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

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Abstract – Double intramolecular iodoetherification reactions of cyclic acetals and ketals, prepared from the same C\textsubscript{2}-symmetric diene diol with aldehydes or ketones, stereoselectively afford \textit{trans/threo/cis} or \textit{cis/threo/cis} bis-THF ring systems.

INTRODUCTION

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

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{1}};
\node (b) at (3,0) {\textbf{2b}};
\node (c) at (1.5,0) {\textbf{OTMS}};
\node (d) at (1.5,-1) {\textbf{NIS (6.0 equiv)}};
\node (e) at (0,-2) {\textbf{CH\textsubscript{2}Cl\textsubscript{2}}};
\node (f) at (0,-3) {-78 °C to rt};
\node (g) at (1.5,-2) {cis/threo/cis};
\node (h) at (1.5,-3) {83% yield, 9:1 dr};
\draw[->] (a) -- (b);
\draw[->] (a) -- (c);
\draw[->] (a) -- (d);
\draw[->] (a) -- (e);
\draw[->] (a) -- (f);
\draw[->] (a) -- (g);
\draw[->] (a) -- (h);
\end{tikzpicture}
\end{center}

\textsuperscript{†} 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. 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 cis/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 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 assigned.

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.  

Although the intramolecular iodoetherification of 3a takes place efficiently, the diastereoselectivity of the process is low. In order to improve the stereoselectivity, 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)₂ClO₄ or I(coll)₂PF₆ in place of NIS leads to increased amounts of 2a, with I(coll)₂PF₆ 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

<table>
<thead>
<tr>
<th>entry</th>
<th>I⁺</th>
<th>yield (%)</th>
<th>dr (2a : 2b : 2c) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NIS</td>
<td>71</td>
<td>3 : 1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>I(coll)₂ClO₄</td>
<td>91</td>
<td>8 : 1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>I(coll)₂PF₆</td>
<td>90</td>
<td>10 : 1 : 1</td>
</tr>
</tbody>
</table>

a Dr was determined by using ¹H 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

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R¹</th>
<th>R²</th>
<th>yield (%)</th>
<th>dr (2a : 2b : 2c) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Me</td>
<td>Me</td>
<td>90</td>
<td>10 : 1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Cy</td>
<td>Cy</td>
<td>54</td>
<td>10 : 1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Ph</td>
<td>Me</td>
<td>95</td>
<td>6 : 1 : 1</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>Me</td>
<td>H</td>
<td>95</td>
<td>6 : 5 : 2</td>
</tr>
</tbody>
</table>

a Dr was determined by using ¹H NMR.
2c in a lower yield (54%) but with a high level of diastereoselectivity (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 iia (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

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R$^3$</th>
<th>yield (%)</th>
<th>dr (2a : 2b : 2c)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3e</td>
<td>t-Bu</td>
<td>69</td>
<td>6 : 5 :1</td>
</tr>
<tr>
<td>2</td>
<td>3f</td>
<td>Ph</td>
<td>90</td>
<td>10 : 7 :2</td>
</tr>
<tr>
<td>3</td>
<td>3g</td>
<td>4-MeOC$_6$H$_4$</td>
<td>78</td>
<td>8 : 8 :3</td>
</tr>
<tr>
<td>4</td>
<td>3h</td>
<td>2,4-diMeOC$_6$H$_3$</td>
<td>88</td>
<td>4 : 5 :1</td>
</tr>
<tr>
<td>5</td>
<td>3i</td>
<td>2,6-diMeOC$_6$H$_3$</td>
<td>80</td>
<td>1 : 4 :0</td>
</tr>
<tr>
<td>6</td>
<td>3j</td>
<td>2,4,6-triMeOC$_6$H$_2$</td>
<td>95</td>
<td>1 : 5 :0</td>
</tr>
<tr>
<td>7</td>
<td>3k</td>
<td>2,6-diClC$_6$H$_3$</td>
<td>74</td>
<td>1 : 4 :0</td>
</tr>
<tr>
<td>8</td>
<td>3l</td>
<td>2,4,6-tri-PrC$_6$H$_2$</td>
<td>54</td>
<td>4 : 3 :1</td>
</tr>
</tbody>
</table>

$^a$ 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. 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 C2-symmetric diene-diol. The preparation of cis/threo/cis bis-THFs and their use in formal syntheses of several acetogenins have already been reported. 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 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. 1H NMR and 13C NMR spectra were recorded on a JEOL JNM-LA 500, JNM-ECS 400, JNM-AL 300, JNM-EX 270 spectrometer in CDCl3 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 F254 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 N2. The mixture was stirred at rt overnight. The resulting solution was quenched by addition of saturated aqueous NaHCO3. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na2SO4 and concentrated in vacuo to give the residue. Purification of the residue by SiO2 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)**

1H NMR (300 MHz, CDCl3) 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$_3$) $\delta$ 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, 737, 652 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$Na 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, 1215, 1165, 737, 652 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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) $m/z$ 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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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) \textit{m/z} 237 (MH\(^+\)); HRMS (FAB) calcd for C\(_{15}\)H\(_{25}\)O\(_2\) 237.1844, found 237.1832.

**Diene acetal (3f)**

\(\text{I} \) (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, 742 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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) \textit{m/z} 281 (MNa\(^+\)); HRMS (FAB) calcd for C\(_{17}\)H\(_{22}\)O\(_2\)Na 281.1517, found 282.1542.

**Diene acetal (3g)**

\(\text{I} \) (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\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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) \textit{m/z} 289 (MH\(^+\)); HRMS (FAB) calcd for C\(_{18}\)H\(_{25}\)O\(_3\) 289.1725, found 289.1827.

**Diene acetal (3h)**

\(\text{I} \) (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\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_3\)Na 341.1729, found 341.1723.

**Diene acetal (3i)**
I (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, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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 C19H26O4Na 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, CDCl3) 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), 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); 13C NMR (100 MHz, CDCl3) δ 162.0, 160.6, 138.3, 138.3, 130.7, 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 C20H29O5 349.1937, found 349.2010.

Diene acetal (3k)

1 (100 mg, 0.59 mmol) was reacted with 2,6-dichlorobenzaldehyde (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, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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 C17H12O2Cl2 327.0840, found 327.0913.

Diene acetal (3l)

1 (32 mg, 0.19 mmol) was reacted with 2,4,6-trisopropylbenzaldehyde (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, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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
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\(_2\)S\(_2\)O\(_3\). The mixture was extracted with AcOEt. The organic layer was
washed with brine, dried over Na\(_2\)SO\(_4\) 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 \(\mu\)l, 0.713 mmol) was added to the solution of 3a (30 mg, 0.143 mmol) in CH\(_2\)Cl\(_2\) (1.43 mL),
then I(coll)\(_2\)PF\(_6\) (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\(_2\)S\(_2\)O\(_3\).
The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na\(_2\)SO\(_4\) 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%).

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\(_4\)Cl. The mixture was extracted with AcOEt. The organic layer was washed with water, then brine, dried over Na\(_2\)SO\(_4\), 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\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta = 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\(_2\)NaS\(_2\) 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\(_2\)O (86.0 \(\mu\)L) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous Na\(_2\)S\(_2\)O\(_3\). The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na\(_2\)SO\(_4\), and evaporated in vacuo. The residue was purified by SiO\(_2\) column chromatography (CH\(_2\)Cl\(_2\)/MeOH = 10/1) to give sulfoxide as a colorless oil. 2,6-Lutidine (28.4 \(\mu\)L, 0.243 mmol) and trifluoroacetic anhydride (34.0 \(\mu\)L, 0.243 mmol) were added to a solution of sulfoxide in CH\(_2\)Cl\(_2\) (0.3 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, H\(_2\)O 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\(_2\)Cl\(_2\)/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\(_3\)) \(\delta = 4.18-4.11\) (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\(_3\)) \(\delta = 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\(_4\)Na 225.1103, found 225.1097.

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REFERENCES

6. Abbreviation ‘dr’ is a diastereomeric ratio.
7. Mootoo et al. reported an intramolecular haloetherification of ene acetonides, their method afforded single *trans*-THF ring only and *cis*-one could not be obtained (H. Zhang and D. R. Mootoo, *J. Org. Chem.*, 1995, **60**, 8134). However, it needed several steps for the conversion of their single THF ring to the bis-THF rings (H. Zhang, M. Seepsaurd, S. Seepsaurd, and D. R. Mootoo, *J. Org. Chem.*, 1998, **63**, 2049). We also have many experiences of the intramolecular haloetherification of ene and diene acetals prepared by the reaction of chiral hydrobenzoin and ene and diene aldehydes or ketones. See: H. Fujioka, *Synlett*, 2012, **23**, 825.
8. Racemic 1 was used.
12. For comparison, diene diol 1 was treated under the same reaction conditions to give 2a and 2c with a low diastereoselectivity (71%, 2a : 2b : 2c = 5 : 0 : 7).