c**, 6:1:1, entry 3). In a similar manner, reaction of the acetaldehyde derived acetal **3d** generates the *cis/threo/cis* isomer **2b** and the *trans/threo/cis* isomer **2a** in nearly equal yields (entry 4).[12]

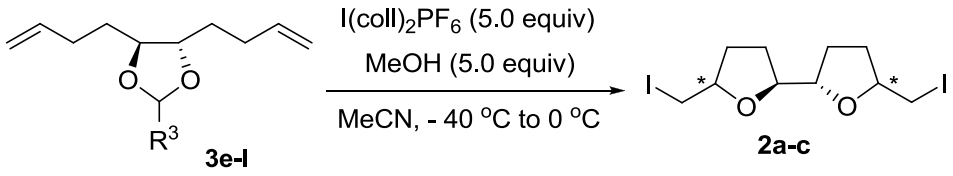
The stereochemical courses of the intramolecular iodoetherification reactions of diene ketals **3a** and **3b** as well as of the acetal **3d** can be rationalized by using the mechanistic schemes displayed in Scheme 6. In these processes, initial iodoetherification reactions occur between a ketal/acetal oxygen atom and the olefin to give the corresponding bicyclic oxonium ion intermediates **ii**. Intermediates **iia** is preferentially generated from **3a** and **3b** owing to the fact that the iodomethyl group is oriented in an exo fashion in the bicyclic ring system, thus minimizing repulsive interations between it and the ketal R groups. As a result, the *trans/threo/cis* isomer **2a** is produced as the major product in the second iodoetherification reaction via oxonium ion **iiia** (eq. 1). On the other hand, first iodoetherification reaction of **3d** occurs between an acetal oxygen atom and the less hindered olefin and the two possible oxonium intermediates **iib** and **iic** would arise. Intermediate **iib**, which leads to *trans*-THF ring formation in the pathway to bis-THF **2a** might have a steric repulsive interaction between the iodomethyl and methyl group, which is absent in the intermediate **iic**. Then, the reaction proceeds through fairly amount of **iic** to give **2b** (eq. 2). In each of these processes, formation of the second THF ring occurs in a *cis* manner (see Scheme 2, intermediate **ia**).



Scheme 6. Mechanistic rationale for stereochemical preferences in iodoetherification reactions of ketals **3a** and **3b**, and acetal **3d**

Utilizing the mechanistic considerations summarized above and in Scheme 6, we reasoned that by properly choosing the acetal groups the iodoetherification reaction could be tuned to give the *cis,cis* bis-THF isomer **2b** selectively. In order to explore this proposal, reactions of acetals **3e-l**, derived from various aldehydes, were examined (Table 3). The use of *tert*-butylidene acetal **3e** and benzylidene acetal **3f** as substrates does not cause an improvement in the ratio of **2a** to **2b** (entries 1, 2). An examination of diene acetals **3g-l**, prepared from substituted benzaldehydes, shows that the 4-methoxy and 2,4-dimethoxy isomers **3g** and **3h** react to generate near equal amounts of **2a** and **2b** (entries 3, 4). In contrast, iodoetherification of the 2,6-dimethoxy acetal **3i** produces **2b** as the major product, and the 2,4,6-trimethoxy analog **3j** reacts to form **2a** and **2b** in the best ratio of 1:5 (entries 5, 6). An examination of the effect of substituents at the 2,6-positions of the arene ring of the acetal revealed that 2,6-dichloro isomer **3k** reacts with the same level of diastereoselectivity as that of 2,6-dimethoxy derivative **3i**, whereas the 2,4,6-triisopropylphenyl acetal **3l**, containing more bulky isopropyl groups reacts to generate **2a** and **2b** in a 4:3 ratio (entries 7, 8). These results show the electronic effects of the substituents at the 2- and 6-positions of the arene ring of benzaldehyde derived acetals contribute to preferential formation of the *cis/threo/cis* isomer **2b**.

Table 3. Stereochemical optimization of the formation of the *cis,cis*-isomer **2b**

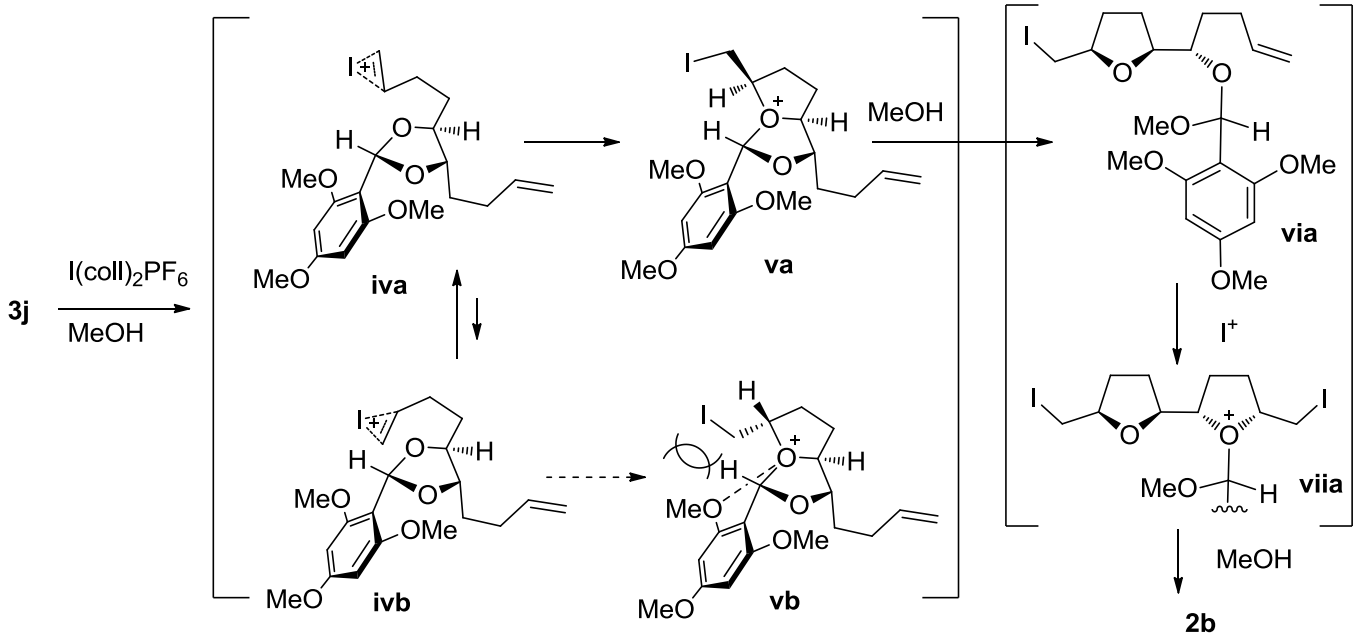


entry	substrate	R^3	yield (%)	dr (**2a** : **2b** : **2c**) [a]
1	**3e**	*t*-Bu	69	6 : 5 :1
2	**3f**	Ph	90	10 : 7 : 2
3	**3g**	4-$MeOC_6H_4$	78	8 : 8 : 3
4	**3h**	2,4-di$MeOC_6H_3$	88	4 : 5 : 1
5	**3i**	2,6-di$MeOC_6H_3$	80	1 : 4 : 0
6	**3j**	2,4,6-tri$MeOC_6H_2$	95	1 : 5 : 0
7	**3k**	2,6-diClC_6H_3	74	1 : 4 : 0
8	**3l**	2,4,6-tri*i*-PrC_6H_2	54	4 : 3 : 1

[a] Dr was determined by using ^{1}H NMR.

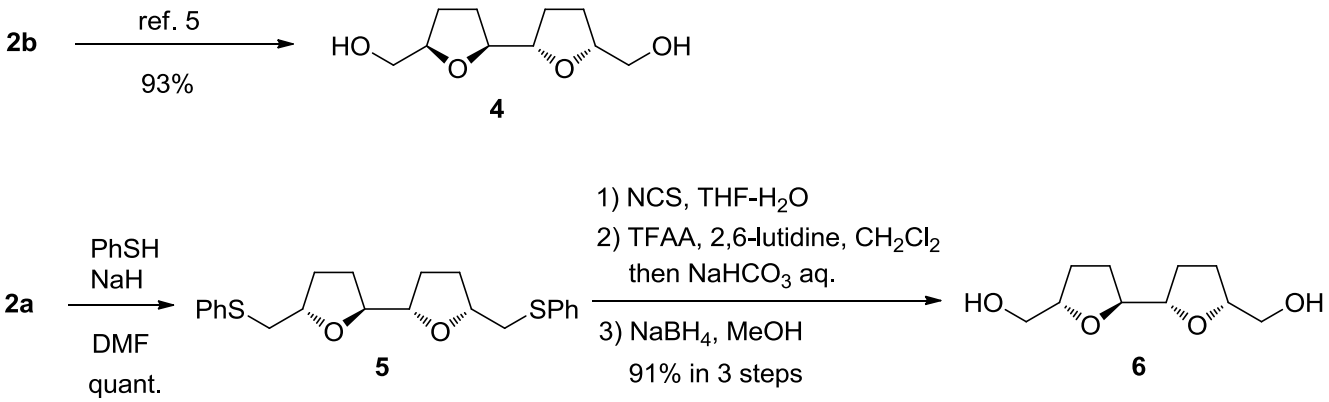
The observations described above suggest that a plausible mechanism for generation of *cis,cis* bis-THF isomer **2b** from diol-acetals involves a pathway in which formation of the second THF takes place in a *cis*

manner (Tables 2, 3) following generation of initial THF ring in a *cis* fashion. As shown in Scheme 7, reaction via transition states **iva** to **va** leads to **via** the precursor of **2b**. Reactions via intermediates **ivb** to **vb**, giving the *trans* THF ring, are possible however, in **vb**, the oxygen atom in the methoxy group might engage in an electronic interaction with the oxonium ion causing big repulsion between the iodomethyl and methyl groups.



Scheme 7. Plausible mechanism for formation of **2b** from **3j**

In an earlier effort, we demonstrated that **2b** can be transformed to the *cis/threo/cis* diol **4** by using a pathway that includes a key Pummerer rearrangement.[5] In a similar fashion, **2a** was converted to the *trans/threo/cis* diol **6**. Specifically, substitution reaction of **2a** with sodium thiophenolate produces bis-sulfide **5** in quantitative yield. Oxidation of **5** yields the corresponding bis-sulfoxide that then undergoes



Scheme 8. Conversion of diiodo compounds **2a,b** to dihydroxy compounds **4** and **6**

Pummerer rearrangement followed by reduction of the resulting bis-aldehyde to afford diol **6** in 91% yield (Scheme 8).

In the effort described above, we developed a stereoselective method for the preparation of *trans/threo/cis* and *cis/threo/cis* bis-THFs that utilizes an intramolecular iodoetherification reaction of cyclic acetals and ketals derived from the same C_2-symmetric diene-diol. The preparation of *cis/threo/cis* bis-THFs and their use in formal syntheses of several acetogenins have already been reported.[5] Consequently, the new method devised in the current study can be employed in an alternative route for the synthesis of this ring system. The *trans/threo/cis* bis-THF synthesis method also developed in this investigation has the potential of being applied to the preparation of natural products such as (+)-carolin A[13] that possess this ring system.

EXPERIMENTAL

General Information

Melting point (mp) was measured by Büchi B-545. Infrared spectra (IR) were recorded by Shimadzu FTIR 8400 using a diffuse reflectance measurement of samples dispersed in KBr powder. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 500, JNM-ECS 400, JNM-AL 300, JNM-EX 270 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet), coupling constant (Hz) and integration. Mass spectra were obtained on a Shimadzu GCMS-QP 5000 instrument with ionization voltages of 70 eV. Column chromatography and TLC were carried out on Merck Silica gel 60 (230-400 mesh), Kanto kagaku Silica gel 60N (40-50 μm, spherical, neutral), and Merck silica gel F_{254} plates (0.25 mm), respectively. The commercially available reagents were used without further purification.

Syntheses of diene ketals and acetals (Scheme 1)

General procedures for the acetalization of diol 1

The corresponding ketone or aldehyde was added to the solution of **1** in benzene (0.1 M), then CSA (0.1 equiv.) was added at rt under N_2. The mixture was stirred at rt overnight. The resulting solution was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the residue. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt = 10/1) gave the desired acetals **3a-l**.

Characterization data for optically active **1** and **3a** were described in ref. 14.

Diene diol (1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90-5.77 (m, 2H), 5.10-4.97 (m, 4H), 3.45 (d, J = 4.2 Hz, 2H), 2.35-2.10 (m, 4H), 1.63-1.51 (m, 4H).

Diene ketal (3a)

1 (544 mg, 3.05 mmol) was reacted with acetone (5 mL) to give **3a** (500.3 mg, 78%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90-5.77 (m, 2H), 5.08-4.97 (m, 4H), 3.65 (t, *J* = 3.6 Hz, 2H), 2.33-2.08 (m, 4H), 1.66-1.57 (m, 4H), 1.39 (s, 6H).

Diene ketal (3b)

1 (300 mg, 1.76 mmol) was reacted with dicyclohexylketone (1.71 g, 8.82 mmol) to give **3b** (138 mg, 23%) as a colorless oil.

IR (KBr) 2930, 1641, 1447, 1215, 1165, 912, 737, 652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.79 (m, 2H), 5.11-4.93 (m, 4H), 3.56-3.54 (m, 2H), 2.32-2.23 (m, 2H), 2.18-2.08 (m, 2H), 1.76-1.49 (m, 16H), 1.25-1.01 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 114.7, 114.3, 81.8, 43.8, 31.8, 30.7, 27.4, 27.3, 26.6, 26.5, 26.5; LRMS (FAB) *m/z* 369 (MNa^+); HRMS (FAB) calcd for $C_{23}H_{38}O_2Na$ 369.2770, found 369.2753.

Diene ketal (3c)

1 (45.3 mg, 0.266 mmol) was reacted with acetophenone (64.0 mg, 0.533 mmol) to give **3c** (63.8 mg, 88%) as a colorless oil.

IR (KBr) 2932, 1641, 1447, 1371, 1244, 1201, 912, 764, 702, 596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.34-7.25 (m, 3H), 5.87-5.74 (m, 2H), 5.08-4.94 (m, 4H), 3.77-3.73 (m, 1H), 3.53-3.48 (m, 1H), 2.36-2.08 (m, 4H), 1.78-1.58 (m, 2H), 1.62 (s, 3H), 1.45-1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.0, 137.9, 128.0, 127.5, 125.1, 115.0, 114.8, 108.1, 81.3, 80.4, 32.4, 31.7, 30.4, 30.2, 29.2; LRMS (FAB) *m/z* 273 (MH^+); HRMS (FAB) calcd for $C_{18}H_{25}O_2$ 273.1854, found 273.1849.

Diene acetal (3d)

1 (300 mg, 1.76 mmol) was reacted with acetaldehyde (777 mg, 17.6 mmol) to give **3d** (248 mg, 72%) as a colorless oil.

IR (KBr) 2249, 1641, 1416, 1265, 1148, 912, 755, 549 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.88-5.76 (m, 2H), 5.14-4.97 (m, 5H), 3.67-3.61 (m, 2H), 2.27-2.12 (m, 4H), 1.70-1.55 (m, 4H), 1.37 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.8, 115.0, 114.9, 100.0, 81.6, 80.3, 32.3, 30.1, 30.1, 20.2; LRMS (FAB) *m/z* 195 (MH^+); HRMS (FAB) calcd for $C_{12}H_{19}O_2$ 195.1385, found 195.1367.

Diene acetal (3e)

1 (150 mg, 0.882 mmol) was reacted with pivalaldehyde (152 mg, 1.76 mmol) to give **3e** (164 mg, 78%) as a colorless oil.

IR (KBr) 2957, 2340, 1641, 1483, 1217, 1109, 914, 771, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88-5.80 (m, 2H), 5.06-4.97 (m, 4H), 4.63 (s, 1H), 3.64-3.55 (m, 2H), 2.26-2.11 (m, 4H), 1.67-1,62 (m, 3H), 1.58-1.51 (m, 1H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 138.1, 114.8, 114.7, 109.0, 81.1, 80.4, 34.4, 32.1, 32.0, 30.1, 30.0, 27.2, 24.3; LRMS (FAB) *m/z* 237 (MH^+); HRMS (FAB) calcd for $C_{15}H_{25}O_2$ 237.1844, found 237.1832.

Diene acetal (3f)

1 (300 mg, 1.76 mmol) was reacted with benzaldehyde (375 mg, 3.53 mmol) to give **3f** (412 mg, 90%) as a colorless oil.

IR (KBr) 3078, 2933, 1641, 1219, 1091, 912, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.46 (m, 2H), 7.42-7.33 (m, 3H), 5.94-5.79 (m, 2H), 5.90 (s, 1H) 5.12-5.05 (m, 2H), 5.04-4.99 (m, 2H), 3.87-3.80 (m, 2H), 2.39-2.14 (m, 4H), 1.87-1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.8, 137.8, 129.2, 128.3, 126.7, 115.1, 115.0, 102.7, 82.0, 80.7, 32.2, 32.2, 30.1, 30.1; LRMS (FAB) *m/z* 281 (MNa^+); HRMS (FAB) calcd for $C_{17}H_{22}O_2Na$ 281.1517, foud 282.1542.

Diene acetal (3g)

1 (102 mg, 0.60 mmol) was reacted with 4-methoxybenzaldehyde (0.36 mL, 2.95 mmol) to give **3g** (155.4 mg, 90%) as a colorless oil.

IR (KBr) 3076, 2931, 1614, 1517, 1247, 1170, 1087, 912, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 6.93-6.88 (m, 2H), 5.93-5.79 (m, 2H), 5.85 (s, 1H), 5.10-4.98 (m, 4H), 3.83-3.79 (m, 5H), 2.31-2.17 (m, 4H), 1.80-1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.3, 138.3, 130.7, 114.7, 114.7, 113.4, 104.5, 97.2, 82.0, 80.2, 55.8, 32.2, 31.3, 30.2, 30.1; LRMS (FAB) *m/z* 289 (MH^+); HRMS (FAB) calcd for $C_{18}H_{25}O_3$ 289.1725, found 289.1827.

Diene acetal (3h)

1 (58 mg, 0.34 mmol) was reacted with 2,4-dimethoxybenzaldehyde (170 mg, 1.02 mmol) to give **3h** (88.0 mg, 81%) as a colorless oil.

IR (KBr) 2935, 1614, 1512, 1284, 1209, 1159, 1068, 912, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8 Hz, 1H), 6.51 (dd, J = 2, 8 Hz, 1H), 6.43 (d, J = 2 Hz, 1H), 6.19 (s, 1H), 5.91-5.80 (m, 2H), 5.08-4.98 (m, 4H), 3.85-3.77 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.35-2.16 (m, 4H), 1.84-1.59 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.8, 138.1, 138.0, 128.4, 118.6, 114.9, 114.9, 104.6, 98.4, 97.6, 81.6, 80.3, 55.6, 55.4, 32.3, 32.2, 30.1, 30.0; HRMS (MALDI-TOF) calcd for $C_{19}H_{26}O_4Na$ 341.1729, found 341.1723.

Diene acetal (3i)

1 (100 mg, 0.59 mmol) was reacted with 2,6-dimethoxybenzaldehyde (490 mg, 2.95 mmol) to give **3i** (152 mg, 90%) as a colorless oil.

IR (KBr) 2933, 1597, 1479, 1253, 1114, 912, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8 Hz, 1H), 6.59 (s, 1H), 6.54 (d, *J* = 8 Hz, 2H), 5.91-5.81 (m, 2H), 5.08-5.03 (m, 2H), 5.00-4.97 (m, 2H), 3.92-3.87 (m, 1H), 3.80 (s, 6H), 3.78-3.72 (m, 1H), 2.37-2.15 (m, 4H), 1.87-1.59 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.3, 138.3, 130.7, 114.7, 114.7, 113.4, 104.5, 97.2, 82.0, 80.2, 55.8, 32.2, 31.3, 30.2, 30.1; HRMS (MALDI-TOF) calcd for $C_{19}H_{26}O_4Na$ 341.1729, found 341.1723.

Diene acetal (3j)

1 (204 mg, 1.20 mmol) was reacted with 2,4,6-trimethoxybenzaldehyde (705 mg, 3.59 mmol) to give **3j** (275 mg, 66%) as a colorless oil.

IR (KBr) 2935, 1608, 1454, 1207, 1157, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.10 (s, 2H), 5.91-5.81 (m, 2H), 5.08-5.03 (m, 2H), 4.99-4.97 (m, 2H), 3.88-3.83 (m, 1H), 3.79 (s, 3H), 3.79 (s, 6H), 3.74-3.69 (m, 1H), 2.36-2.14 (m, 4H), 1.85-1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 160.6, 138.3, 114.7, 114.7, 106.3, 97.3, 91.1, 81.9, 80.0, 55.8, 55.3, 35.2, 32.2, 31.4, 30.2, 30.1, 26.9; HRMS (MALDI-TOF) calcd for $C_{20}H_{29}O_5$ 349.1937, found 349.2010.

Diene acetal (3k)

1 (100 mg, 0.59 mmol) was reacted with 2,6-dichrolobenzaldehyde (516 mg, 2.95 mmol) to give **3k** (161 mg, 85%) as a colorless oil.

IR (KBr) 2929, 1566, 1444, 1193, 1109, 912, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.20 (dd, *J* = 7.4, 8.5 Hz, 1H), 6.56 (s, 1H), 5.91-5.80 (m, 2H), 5.10-5.05 (m, 2H), 5.02-4.99 (m, 2H), 3.98 (dq, *J* = 3.6, 6.3 Hz, 1H), 3.84 (dq, *J* = 3.6, 8.0 Hz,1H), 2.37-2.16 (m, 4H), 1.98-1.88 (m, 1H), 1.82-1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.8, 136.0, 131.0, 130.6, 129.5, 115.1, 115.1, 99.6, 82.8, 80.8, 32.5, 31.0, 30.3, 30.2; HRMS (MALDI-TOF) calcd for $C_{17}H_{21}O_2Cl_2$ 327.0840, found 327.0913.

Diene acetal (3l)

1 (32 mg, 0.19 mmol) was reacted with 2,4,6-triisopropylbenzaldehyde (65 mg, 0.28 mmol) to give **3l** (39 mg, 53%) as a colorless oil.

IR (KBr) 2960, 1608, 1462, 1060, 912, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 6.31 (s, 1H), 5.88-5.81 (m, 2H), 5.07-4.98 (m, 4H), 3.78 (s, 2H), 3.55-3.50 (m, 2H), 2.87-2.82 (m, 1H), 2.29-2.19 (m, 4H), 1.79-1.64 (m, 4H), 1.26-1.20 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 148.9, 138.0, 137.9, 126.6, 121.7, 115.1, 115.0, 99.3, 82.1, 79.9, 34.3, 32.9, 30.4, 30.2, 28.7, 24.5, 24.2, 23.9; HRMS

(MALDI-TOF) calcd for $C_{26}H_{40}O_2Na$ 407.2926, found 407.2921.

General procedures for the intramolecular iodoetherification of diene ketals and acetals (Tables 1-3)

The corresponding alcohol (5.0 equiv.) was added to the corresponding solution of **3** (0.1 M, 1.0 equiv.), then the corresponding I^+ reagent (5.0 equiv.) was added at -40 °C under N_2 and the mixture was allowed to warm to 0 °C under stirring for 4 h. After checking the reaction by TLC, the resulting solution was quenched by addition of saturated aqueous $Na_2S_2O_3$. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the residue. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt = 8/1) gave **2a-c**.

Compounds **2b** and **2c** are already reported in refs. 5 and 9.

Diiodide (2a)

MeOH (28.9 μl, 0.713 mmol) was added to the solution of **3a** (30 mg, 0.143 mmol) in CH_2Cl_2 (1.43 mL), then $I(coll)_2PF_6$ (367 mg, 0.713 mmol) was added at -78 °C under N_2. The mixture was allowed to warm to 0 °C under stirring for 4 h. The resulting solution was quenched by addition of saturated aqueous $Na_2S_2O_3$. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the residue. Purification of the residue by SiO_2 column chromatography (hexane/AcOEt = 8/1) gave **2a** (40.7 mg, 75%), **2b** (4.1 mg, 7.5%) and **2c** (4.1 mg, 7.5%).

2a: colorless oil; IR (KBr) 2987, 2885, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.16-4.02 (m, 3H), 3.87 (dd, *J* = 6.9, 12.6 Hz, 1H), 3.32-3.26 (m, 2H), 3.17 (dd, *J* = 7.8, 9.6 Hz, 2H), 2.28-2.20 (m, 1H), 2.12-2.01 (m, 2H), 1.93-1.63 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.1, 82.1, 79.1, 32.5, 31.3, 28.7, 27.5, 10.5, 10.5; HRMS (MALDI-TOF) calcd for $C_{10}H_{16}I_2O_2Na$ 444.9137, found 444.9131.

Conversion of 2a to dihydroxy compound 6 (Scheme 8)

Sulfide (5)

Under a nitrogen atmosphere, NaH (218 mg, 5.45 mmol) was added to a solution of PhSH (0.57 mL, 5.45 mmol) in DMF (7 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h. A solution of **2a** (591.9 mg, 1.402 mmol) in DMF (0.5 mL) was added to the mixture at rt. The reaction mixture was stirred for 1 h at rt, then the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt. The organic layer was washed with water, then brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (AcOEt/hexane = 1/5) to give **5** (552.2 mg, quant.) as a colorless oil.

IR (KBr) 2968, 2872, 1047, 912, 742, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H),

7.28-7.23 (m, 4H), 7.18-7.12 (m, 2H), 4.24-4.06 (m, 2H), 3.96 (dd, *J* = 7.2, 13.2 Hz, 1H), 3.79 (dd, *J* = 6.9, 12.9 Hz, 1H), 3.79 (m, 1H), 3.30-3.20 (m, 2H), 2.94-2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 136.4, 129.1, 129.0, 128.9, 128.9, 125.9, 125.9, 82.5, 81.8, 78.5, 76.7, 38.6, 38.4, 31.5, 30.5, 28.5, 27.6; HRMS (MALDI-TOF) calcd for $C_{22}H_{26}O_2NaS_2$ 409.1272, found 409.1266.

Diol (6)

NCS (10.2 mg, 0.0763 mmol) was added to a solution of **5** (13.4 mg, 0.0347 mmol) in THF (0.3 mL) and H_2O (86.0 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 10/1) to give **sulfoxide** as a colorless oil. 2,6-Lutidine (28.4 μL, 0.243 mmol) and trifluoroacetic anhydride (34.0 μL, 0.243 mmol) were added to a solution of **sulfoxide** in CH_2Cl_2 (0.3 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, H_2O and excess solid $NaHCO_3$ were added to the mixture at rt. After being stirred at rt for 2 h, the mixture was evaporated in vacuo and the crude product was used without further purification. Excess $NaBH_4$ was added to the solution of the crude product in MeOH (0.3 mL) at 0 °C (checked by TLC). After being stirred at 0 °C for 6 h, the reaction was quenched with 1 N HCl and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 10/1) to give **6** (6.39 mg, 91%) as a colorless oil.

IR (KBr) 3323, 2924, 2874, 1659, 1045, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18-4.11 (m, 2H), 3.99-3.87 (m, 2H), 3.80-3.71 (m, 2H), 3.54-3.47 (m, 2H), 2.04-1.80 (m, 5H), 1.78-1.72 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 82.1, 82.0, 80.3, 80.2, 64.8, 64.2, 28.9, 28.2, 27.2, 26.8; HRMS (MALDI-TOF) calcd for $C_{10}H_{18}O_4Na$ 225.1103, found 225.1097.

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