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Asymmetric Spirocyclization: A New Type of Acid-catalyzed Intramolecular 1,4-Addition to Form Carba-spirocyclic Compounds

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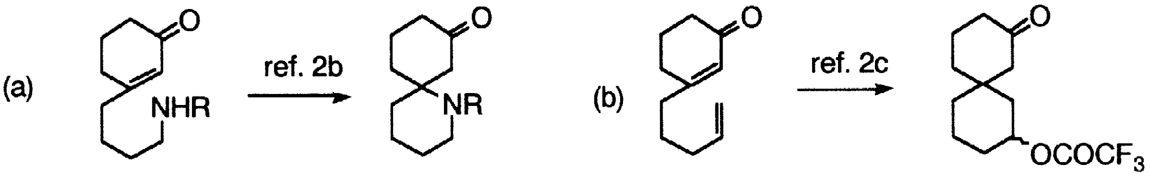
Abstract: Novel spirocyclization based on intramolecular 1,4-addition and its asymmetric version have been developed using a combination of Lewis acid and 1,2-diol. Treatment of five- and six-membered α,β-unsaturated cyclic ketones having a 4-oxopentyl group at the β-position with Lewis acid and ethylene glycol gave spiro[4.5]decane-2,7-dione and spiro[5.5]undecane-2,8-dione, respectively. The asymmetric version of this reaction has been developed by using optically active 1,2-diol such as cyclohexane-1,2-diol to afford the spirocyclic products of up to 85% e.e. © 1998 Elsevier Science Ltd. All rights reserved.

Previously, we had reported asymmetric ring transformations based on an intra- and/or inter-molecular aldol reaction by using a combination of Lewis acid and chiral 1,2-diol.[1] Throughout these studies, we postulated a new concept for asymmetric induction, namely, that activation of the carbonyl function as a chiral enol ether provides a new type of nucleophile. In application of this concept, we studied a new type of spirocyclization based on intramolecular 1,4-addition together with its asymmetric version.[2a]

Easy accesses to construction of spiro[5.5]undecane ring systems based on intramolecular 1,4-addition had been reported by several groups,[2] which could be divided into two types of reactions. One is amine spirocyclization, in which a nitrogen atom acts as a nucleophile to afford 7-aza product[2b] (Scheme 1 (a)). The other is a reaction to afford carba-spirocyclic products. As its typical example, cationic π-cyclization under acidic conditions had been reported by Danishefsky *et al.*[2c] (Scheme 1 (b)). And there had been no precedent for spirocyclization, in which a carbon nucleophile such as an enol (or enolate) intramolecularly attacks to the enone system.

Scheme 1



Spirocyclization in an achiral version

Substrates **3**, **4** and **6** were designed for the spirocyclization and prepared in reasonable yields by a conventional sequence of reactions as shown in Scheme 2.

At first, a preliminary study of spirocyclization of compound **3** into spiro[5.5]undecane-2,8-dione **7** was made under the basic conditions using lithium diisopropylamide (LDA) in THF at -78°C. This reaction actually afforded **7**, but the yield was very low (4 %). In this reaction, we suspected that compounds **3** and **7** might be in equilibrium under the basic conditions employed. But a treatment of **7** under the same reaction conditions did not afford **3**, and **7** was recovered. It was found that the basic conditions were not suitable for this spirocyclization.

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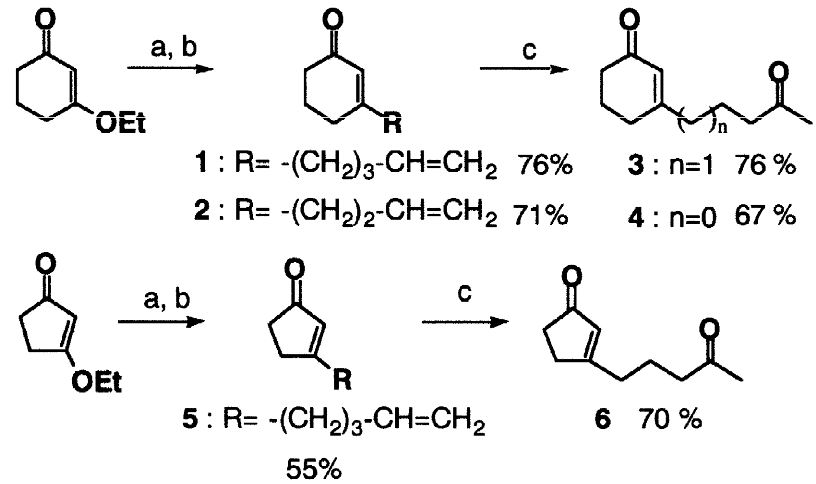
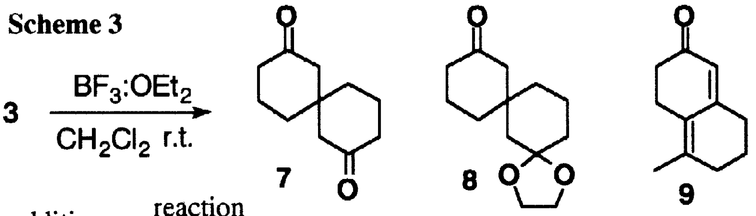
Scheme 2[a]



[a]Reagents: a) RMgBr; b) HCl; c) $PdCl_2$, CuCl, O_2

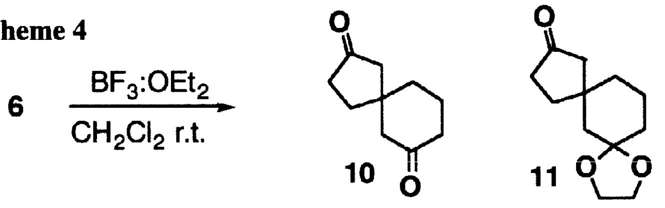
Next, the reaction of **3** under acidic conditions was studied. Treatment of **3** with boron trifluoride etherate (BF_3:OEt_2; 2 equiv.) in CH_2Cl_2 at room temperature gave the desired **7** in 31% yield and bicyclic product **9** in 30 % yield with recovery of **3** in 28% yield. This reaction was so slow that prolonged reaction time (3 days) was required. Taking into consideration the role of ethylene glycol in our previous studies on ring transformations,[1] addition of ethylene glycol (3 equiv.) to this reaction system remarkably accelerated the reaction rate to give **7** and monoethylene acetal **8** in 55% and 16% yields, respectively. Totally, the spirocyclized products were obtained in 71% yield and the consumption of **3** was confirmed in 2 h. The formation of aldol-dehydration product **9** was not observed in this reaction (Scheme 3).

Scheme 3



additive	reaction time	**7**	**8**	**9**	recovery of **3**
—	3 d	31 %	—	30 %	28 %
HO OH	2 h	55 %	16 %	—	—

Scheme 4



additive	reaction time	**10**	**11**	recovery of **6**
—	3 d	12 %	—	83%
HO OH	2 h	33 %	18 %	—

Similar results were also observed in the case of using compound **6** as a substrate. In treatment of **6** with BF_3:OEt_2 (2 equiv.) without ethylene glycol for 3 d, the desired spiro[4.5]decane-2,7-dione **10** was obtained in 12% yield. On the other hand, in the presence of ethylene glycol (3 equiv.), substrate **6** was completely consumed after 2 h to give **10** and **11** in 33% and 18% yields, respectively (Scheme 4). The structure of spirocyclic compounds **7**, **8**, **10** and **11** was determined by spectroscopic analyses. Among them, the position of the ethylene acetal function in **11** was determined based on the following data. In the IR spectrum of **10**, signals attributable to the five-membered ketone (1745 cm^{-1}) and six-membered ketone (1709 cm^{-1}) were observed. And the former signal (1740 cm^{-1}) was only observed in that of **11**. Additionally, in the ^{13}C NMR spectrum of **10**, the ketonic carbons on the five-membered ring (217 ppm) and six-membered ring (210 ppm) were observed. In that of **11**, the former signal (220 ppm) was retained and the latter disappeared. This regioselective acetalization might be a remarkable result for mechanistic consideration of this spirocyclization as discussed later.

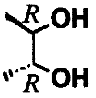
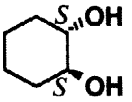
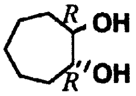
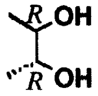
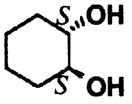
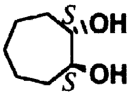
Contrary to the above successful results under acidic conditions, spirocyclization of compound **4** did not proceed at all even in the presence of ethylene glycol and resulted in recovery of the substrate. The results of three types of substrates **3**, **4** and **6** were rationalized based on Baldwin's rule.[3] That is to say, cyclization of **3** and **6** (six-membered formation) could be considered as favorable 6-*(enolendo)-exo-trig* and that of **4** (five-membered formation) as unfavorable 5-*(enolendo)-exo-trig*. These considerations prompted us to assume that the contribution of ethylene glycol to this reaction might be an activation of the carbonyl function to form an intermediary enol ether **C** in Scheme 9 as an enol equivalent.

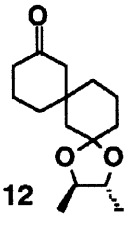
Asymmetric spirocyclization

Asymmetric siprocyclization of **3** and **6** was studied by using optically active 1,2-diols such as butane-2,3-diol, cyclohexane-1,2-diol and cycloheptane-1,2-diol[4] instead of ethylene glycol. The results are summarized in Table 1. In the cases of using **3** as a substrate, spirocyclic diketone **7** (entries 1-3) and the corresponding acetals **12**-**14** (entries 1 and 3) were afforded. But the reaction was highly affected by the diol employed. Among them, the best result in terms of both chemical and asymmetric yields was obtained in the case of using (*S*,*S*)-cyclohexane-1,2-diol, which gave (-)-**7** of 56% e.e. in 55% yield (entry 2). (*R*,*R*)-Butane-2,3-diol gave a moderate chemical yield of cyclized products (+)-**7** and **12** (totally 51% yield), but with poor e.e. and/or d.e. (entry 1). (*R*,*R*)-Cycloheptane-1,2-diol did not afford a satisfactory result (entry 3). Similar results were also obtained in the reaction of **6** (entries 4-6), in which the use of (*S*,*S*)-cyclohexane-1,2-diol gave (+)-**10** of 51% e.e. in 52% yield. The use of two other types of diol afforded acetal products **17** and/or **18** as major products.

The e.e. of **7** and **10** was determined by the ^{13}C NMR spectrum after conversion into the corresponding bisacetals (**21** type) using (*R*,*R*)-butane-2,3-diol under azeotropic conditions (*p*-TsOH, benzene). In this reaction, no decrease of e.e. was confirmed by repeating acetalization and deacetalization (5% aqueous HCl, Et_2O, room temp.), which suggests that asymmetric spirocyclization proceeded in an irreversible manner. The absolute configuration of **7** and **10** was determined by the correlation to the configurationally known spiro-1,7-diketone (*S*)-(-)-**19** and spiro-hydroxyketone (5*R*,6*R*)-(+)-**22**, respectively, which had been synthesized by us based on the asymmetric quaternary alkylation methodology.[5] That is to say, reduction of the enantiomerically pure (*S*)-(-)-**19** with $LiAlH_4$ afforded the corresponding diols as a diastereomeric mixture. Subsequent formation of triflates and their treatment with silica-gel gave a diene **20** as a crude product. Hydroboration of **20** and following oxidation by RuO_2 gave enantiomerically pure (*S*)-(+)-**7** in 15% overall yield from (*S*)-(-)-**19**. The authentic (*S*)-(+)-**7** was also converted to the bisacetal **21** (Scheme 5).

Table 1. Asymmetric Spirocyclization of 3 and 6 Using Chiral 1,2-Diols and BF_3:OEt_2

entry	substrate	chiral diol	reaction time	products
1	**3**		4 h	(+)-**7** + **12** 12% (25 %e.e.) 39% (24 %d.e.)
2	**3**		4 h	(-)-**7** 55% (56 %e.e.)
3	**3**		2 h	**7** 4% + **13** 13% (20 %d.e.) + **14** 9% + **15** 33%
4	**6**		3 h	**16** + **17** 15% 54%
5	**6**		2 h	(+)-**10** 52% (51 %e.e.)
6	**6**		3 h	**18** 87%



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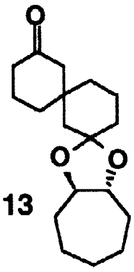

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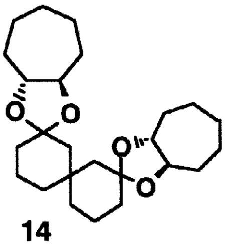

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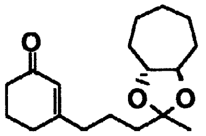

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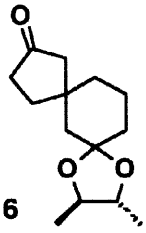
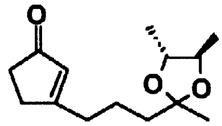
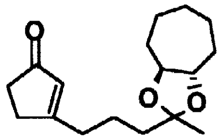


16



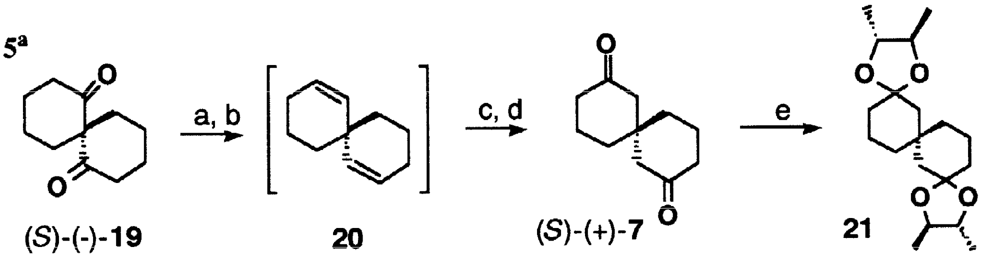
17



18

Reaction was performed with 3 equiv. of diol and 2 equiv. of BF_3:OEt_2 in CH_2Cl_2 at room temp.

Scheme 5[a]

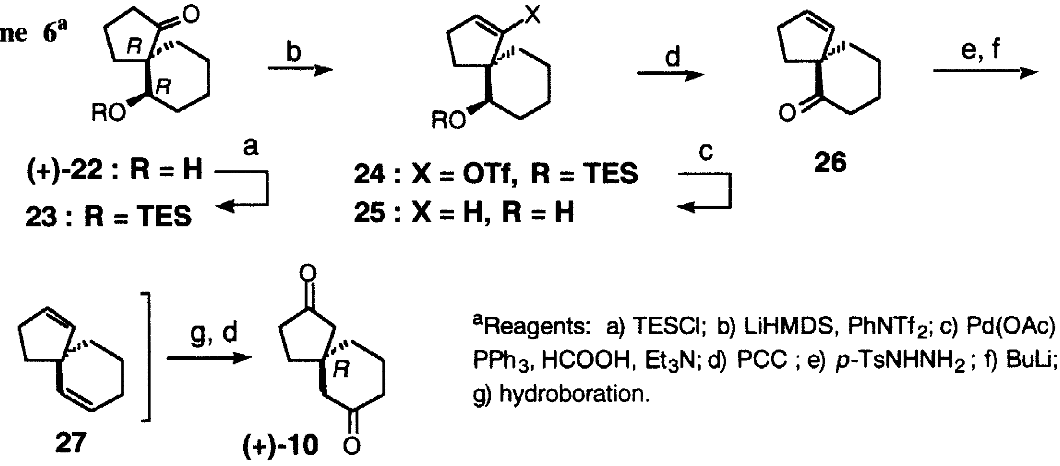


[a]Reagents: a) $LiAlH_4$; b) Tf_2O, pyridine; c) BH_3; d) RuO_2, $NaIO_4$; e) (R,R)-butane-2,3-diol, p-TsOH.

Thus, the absolute stereochemistry of spirocyclized **7** could be determined by both the sign of specific rotation of **7** and the ^{13}C NMR spectrum of bisacetal **21**.

Similarly, the authentic (*R*)-(+)-**10** was synthesized from (+)-**22**. After protection of hydroxy group as triethylsilyl (TES) ether, compound **23** was converted into enol triflate **24**.[6] Treatment of **24** with Pd(0) and formic acid[7] gave the deprotected alcohol **25**, which was oxidized into the ketone **26**. Compound **26** was coverted into the crude diene **27** by Shapiro reaction.[8] Hydroboration of **27** followed by PCC oxidation gave enantiomerically pure (*R*)-(+)-**10** (Scheme 6).

Scheme 6[a]



[a]Reagents: a) TESCl; b) LiHMDS, $PhNTf_2$; c) $Pd(OAc)_2$, PPh_3, HCOOH, Et_3N; d) PCC ; e) *p*-$TsNHNH_2$; f) BuLi; g) hydroboration.

Next, the reaction conditions were studied by using substrate **3** and (*S*,*S*)-cyclohexane-1,2-diol as a chiral source with reference to the reaction temperature and equivalences of the Lewis acid and diol (Table 2). As shown in entries 1 and 2, a large excess amount of BF_3:OEt_2 did not afford satisfactory results. The ratio between BF_3:OEt_2 and diol affected both chemical and asymmetric yields. Furthermore, reaction at lower temperature gave better results in connection with e.e. of (-)-**7** (entries 3-6), but the reaction at -40°C did not proceed at all (entry 7) and resulted in recovery of the substrate. Also, in the cases using TMSOTf and TBDMSOTf as the Lewis acid, moderate results were obtained (entries 8 and 9). The best result was obtained in entry 6 (BF_3:OEt_2; 2 equiv.; diol: 3 equiv, 0°C), which gave (-)-**7** (86% yield) of 85% e.e.[9] In addition, the same reaction in the case of using (*R*,*R*)-cyclohexane-1,2-diol afforded (+)-**7** (83% yield) of 85% e.e.

The solvent effect on this reaction was studied by using substrate **3**. The obtained results are summarized in Table 3. It was found that the reaction was highly affected by the solvent in both chemical and asymmetric yields of (-)-**7**. Among them, CH_2Cl_2 gave the best results (entry 1).

Based on above successful results, reaction conditions using substrate **6** were studied, and results are summarized in Table 4. Among the reaction conditions employed, the best e.e. of (-)-**10** (67% e.e.) was observed in entry 1 under the same conditions as those of entry 6 in Table 2. As shown in entry 3, the use of TMSOTf increased the chemical yield of (-)-**10** even at 0°C.

Scheme 7

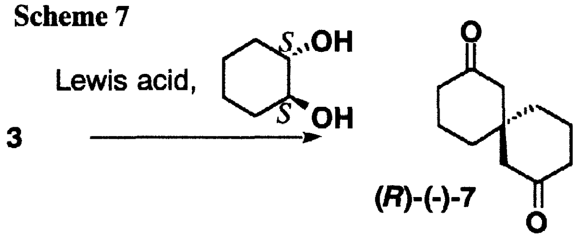


Table 2. Optimization of Asymmetric Spirocyclization of 3

entry	Lewis acid (equiv.)		diol (equiv.)	temp.	time (h)	yield (%)	%e.e.
1	BF_3:OEt_2	7	1	r.t.	4	36	21
2	BF_3:OEt_2	7	3	r.t.	4	55	56
3	BF_3:OEt_2	2	1	r.t.	4	62	74
4	BF_3:OEt_2	2	3	r.t.	1.5	86	70
5	BF_3:OEt_2	2	1	0°C	6	23	81
6	BF_3:OEt_2	2	3	0°C	6	**86**	**85**
7	BF_3:OEt_2	2	3	-40°C	4 days	no reaction	
8	TMSOTf	1	1	0°C	1	42	63
9	TBDMSOTf	1	1	0°C	1.5	64	70

Reaction was performed in CH_2Cl_2.

Table 3. Effect of Solvent

entry	solvent	time (h)	yield (%)	%e.e.
1	CH_2Cl_2	1.5	86	70
2	C_6H_6	1	82	62
3	toluene	1.5	78	49
4	CH_3CN	1	71	20
5	DME	26	22	5
6	Et_2O	1	monoacetal of (-)-7 (45% y., 54% d.e.) bisacetal of 7 (21% y.)	
7	THF	24	no reaction	

Reaction was performed under the same conditions of entry 4 in Table 2.

Scheme 8

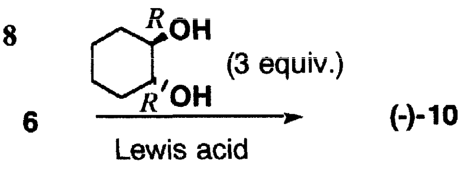


Table 4. Asymmetric Spirocyclization of 6

entry	Lewis acid (equiv.)		temp.	time (h)	yield (%)	%e.e.
1	BF_3:OEt_2	2	0°C	6	22	67
2	BF_3:OEt_2	2	r.t.	2	52	51
3	TMSOTf	1	0°C	7	81	59
4	TMSOTf	1	r.t.	1.5	72	63

Mechanistic consideration

Reaction mechanisms of this spirocyclization under acidic conditions assisted by 1,2-diol are proposed as shown in Scheme 9. We assumed the enol ether **C** as an intermediary enol equivalent, which is one of the intermediates **A-C** for the usual acetal formation. Based on this assumption, the results obtained in the asymmetric version were rationalized as follows. For asymmetric induction at the C6-position of **7**, the selection of enantiotopic (or diastereotopic) faces in both π-systems (enone and enol ether) must be required, but their combinations might be restricted based on the conformational aspects. That is to say, two types of conformations **C1** (chair conformation) and **C2** (boat conformation) in Fig. 1 could be postulated for further intramolecular conjugate addition. Taking into consideration the orbital interaction in both π-systems based on Baldwin's rule, the conformation **C1** might be more favorable than **C2**.

Scheme 9

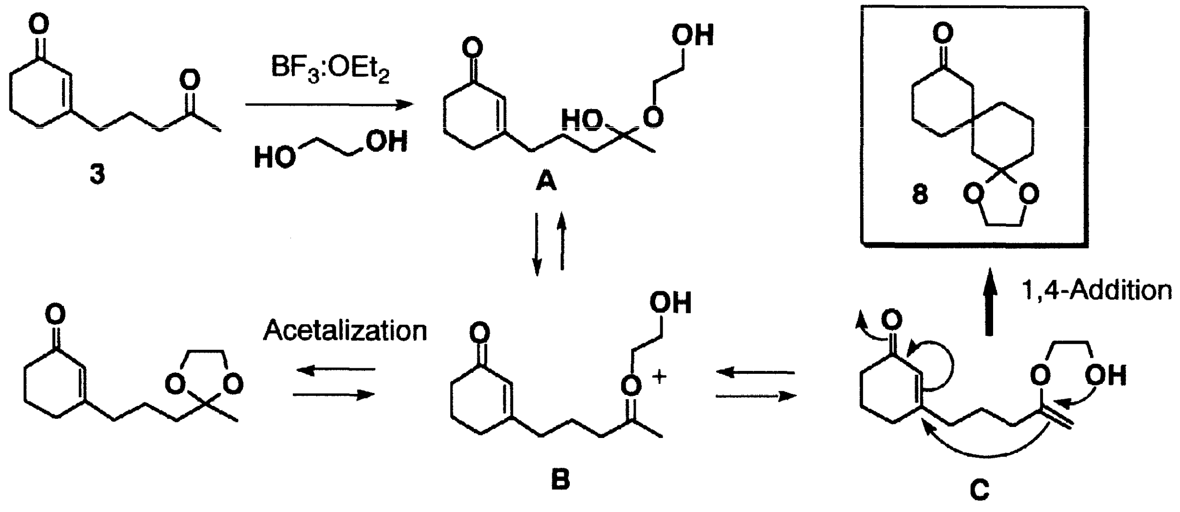
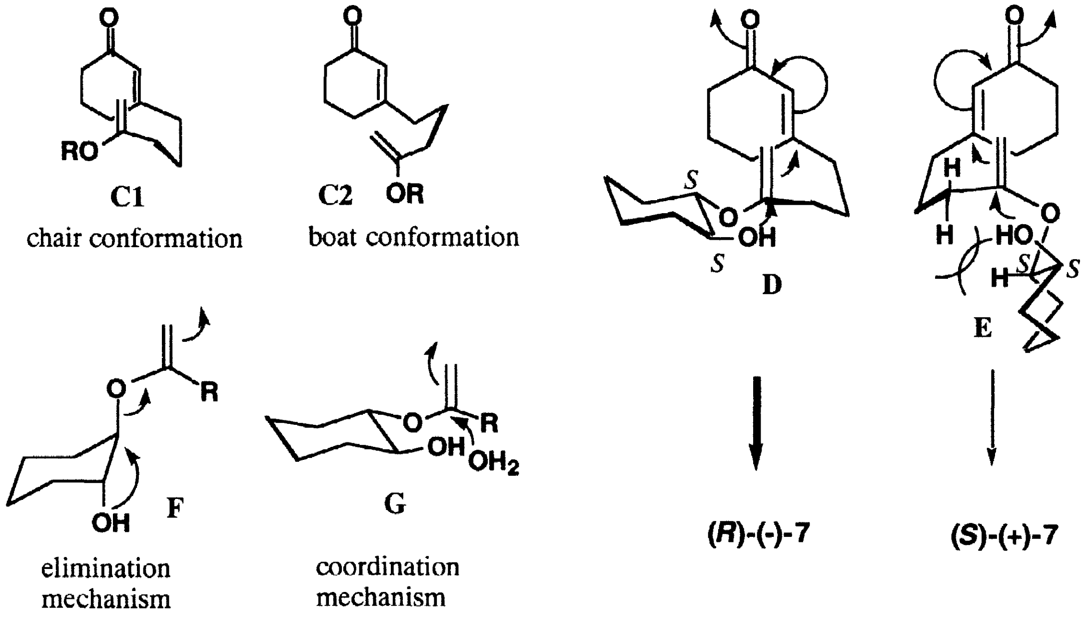


Fig. 1



C1 chair conformation

C2 boat conformation

F elimination mechanism

G coordination mechanism

In the asymmetric reaction using (*S*,*S*)-cyclohexane-1,2-diol, two further types of reaction intermediates **D** and **E** could be replaced with **C1** for stereoselection, which correspond to spirocyclized products (*R*)-(-)-**7** and (*S*)-(+)-**7**, respectively. Among them, the intermediate **D** might be favorable because of steric repulsion in **E** as depicted in Fig. 1.

The above assumption may or may not rationalize all the results obtained. If the reaction proceeded in the above reaction course, a mono-acetalized product must be obtained as the major product. This point is still unclear. Two possible routes were considered in this connection. One is "elimination mechanism **F**", in which the free hydroxy oxygen attacks the vicinal carbon to eliminate the enol and to form cyclohexene oxide. But, this route was less likely for the following reasons: i. no cyclohexene oxide could be detected in the reaction; ii. the chemical yield of the recovered (*S*,*S*)-cyclohexane-1,2-diol was quantitative; iii. the e.e. of the recovered diol was not reduced. The other is "coordination mechanism **G**", in which H_2O molecule, produced *via* the enol ether formation, around the hydroxy group attacks the 4'-carbon of the substituent to form the hemiacetal intermediate, an easily accessible species to the corresponding ketone. The latter course was considered to be plausible, and might be competitive with the course *via* **D**. Further studies of intramolecular cyclization based on this new concept are now under way.

EXPERIMENTAL

General. Melting points were measured on Yanaco micro melting point apparatus without correction. ^1H NMR spectra were taken on JEOL GX-270 (270 MHz) or JEOL JMN-GX-500 (500 MHz) spectrometer. ^{13}C NMR were recorded on JEOL GX-270 (67.8 MHz) spectrometer. IR spectra were measured on JASCO IR A-100 infrared spectrophotometer. Mass spectra (EI and FAB) were measured on JEOL JMS-D300 or JEOL JMS-SX102 spectrometer. Specific rotations were measured on JASCO DIP-360 digital polarimeter. The elemental analyses were performed on a Yanaco MT2 CHN recorder. Analytical thin-layer chromatography (TLC) was performed with precoated TLC plates (Merck, Kieselgel 60 F254). Column chromatography were carried out on silica gel 70-230 mesh (Merck, Kieselgel 60). Solvents were distilled and dried before use.

3-(4-Pentenyl)cyclohex-2-en-1-one (1). To a solution of 4-pentenylmagnesium bromide prepared from magnesium (564 mg, 23.2 mmol) and 5-bromo-1-pentene (2.86 ml, 24.1 mmol) in THF (25 ml) was added dropwise a solution of 3-ethoxy-2-cyclohexen-1-one (2.5 g, 17.8 mmol) in THF (20 ml), and the mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (Hexane / AcOEt = 10 : 1) to give **1** (2.22 g, 76%): a colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 5.88 (t, J = 1.3 Hz, 1H), 5.82-5.72 (m, 1H), 5.07-4.97 (m, 2H), 2.39-2.23 (m, 6H), 2.20-1.94 (m, 4H), 1.66-1.55 (m, 2H); IR (neat) 2925, 1670, 1620 cm^{-1}; FAB-MS (*m*/*z*) 165 $[M^++H]$.

3-(3-Butenyl)-2-cyclohexen-1-one (2). The compound **2** (71% yield) was prepared by the similar manner to that described for **1**: a colorless oil; ^1H NMR (100 MHz, $CDCl_3$) δ 6.00-5.61 (m, 2H), 5.18-5.04 (m, 2H), 2.62-1.85 (m, 10H); IR (neat) 2925, 1675, 1620 cm^{-1}; FAB-MS (*m*/*z*) 151 $[M^++H]$.

3-(4-Oxopentyl)-2-cyclohexen-1-one (3). A solution of palladium (II) chloride (1.12 g, 6.70 mmol) and copper (I) chloride (5.30 g, 53.6 mmol) in DMF (50 ml) and water (8.5 ml) was stirred for 2 h at room temperature under an O_2 atmosphere. To the solution was added a solution of **1** (2.2 g, 13.4 mmol) in DMF (10 ml) and water (3 ml), and the mixture was stirred for 30 min at room temperature. The resulting mixture was washed with saturated NH_4Cl, and extracted with ether. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (Hexane /

AcOEt = 2 : 1) to give **3** (1.83 g, 76%): a pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.86 (s, 1H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.36 (t, *J* = 6.6 Hz, 2H), 2.30 (t, *J* = 5.9 Hz, 2H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.15 (s, 3H), 2.02 (q, *J* = 6.2 Hz, 2H), 1.80 (q, *J* = 7.3 Hz, 2H); IR (neat) 2950, 1710, 1670, 1615 cm^{-1}; FAB-MS (*m/z*) 181 [M$^+$+H]; HRMS for $C_{11}H_{17}O_2$ (M$^+$+1): Calcd *m/z* 181.1228; Found 181.1233.

3-(3-Oxobutyl)-2-cyclohexen-1-one (4). The compound **4** (67% yield) was prepared by the similar manner to that described for **3**: a pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.88-5.80 (s, 1H), 2.70-2.65 (m, 2H), 2.55-2.46 (m, 2H), 2.42-2.29 (m, 4H), 2.19 (s, 3H), 2.04-1.97 (m, 2H); IR (neat) 2950, 1720, 1680-1660, 1625 cm^{-1}; FAB-MS (*m/z*) 167 [M$^+$+H]; HRMS for $C_{10}H_{15}O_2$ (M$^+$+1): Calcd *m/z* 167.1072; Found 167.1085.

3-(4-Pentenyl)-2-cyclohexen-1-one (5). The compound **5** (55% yield) was prepared from 3-ethoxy-2-cyclopenten-1-one by the similar manner to that described for **1**: a colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.94 (t, *J* = 1.3 Hz, 1H), 5.85-5.71 (m, 1H), 5.05-4.96 (m, 2H), 2.58-1.59 (m, 10H); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 205.7 (s), 182.5 (s), 137.8 (q), 129.6 (d), 115.9 (t), 35.6 (t), 33.9 (t), 33.3 (t), 31.9 (t), 26.4 (t); FAB-MS (*m/z*) 151 [M$^+$+H].

3-(4-Oxopentyl)-2-cyclohexen-1-one (6). The compound **6** (70% yield) was prepared from **5** by the similar manner to that described for **3**: a pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.96 (t, *J* = 1.3 Hz, 1H), 2.61-2.39 (m, 8H), 2.16 (s, 3H), 1.86 (q, 2H); ^{13}C NMR (67.8 MHz, CDCl3) δ 210.0 (s), 207.9 (s), 182.0 (s), 129.6 (d), 42.6 (t), 35.3 (t), 32.7 (t), 31.5 (t), 30.0 (t), 20.9 (t); IR (neat) 2940, 1712, 1675, 1615 cm^{-1}; FAB-MS 167 [M$^+$+H]; HRMS for $C_{10}H_{15}O_2$ (M$^+$+1): Calcd *m/z* 167.1072; Found 167.1079.

General procedure for spirocyclization

Reaction without diol: To a solution of substrate (2 mmol) in CH$_2$Cl$_2$ (10 ml) was added dropwise BF$_3$:OEt$_2$ (4 mmol), and the mixture was stirred for 3 d at room temperature. The resulting mixture was washed with saturated aqueous NaHCO$_3$ and extracted with AcOEt. The combined organic layers were washed with brine, and dried over MgSO$_4$. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (Hexane / AcOEt = 4 : 1 to 2 : 1).

Reaction with diol: To a solution of substrate and diol in CH$_2$Cl$_2$ were added dropwise BF$_3$:OEt$_2$ and the mixture was stirred. The reaction mixture was treated by a similar manner as above mentioned.

Spiro[5.5]undecane-2,8-dione (7): A colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.34-2.20 (m, 8H), 1.97-1.58 (m, 8H); ^{13}C NMR (25.1 MHz, CDCl$_3$) δ 209.8 (s), 53.0 (t), 42.5 (s), 40.8 (t), 34.2 (t), 21.4 (t); IR (neat) 2950, 1710 cm^{-1}; FAB-MS (*m/z*) 181 [M$^+$+H]; HRMS for $C_{11}H_{17}O_2$ (M$^+$+1): Calcd *m/z* 181.1228; Found 181.1222. **(*R*)-(-)-7** (Table 2, entry 6): (85%e.e): $[\alpha]_D^{21}$ -14.3 (*c* = 2.15, CHCl$_3$).

Spiro[5.5]undecane-2,8-dione Monoethyleneacetal (8): A colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 3.90 (s, 4H), 2.35-2.26 (m, 4H), 1.89 (m, 12H); ^{13}C NMR (25.1 MHz, CDCl$_3$) δ 211.8 (s), 108.8 (s), 64.1 (t), 52.8 (t), 44.2 (t), 41.2 (t), 40.3 (s), 36.3 (t), 35.9 (t), 35.0 (t), 21.7 (t), 19.3 (t); IR (neat) 2875, 1710 cm^{-1}; FAB-MS (*m/z*) 225 [M$^+$+H].

5-Methyl-4,6,7,8-pentahydro-2(3H)-naphthalenone (9): A pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.68 (s, 1H), 2.66 (br t, *J* = 7.3 Hz, 2H), 2.48-2.40 (m, 4H), 2.25 (br t, *J* = 6.3 Hz, 2H), 1.87, s, 3H), 1.83-1.76 (m, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 199.5 (s), 156.9 (s), 141.0 (s), 126.3 (s), 121.6 (d), 37.0 (t), 33.1 (t), 31.6 (t), 25.2 (t), 22.3 (t), 20.2 (q); IR (neat) 2920, 1650, 1610, 1570 cm^{-1}; FAB-MS (*m/z*) 163 [M$^+$+H]; HRMS for $C_{11}H_{15}O$ (M$^+$+1): Calcd *m/z* 163.1123; Found 163.1136.

Spiro[4.5]decane-2,7-dione (10): A colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.41-2.13 (m, 8H), 2.05-1.72 (m, 6H); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 217.3 (s), 210.0 (s), 108.5 (t), 52.8 (t), 50.4 (t), 44.4 (s), 40.8 (t), 36.3 (t), 35.7 (t), 33.9 (t), 22.7 (t); IR (CHCl$_3$) 2850, 1740, 1709 cm^{-1}; FAB-MS (*m/z*) 166 [M$^+$+H]. **(-)-10** (Table 7, entry 1) (67%e.e): $[\alpha]_D^{20}$ -24.1 (*c* = 1.22, CHCl$_3$).

7,7-Ethylenedioxyspiro[4.5]decan-2-one (11): A colorless oil;^{1}H NMR (270 MHz, CDCl$_3$) δ 3.91 (s, 4H), 2.35-2.15 (4H, m), 1.93-1.85 (2H, m). ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 220.1 (s), 108.9 (s), 64.3 (t), 64.2 (t), 50.9 (t), 45.0 (t), 41.1 (s), 36.2 (t), 35.7 (t), 34.8 (t), 29.7 (t), 20.4 (t); IR (CHCl$_3$) 2870, 1745 cm^{-1}.

3-{3-((1*R*,7*R*)-9-Methyl-8,10-dioxabicyclo[5.3.0]decan-9-yl)propyl}-2-cyclohexen-1-one (15): ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.89 (s, 1H), 3.87-3.62 (m, 2H), 2.38-1.44 (m, 22H), 1.34 (3H); IR (neat) 2900, 2830, 1650, 1605 cm^{-1}; $[\alpha]_D^{27}$ -37.9 (c = 1.5, $CHCl_3$).

3-[3-((4*R*,5*R*)-2,4,5-Trimethyl-1,3-dioxolan-2-yl)propyl]cyclopentent-2-en-1-one (17): A colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.97 (q, J = 1.7 Hz, 1H), 3.68 (dq, J = 8.4, 5.9 Hz, 1H), 3.57 (dq, J = 8.4, 5.9 Hz, 1H), 2.60-2.57 (m, 2H), 2.42-2.32 (m, 4H), 1.74-1.64 (m, 4H), 1.35 (s, 3H), 1.25 (d, J = 5.9 Hz, 3H), 1.24 (d, J = 5.9 Hz, 3H); ^{13}C NMR (25.1 MHz, $CDCl_3$) δ 209.9 (s), 182.6 (s), 129.6 (d), 108.8 (s), 79.0 (d), 78.0 (d), 39.9 (t), 35.3 (t), 33.5 (t), 31.5 (t), 25.7 (q), 21.4 (t), 17.3 (q), 16.4 (q); IR (neat) 2930, 1705, 1672 cm^{-1}; EI-MS (m/z) 238 [M$^+$]; $[\alpha]_D^{20}$ -19.4 (c = 0.43, $CHCl_3$).

3-(3-((1*S*,7*S*)-9-Methyl-8,10-dioxabicyclo[5.3.0]decan-9-yl)propyl)-2-cyclopenten-1-one (18): A colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.97 (q, J = 1.7 Hz, 1H), 3.84-3.63 (m, 2H), 2.60-1.40 (m, 20H), 1.36 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 210.1 (s), 182.8 (s), 129.6 (d), 109.2 (s), 81.7 (d), 80.6 (d), 39.9 (t), 35.3 (t), 33.5 (t), 31.5 (t), 30.2 (t), 29.2 (t), 25.8 (q), 25.2 (q), 24.91 (t), 24.85 (q), 21.4 (q); IR (neat) 2930, 1705, 1675 cm^{-1}; EI-MS (m/z) 278 [M$^+$]; $[\alpha]_D^{20}$ +42.7 (c = 0.56, $CHCl_3$).

Determination of the enantiomeric excess of 7 and 10

To a solution of compound (-)-**7** (55 mg, 0.31 mmol) and (*R,R*)-2,3-butanediol (55 mg, 0.61 mmol) in benzene (20 ml) was added *p*-TsOH-H_2O (10 mg), and the whole was refluxed with azeotropic removal of water for 1.5 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with brine, and dried over $MgSO_4$. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane / AcOEt = 19 : 1) to give the corresponding bisacetal (**21**-type) (90 mg, 90% yield): A colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.68-3.49 (m, 4H), 1.95-1.25 (m, 16H), 1.23-1.21 (m, 12H); ^{13}C NMR (25.1 MHz, $CDCl_3$) δ 108.8 [108.6] (s), 77.9 (d), 77.7 (d), 44.9 [47.3] (t), 38.4 (t) [37.2] (t), 37.4 [36.7] (t), 36.4 [35.9] (s), 19.3 [19.6] (t), 17.2 (q), 17.1 (q). Chemical shifts are those of the major diastereomer, bisacetal of (+)-**7**, and those in paretheses are based on the minor diastereomer, bisacetal of (-)-**7**. The e.e. of **7** was determined based on the average ratio of these peak intensities.

The similar treatment of compound (+)-**10** gave the corresponding bisacetal (92% yield): A colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.67-3.50 (m, 4H), 2.05-1.44 (m, 14H), 1.28-1.20 (m, 12H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 117.4 [117.3] (s), 108.5 [108.4] (s), 78.14 [78.00] (d), 78.06 (d), 77.8 [77.7] (d), 77.6 (d), 50.0 [49.8] (d), 47.7 [46.3] (t), 42.0 [41.8] (q), 37.4 [37.0] (t), 36.84 [36.78] (t), 36.66 [36.4] (t), 29.7 (t), 20.8 [20.6] (t), 17.2 [17.04] (q), 17.05 (q), 16.98 (q), 16.85 (q). Chemical shifts are those of the major diastereomer, bisacetal of (+)-**10**, and those in paretheses are based on the minor diastereomer, bisacetal of (-)-**10**; EI-MS (m/z) 310 [M$^+$].

Determination of absolute configuration of 7. Synthesis of the authentic (+)-7 from (*S*)-spiro[5.5]undecane-1,7-dione. To a suspension of $LiAlH_4$ (21 mg, 0.55 mmol) in THF (5 ml) was added (*S*)-**19** (100 mg, 0.55 mmol) at room temperature. After being stirred for 30 min, AcOEt (1 ml) and saturated aqueous NH_4Cl (0.5 ml) were added to the mixtre, and then the mixture was filtered through a celite. The filtrate was concentrated *in vacuo* to give the crude diol. The crude diol was dissolved in CH_2Cl_2 (5 ml) and pyridine (1 ml), and cooled to -20 °C, then trifluoromethanesulfonic anhydride (Tf_2O) (0.46 ml, 2.78 mmol) was added to the solution, and the mixture was stirred for 3 days. The resulting mixture was washed with saturated aqueous NH_4Cl, and extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. After removal of solvent, the residue was purified by cloumn chromatgraphy (pentane) to give **20** as a pentane solution. ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.63 (dt, J = 10.0, 4.1 Hz, 2H), 5.46 (dt, J = 10.0, 1.6 Hz, 2H), 2.00-1.93 (br. s, 4H), 1.71-1.45 (m, 8H).

To a solution of BH_3:THF (1M soln. in THF, 3.34 ml, 3.34 mmol) in THF (10 ml) was added a solution of **20** in pentane and the mixture was refluxed for 24 h. After the excess BH_3 was quenched with MeOH, aqueous 6N NaOH (1 ml) and 30% H_2O_2 (1 ml) were added to the mixtrue. The whole was stirred for 3 h at 60 °C, then washed with brine and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated to give the crude diol. The crude diol was used to the next oxidation without further purification.

To the solution of the diol in CCl_4 (0.2 ml) and CH_3CN (0.2 ml) were added H_2O (0.5 ml), RuO_2 (1.7 mg, 0.01 mmol), and $NaIO_4$ (120 mg, 0.56 mmol), and the whole was stirred for 24 h at room temperature. The resuluting mixture was washed with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography to give (+)-**7** (15 mg, 15% overall yield from (*S*)-(-)-**19**) as a colorless oil with a small amount of inseparable contamitant. $[\alpha]_D^{22}$ +15.5 (*c* = 1.0, $CHCl_3$).

The obtained enantiomerically pure (+)-**7** was converted to the corresponding bisacetal **21**. A colorless oil. ^{13}C NMR (25.1 MHz, $CDCl_3$) δ 108.6 (s), 77.9 (d), 77.7 (d), 47.3 (t), 37.2 (t), 36.7 (t), 35.9 (s), 19.6 (t), 17.2 (q), 17.1 (q). HRMS for $C_{19}H_{33}O_4$ (M^++1): Calcd *m/z* 325.2379; Found 325.2384.

Determination of absolute configuration of 10. Synthesis of the authentic (+)-10 from (+)-22. To a solution of (+)-**22** (989 mg, 5.88 mmol) in DMF (10 ml) was added imidazole (1.00 g, 14.7 mmol), chlorotriethylsilane (2.0 ml, 11.8 mmol), and 4-(dimethylamino)pyridine (DMAP) (72 mg, 0.59 mmol). The resulting mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl, and extracted with Et_2O. The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane / AcOEt = 50 : 1) to give **23** (1.64 g, 99%): A colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 3.53 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.38-1.59 (m, 10H), 1.37-1.10 (m, 4H), 0.93 (t, *J* = 8.1 Hz, 9H), 0.58 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 221.0 (s), 76.2 (d), 52.3 (s), 40.8 (t), 36.9 (t), 33.2 (t), 30.9 (t), 24.1 (t), 20.8 (t), 19.3 (t), 6.9 (q x3), 5.2 (t x3); IR (neat) 2970, 2890, 1740 cm^{-1}; FAB-MS (*m/z*) 283 [M^++H]; $[\alpha]_D^{25}$ +16.4 (*c* = 1.3, $CHCl_3$).

To a cooled (0 °C) heterogeneous mixutre of **23** (1.61 g, 5.69 mmol) and *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$) (3.05 g, 8.53 mmol) in THF (30 ml) was added dropwise lithium hexamethyldisilazide (LiHMDS) (1.0 M soln in THF, 8.5 ml, 8.5 mmol) and the whole was stirred for 5 min at 0 °C. The resulting mixture was washed with saturated aqueous NH_4Cl, and extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane) to give **24** (2.27 g, 96%): A colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 5.65 (t, J = 2.6 Hz, 1H), 3.69 (br t, J = 4.6 Hz, 1H), 2.37-2.20 (m, 2H), 2.07-1.95 (m, 2H), 1.78-1.58 (m, 5H), 1.40-1.18 (m, 3H), 0.94 (t, J = 8.1 Hz, 9H), 0.58 (q, J = 8.1 Hz, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 154.7 (s), 118.5 (q, J = 320 Hz), 115.3 (d), 73.9 (d), 52.0 (s), 34.6 (t), 32.1 (t), 31.5 (t), 25.3 (t), 22.1 (t), 6.8 (q x3), 5.0 (t x3); IR (neat) 2930, 2860, 1405 cm^{-1}; FAB-MS (*m/z*) 413 [M^+-H]; $[\alpha]_D^{25}$ -53.0 (*c* = 1.3, $CHCl_3$).

To a solution of **24** (2.25 g, 5.42 mmol) in DMF (15 ml) was added palladium (II) acetate (36.5 mg, 0.016 mmol), triphenylphosphine (107 mg, 0.041 mmol), triethylamine (2.28 ml, 16.3 mmol), and formic acid (0.62 ml, 16.3 mmol). The whole was stirred for 2 h at 60 °C. After addition of aqueous HCl at room temperature, the aqueous layer was passed through a celite, and rinsed with Et_2O. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane to hexane / AcOEt = 10 : 1) to give **25** (370 mg, 45%). A colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 5.95 (dt, *J* = 5.8, 2.3 Hz, 1H), 4.80 (dt, *J* = 5.8, 2.3 Hz, 1H), 3.39 (br d, *J* = 4.9 Hz, 1H), 2.45-2.26 (m, 2H), 2.05-1.96 (m, 1H), 1.85-1.26 (m, 10H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 134.3 (d), 132.1 (d), 76.3 (d), 55.5 (s), 37.3 (t), 35.1 (t), 32.7 (t), 31.8 (t), 24.3 (t), 23.1 (t); IR (neat) 3400, 2925, 2850 cm^{-1}; EI-MS (*m/z*) 153 [M^++H]; $[\alpha]_D^{26}$ -14.1 (*c* = 1.3, $CHCl_3$)

To a solution of **26** (370 mg) in CH_2Cl_2 (25 ml) was added celite (2.6 g) and pyridinium chlorochromate (PCC) (1.31 g, 6.08 mmol), and the whole was stirred for 2 h at room temperature. The resulting mixture was diluted with Et_2O, passed through a florisil short column, and rinsed with Et_2O. The filtrate was concentrated *in vacuo*, the residue was purified by column chromatography (hexane / AcOEt = 50 : 1) to give **26** (278 mg, 76%): A colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 5.87-5.76 (m, 2H), 2.51-2.30 (m, 4H), 1.94-1.57 (m, 8H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 212.9 (s), 133.3 (d), 132.6 (d), 64.0 (s), 39.9 (t), 39.6 (t), 32.3 (t), 31.2 (t), 27.5 (t), 22.8 (t); IR (neat) 2920, 2850, 1700 cm^{-1}; EI-MS (*m/z*) 149 [M^+-H]; $[\alpha]_D^{28}$ -71.1 (*c* = 0.8, $CHCl_3$)

To a solution of **26** (268 mg, 1.78 mmol) in MeOH (5 ml) was added *p*-toluenesulfonyl hydrazide (498 mg, 2.67 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol). After being stirred for 2 h at room temperature, the whole was diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, an obtained crude hydrazone (773 mg) was used for the next reaction without further purification. To a cooled (0 °C) suspension of the crude hydrazone (773 mg) in Et_2O (5 ml) was added dropwise butyllithium (1.56 M soln. in hexane) (5.7 ml, 8.91 mmol). After being stirred for 2 h at 0 °C, the resulting mixture was washed with aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was purified by column chromatography (pentane) to give **27** as a pentane solution.

To a solution of 9-borabicyclo[3.3.1]nonane (9-BBN) (869 mg, 7.12 mmol) in THF (20 ml) was added dropwise a solution of **28** in pentane and the whole was stirred for 2 h at room temperature. After addition of aqueous NaOH (3N, 5 ml) and 30% H_2O_2 (5 ml) at 0 °C, reaction mixture was stirred for 1 h at at room temperature. The whole was washed with aqueous NH_4Cl and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane / AcOEt = 4 : 1) to give the crude mixture of the corresponding mono-alcohol (174 mg). (On this stage, mono-hydroboration might occur.) To a cooled (0 °C) solution of mono-alcohol (174 mg) in THF was added dropwise BH_3:THF (1.0 M soln. in THF, 3.4 ml. 3.4 mmol) and the whole was stirred for 2 h at 0 °C. To the resulting mixture was added dropwise aqueous NaOH (3N, 3 ml) and 30% H_2O_2 (3 ml). After being stirred for 15 min at 0 °C and for 45 min at room temperature, the resulting mixture was cooled to 0 °C again. To the mixture was added $Na_2S_2O_3$ (300 mg), and the whole was stirred for 1 h at 0 °C. The resulting mixture was diluted with $CHCl_3$, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude mixture of the corresponding diol (202 mg). To a solution of diol (202 mg) was added a celite (2.04 g) and PCC (1.02 g, 4.74 mmol), and the whole was stirred for 12 h at room temperature. The resulting mixtre was diluted with Et_2O, passed through a florisil short column, and rinsed with Et_2O. The filtrate was concentrated *in vacuo*, the residue was purified by column chromatography (hexane / AcOEt = 5 : 1 to 3 : 1) to give (*R*)-(+)-**10** (41.2 mg, 41% from **26**): A colorless oil; $[\alpha]_D^{26}$ +31.9 (c = 0.9, $CHCl_3$).

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