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Convenient Methods for the Preparation of Unsymmetrical Double Aldols

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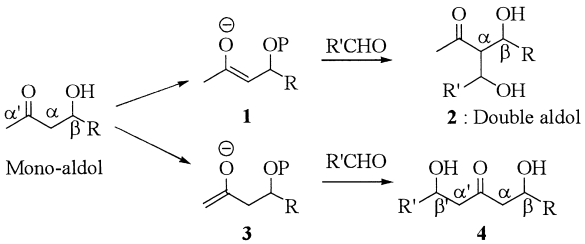
Double aldol reaction proceeded stereoselectively at one α-carbon of ketones to give α-(1-hydroxyalkyl)-β-hydroxyalkyl ketones (double aldols) in good to high yields by the following three methods: i) tin(II) trifluoromethanesulfonate-mediated aldol reaction of aldehydes with β-hydroxy ketones (mono-aldols) in the presence of tertiary amines, ii) samarium(II) iodide-mediated aldol reaction of aldehydes with alkyl or aryl oxiranyl ketones, iii) $Sn(OTf)_2$-promoted aldol reaction of α-bromo ketones with aldehydes giving α-bromo-β-stannyloxy ketones which were then converted to titanium enolates on treatment with low-valent titanium. Double aldols were formed by subsequent reaction of the above titanium enolates with aldehydes in one-pot procedure. Further, small and medium-sized carbocyclic compounds whose ring skeletons were composed of double aldol structure were synthesized by SmI_2-mediated intramolecular cyclization between oxiranyl ketone and aldehyde functions.

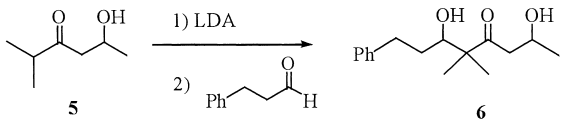
A number of biologically active natural products contain several oxygenated carbons in their structures. Aldol reaction has frequently been employed as one of the most useful synthetic tools for the synthesis of such compounds since it constructs a new C–C bond and a hydroxy group synchronously. The stereoselective formation of such groups has been achieved by various types of aldol reactions via metal enolates such as lithium, boron, silicon, and tin enolates.[1] However, very few examples are known for the synthesis of double aldols **2**[2,3] although the aldol chemistry has widely been developed to date. It was considered then that the double aldol reaction at one α-carbon of ketones to form double aldols **2** would proceed by treating aldehydes with enolate anions **1** which were regioselectively generated from alkyl or aryl β-hydroxy ketones (mono-aldols).

It is generally known that the undesired enolate anion **3** is generated from mono-aldol by deprotonation with strong base such as LDA, and that **3** reacts with aldehyde to afford β,β'-dihydroxy ketone **4** (Scheme 1).[4,5] For example, a double aldol product **6** was obtained in 60% yield by deprotonation of mono-aldol **5** with LDA, and by aldol reaction with 3-phenylpropionaldehyde that followed (Scheme 2).

Luke and Morris reported the synthesis of boron-mediated double aldols.[2] They showed that aldol reaction of mono-aldols with isobutyraldehyde by a combination using 1 molar amount of dichloroborane or trichloroborane and 2 molar amounts of ethyldiisopropylamine gave double aldols in moderate yields. On the other hand, the reaction of mono-aldols by using $TiCl_4$ and ethyldiisopropylamine afforded regioisomer **3**. Masamune et al. reported that symmetrical or unsymmetrical alkyl 3-hydroxy-2-(1-hydroxyalkyl)alkanoates (double aldolates) were formed by double aldol-type reaction using 1-phenyl-2-[benzyl(phenylsulfonyl)amino]propyl acetate.[6] The alkyl acetates gave the double aldolates when in situ formed enol borates[7] were treated with isobutyraldehyde or benzaldehyde;



Scheme 1.



Scheme 2.

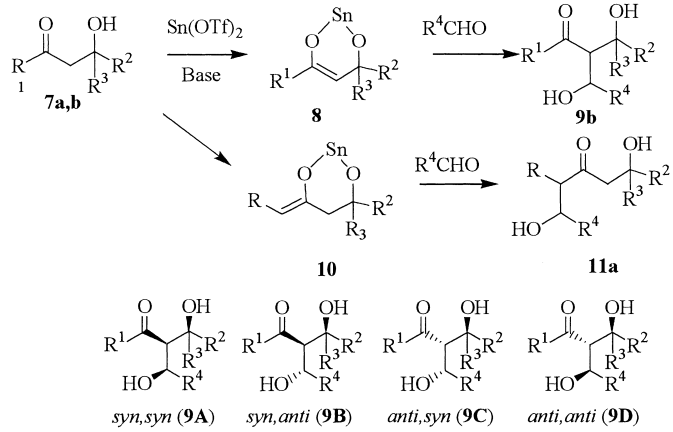
however, double aldols **2** were not obtained by that method.

Then, the importance of developing general and effective methods for the stereoselective preparation of double aldols is recognized as one of the most challenging topics in organic synthesis. In this paper, we would like to describe the full details of three useful methods for the formation of double aldols as well as the formation of small- and medium-sized carbocycles whose ring skeletons contain the double aldol structure.

Results and Discussion

Tin(II) Trifluoromethanesulfonate-Mediated Aldol Reaction of Aldehydes with β-Hydroxy Ketones (Mono-Aldols). The aldol reaction of mono-aldols for the synthesis of double aldols was tried by using tin(II) trifluoromethanesulfonate ($Sn(OTf)_2$) and triethylamine. In the case of the reaction between mono-aldol **7a** and benzaldehyde or isobutyraldehyde, double aldol **9** was not obtained while undesired regioisomer

Table 1. Stereoselective Double Aldol Formation by the Aldol Reaction of β-Hydroxy Ketones with Aldehydes in the Presence of $Sn(OTf)_2$ and Amine Bases



Entry	Mono-aldol				Aldehyde	Base	Yield/%	Product and ratio[a)]
	R^1	R^2	R^3		R^4			
1	Me	$Ph(CH_2)_2$	H	**7a**	Ph	Et_3N	43	**11a**
2	Me	$Ph(CH_2)_2$	H	**7a**	^{i}Pr	Et_3N	33	**11a**
3	Ph	^{i}Pr	H	**7b**	$Ph(CH_2)_2$	Et_3N	11	**9bB:9bD** (55:45)
4	Ph	^{i}Pr	H	**7b**	$Ph(CH_2)_2$	DBU	81	**9bB:9bD** (<1:99>)

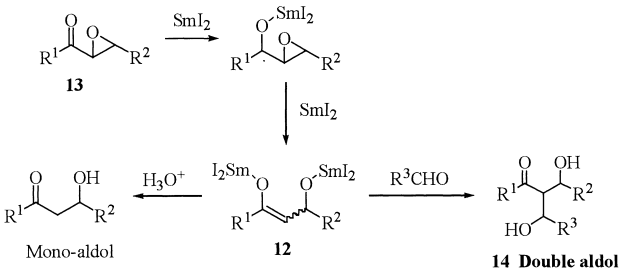
a) The ratio of the possible four double aldol isomers was determined by integration of the ^{1}H NMR spectrum of a mixture of the corresponding acetonide derivatives.

11 was formed as a major product in these cases (Table 1, Entries 1 and 2).

In the case of $Sn(OTf)_2$-mediated aldol reaction of mono-aldol **7b**, only having active hydrogen at the central carbon, and 3-phenylpropionaldehyde, double aldol **9b** was obtained in only 11% yield with low diastereoselectivity (Entry 3) while double aldol **9b** was obtained in 81% yield with high diastereoselectivity by using DBU as a base (Entry 4). Thus, exclusive double aldol reaction is performed only in the above case.

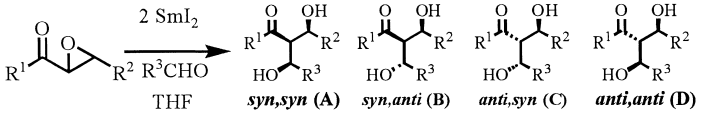
Samarium(II) Iodide-Mediated Aldol Reaction of Aryl or Alkyl Oxiranyl Ketones and Aldehydes. It is known that a wide variety of 2-hydroxy-, 2-acetoxy-, 2-alkoxy-, 2-alkylthio- or 2-haloalkyl ketones are reduced under mild conditions by using 2 molar amounts of SmI_2 to give the corresponding deoxygenated, desulfurated or dehalogenated ketones.[8–10] It has also been reported that the reduction of alkyl or aryl oxiranyl ketones with SmI_2 in the presence of protic compounds such as methanol afforded mono-aldols.[11] It is probably because of protonation of alkoxy samarium enolates **12** which were formed by reduction of oxiranyl ketones with SmI_2 (Scheme 3). These intermediates, alkoxy samarium enolates **12**, have the desirable enolate structures similar to those described in the above $Sn(OTf)_2$-mediated aldol reaction of mono-aldols. Then, it was considered that the corresponding double aldols would be selectively obtained from alkyl or aryl oxiranyl ketones on treatment with SmI_2 and carbonyl compounds in aprotic solvents via samarium enolates **12**.

In the first place, the aldol reaction of aryl oxiranyl ketone **13a** with several aldehydes was examined (Table 2, Entries 1–4). The reaction of **13a** with benzaldehyde gave the corresponding double aldols as a mixture of diastereomers in 55% combined yield along with a small amount of 2-hydroxypropyl phenyl ketone (mono-aldol). Since these double aldol adducts had 1,3-diphenyl structure, dehydration or retro-aldol reaction took place during the usual purification procedure. The desired double aldols **14a** were obtained up to 70% in total when the reaction was carried out at −100 °C for 1 h and at −45 °C for 5 h; however, these double aldol adducts were not stable enough to determine their stereochemistries (Table 2, Entry 1). On the other hand, the double aldols formed from **13a** with aliphatic aldehydes were relatively stable (Entries 2–4), and alkyl oxiranyl ketones, **13c** and **13d**, also reacted with aldehydes to give double aldols in high yields (Entries 7–9). In these cases, undesired by-products, α,β-unsaturated ketones, were not formed because double aldol adducts were rather stable under the above reaction conditions. The isomeric ratios of the formed double aldols **14** were determined by isolating the corresponding acetonides. It was confirmed that the isomeric ra-



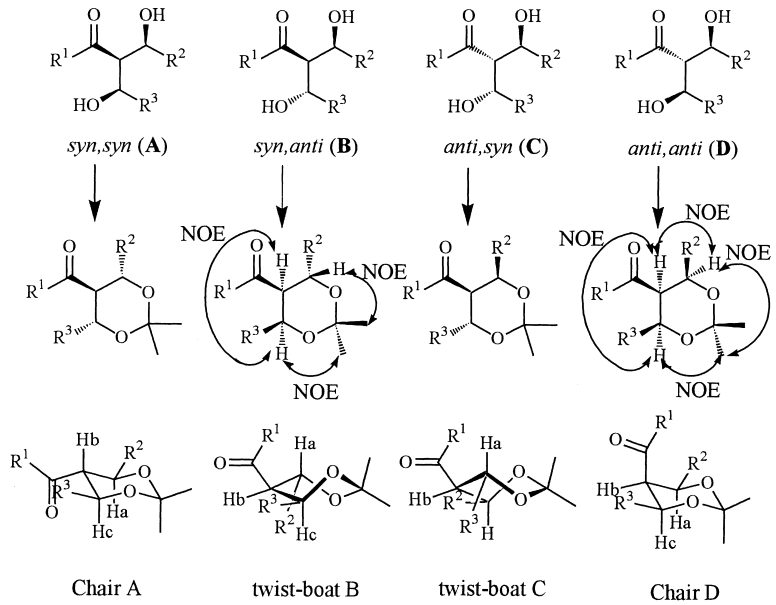
Scheme 3.

Table 2. SmI_2-Mediated Aldol Reaction of Oxiranyl Ketones and Aldehydes



Entry	Oxiranyl ketone			Aldehyde	Product	Yield/%	
	R^1	R^2		R^3			(**A**/**B**/**C**/**D**)[a]
1	Ph	Me	**13a**	Ph	**14a**	70	(nd)[b]
2	Ph	Me	**13a**	Et	**14b**	75	(0/67/0/33)
3	Ph	Me	**13a**	$Ph(CH_2)_2$	**14c**	83	(0/61/0/39)
4	Ph	Me	**13a**	^{i}Pr	**14d**	88	(0/40/0/60)
5	Ph	^{n}Pr	**13b**	$Ph(CH_2)_2$	**14e**	90	(0/35/0/65)
6	Ph	^{n}Pr	**13b**	^{i}Pr	**14f**	84	(0/50/0/50)
7	Me	^{i}Pr	**13c**	Et	**14g**	85	(0/88/0/12)
8	Me	^{i}Pr	**13c**	$Ph(CH_2)_2$	**14h**	95	(0/75/0/25)
9	Me	Ph	**13d**	$Ph(CH_2)_2$	**14i**	84	(0/60/0/40)
10	$-(CH_2)_3-$		**13e**	$Ph(CH_2)_2$	**14j**	77	(97/3/0/0)

a) The ratio of possible four isomers was determined by integration of the ^{1}H NMR spectrum of the mixture of corresponding acetonide derivatives. b) Not determined.

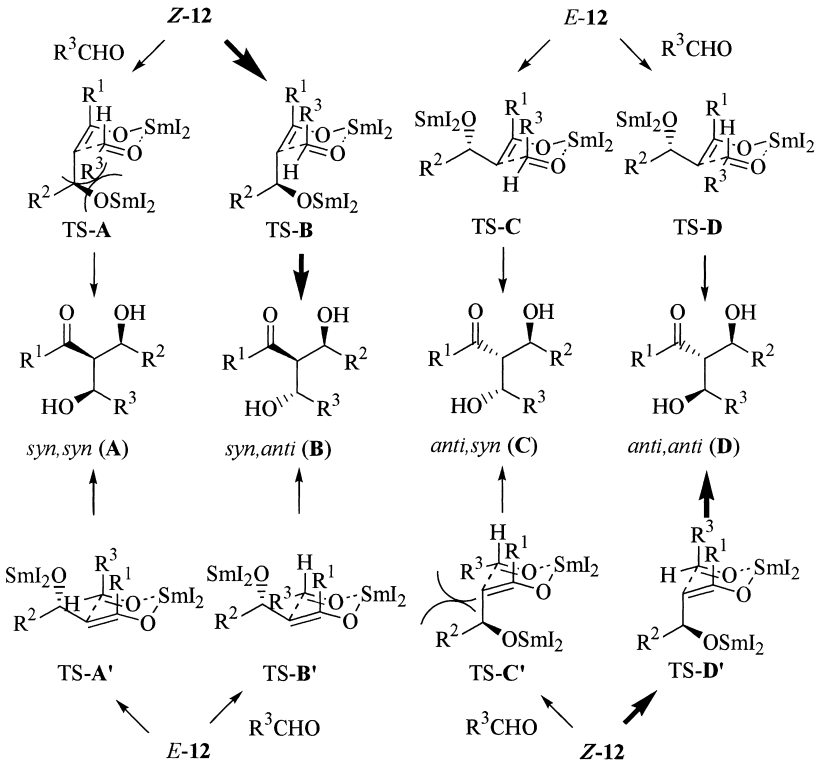


Scheme 4.

tios were not dependent on yields of acetonization of double aldols. The relative configuration of the formed double aldols **14** was determined by ^{1}H NMR measurement of the corresponding acetonides (Scheme 4).

As mentioned in our previous communication,[12,13] stereochemistries of double aldols were deduced from the coupling constants of their acetonides (H_a–H_b and H_b–H_c) whose conformations were considered to be in chair forms. However, the conformational analysis[14] of these acetonides showed that the two acetonide derivatives derived from ***syn,anti*(B)** and ***anti,syn*(C)** double aldols were in twist-boat forms as shown in Scheme 4. In this paper, relative configurations of the acetonides derived from double aldols **14** were determined as **B** and **D** by measuring the NOE relationship as shown in Scheme 4. Therefore, we have to correct the stereochemistry reported in our previous communications to what are shown in this paper. Concerning the stereochemistry of the present SmI_2-mediated double aldol forming reaction, it was found that the two stereoisomers **B** and **D** were formed when acyclic oxiranyl ketones were used (Table 2, Entries 2–9). These results were reasonably explained by assuming selective formation of *Z*-enolates **12** by the reduction of oxiranyl ketones **13a–d** with SmI_2. Two isomeric double aldol adducts **B** and **D** were formed via Zimmermann-type transition state,[15] TS-B and TS-D. Formation of double aldols via TS-A and TS-C seemed unfavorable because of steric repulsion between R^3 and samarium alkoxide or R^2 as shown in Scheme 5. On the other hand, double aldol reaction of cyclic oxiranyl ketones gave two stereoisomers **A** and **B** (Table 2, Entry 10).

Formation of Small and Medium-Sized Double Aldols by



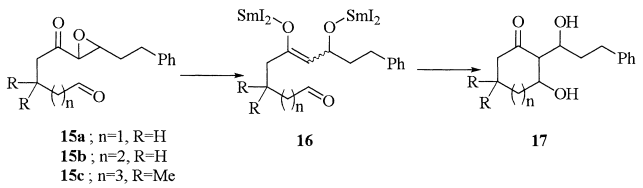
Scheme 5. Proposed reaction pathway for SmI_2-mediated double aldol formation from oxiranyl ketones and aldehydes.

Samarium(II) Iodide-Mediated Intramolecular Cyclization of Oxiranyl Ketone and Aldehyde Functionality. There are a number of biologically active natural products like the taxane family which contain small or medium-sized ring skeletons composed of many oxygenated carbons. To construct such carbocyclic compounds, direct cyclization of open chain precursors would be the most straightforward and versatile method. It was considered that small or medium-sized ring compounds having the double aldol structure should be formed by the intramolecular cyclization of oxiranyl ketone and aldehyde functions with SmI_2.

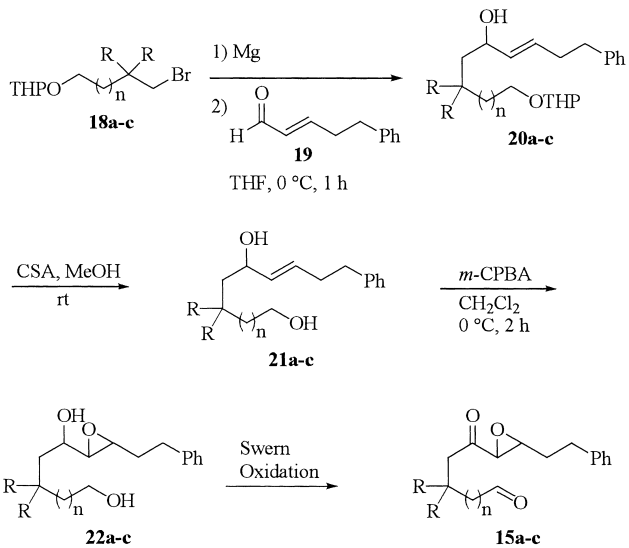
Formation of six to eight-membered cyclic double aldols **17** by samarium(II) iodide-mediated intramolecular cyclization of oxiranyl keto aldehydes **15** was then studied (Scheme 6).[16]

The open chain precursors **15** were prepared as follows: Grignard reaction between THP-protected bromo alcohols **18a–c** and 5-phenyl-2-pentenal **19**, and deprotection of THP group of the Grignard adducts afforded the corresponding allyl alcohols **21a–c**. Epoxidation of **21a–c** with *m*-CPBA gave epoxy diols **22a–c** and the subsequent Swern oxidation of diols **22a–c** gave the desired oxiranyl ketones **15a–c** (Scheme 7).

Formation of the six-membered ring compound **17a** was successfully carried out by cyclization of **15a** by using SmI_2 at



Scheme 6.



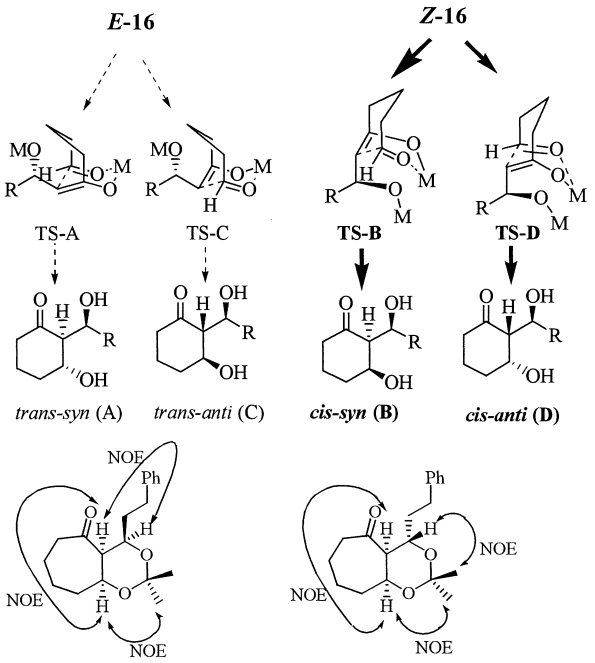
Scheme 7.

−23 °C (60% yield, Table 3, Entry 1). It is generally known that the reducing ability of low-valent samarium species is intensified by the coordination of electron rich ligands such as H_2O to samarium ion. This interesting phenomenon was observed by Kamochi and Kudo on the reduction of carboxylic acids, esters, amides and nitriles by using SmI_2–H_2O.[17] Based on these backgrounds, cyclization reaction was tried at −90 °C in the presence of 3 molar amounts of H_2O, and then the cyclized product **17a** was obtained in 80% yield (Entry 2). Similarly, the cyclization of **15b** proceeded efficiently in the presence of 5 molar amounts of H_2O, leading to the seven-mem-

Table 3. SmI_2-Mediated Intramolecular Double Aldol Formation of Oxiranyl Keto Aldehydes **15a–c**

Entry	Oxiranyl keto aldehyde	Additive (equiv.)	Temp/°C	Product	Yield/% (**A/B/C/D**)[a)]	
1	**15a**	None	−23	**17a**	60	(0/50/0/50)
2	**15a**	H_2O (3)	−90	**17a**	80	(0/80/0/20)
3	**15b**	None	−23	**17b**	65	(0/50/0/50)
4	**15b**	H_2O (5)	−90	**17b**	82	(0/70/0/30)
5	**15c**	None	−23	**17c**	56	(0/50/0/50)
6	**15c**	H_2O (3)	−90	**17c**	78	(0/50/0/50)

a) The ratio of the possible four isomers was determined by integration of the ^1H NMR spectrum of a mixture of the corresponding acetonide derivatives.



Scheme 8. Proposed reaction pathway for SmI_2-mediated intramolecular cyclization of oxiranyl keto aldehydes.

bered ring compound **17b** in 82% yield (Entry 4) whereas only 65% yield of **17b** was obtained in the absence of H_2O (Entry 3).

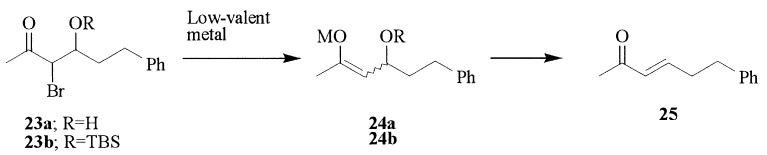
The open chain precursor **15c** having a geminal dimethyl-substituted carbon was used for the present double aldol cyclization, and the desired eight-membered cyclic double aldol **17c** was obtained in 78% yield by using 3 molar amounts of H_2O while 56% yield of **17c** was obtained in the absence of H_2O (Entry 5 and 6). The stereochemistries of cyclic double aldols **17** were determined by NOE after their conversion to the corresponding acetonides (Scheme 8).

Concerning the diastereoselectivities of the present reaction, two stereoisomers, *cis-syn*-(**B**) and *cis-anti*-isomer (**D**), were formed preferentially. On the assumption that the present intramolecular double aldol cyclization proceeded via Zimmermann-type six-membered transition states, *Z* samarium enolates **16** were selectively formed by the reduction of oxiranyl keto aldehydes **15** with SmI_2 as described in the intermolecular double aldol reaction. The cyclization was then thought to proceed via transition states, TS-B or TS-D, to give double aldol adducts **B** or **D**, respectively (Scheme 8).

A Convenient Method for the Preparation of Unsymmetrical Double Aldols by Way of Two Sequential Aldol Reactions. In the third place, an alternative method for the formation of double aldols was studied. It was first thought that β-metalloxy enolate **24a**, the key intermediate for preparing double aldols, might be prepared by reduction of α-halo-β-hydroxy ketone **23a** by using low-valent metal species generated from $ZnCl_2$,[18] $SnCl_2$[19] or $TiCl_2$[20] (Scheme 9). However, **23a** was generally known to be unstable and thus could not be utilized as a substrate for the double aldol reaction.[21] Then, α-halo-β-*t*-butyldimethylsiloxy ketone **23b** was used to form enolate **24b**. However, double aldol formation reaction did not take place, and only 6-phenyl-3-hexen-2-one **25** was obtained, which was probably due to desilyloxylation of the formed enolate anion **24b** (Scheme 9).

Next, it was considered that the above-mentioned β-elimination would not proceed in the case of in situ formed β-metalloxy metal enolate **26** since the metalloxy group was not easy to be eliminated. Then, the synthesis of double aldols was carried out according to the sequential reactions shown in Scheme 10. That is, $Sn(OTf)_2$-mediated aldol reaction of α-bromo ketone with 3-phenylpropionaldehyde in the presence of triethylamine[8] gave α-bromo-β-stannyloxy ketone which was further in situ treated with a low-valent metal species such as Ti, Sn, Zn and so on to give β-metalloxy enolate **26**. Thus formed **26** reacted with aldehydes to give double aldols (Method A).

When lower-valent metal species generated from $ZnCl_2$,

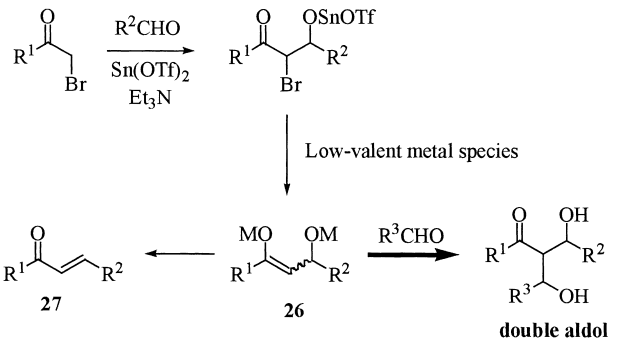


Scheme 9.

Table 4. Double Aldol Formation Reaction by Two Sequential Aldol Reaction of α-Bromo Ketones

Entry	R^1	R^2	R^3	Product	Yield/%	(**A**/**B**/**C**/**D**)[a]	Method[b]
1	Me	$Ph(CH_2)_2$	^{i}Pr	**14h**	88	(0/30/10/60)	A
2	Me	$Ph(CH_2)_2$	^{i}Pr	**14h**	84	Only **D**	B
3	Me	^{i}Pr	$Ph(CH_2)_2$	**14h**	86	Only **D**	B
4	Me	$Ph(CH_2)_2$	Ph	**14i**	93	(0/10/0/90)	B
5	Me	Ph	$Ph(CH_2)_2$	**14i**	84	(0/15/0/85)	B
6	Et	$Ph(CH_2)_2$	^{i}Pr	**14k**	87	Only **D**	B
7	Et	^{i}Pr	$Ph(CH_2)_2$	**14k**	79	Only **D**	B
8	^{i}Pr	$Ph(CH_2)_2$	^{i}Pr	**14l**	86	Only **D**	B
9	^{i}Pr	^{i}Pr	$Ph(CH_2)_2$	**14l**	78	Only **D**	B

a) The ratio of the possible four isomers was determined by the integration of ^{1}H NMR spectrum of a mixture of the corresponding dimethyl acetonide derivatives. b) Method A: $TiCl_4$ was not added after the first reaction. Method B: 1.2 molar amounts of $TiCl_4$ were added after the first reaction.



Scheme 10.

$SnCl_2$ or $TiCl_2$ was used after the first aldol reaction between bromoacetone and 3-phenylpropanal, β-elimination took place as well to afford α,β-unsaturated ketone **27**, 6-phenyl-3-hexen-2-one. It was probably because the reduction was carried out above 0 °C. On the other hand, low-valent titanium iodide species which was generated from titanium tetraiodide and Cu in the presence of pivalonitrile gave a mixture of stereoisomers of the desired double aldols in 88% yield without the formation of α,β-unsaturated ketone **27** (Table 4, Entry 1).

Further, 1.2 molar amounts of $TiCl_4$ were added after the first aldol reaction in order to form α-bromo-β-titaniumoxy ketones before the reduction with low-valent titanium species. Thus formed α-bromo-β-titaniumoxy ketones were allowed to react in turn with low-valent titanium and aldehydes (Method B). The double aldols were obtained in 78–93% yields and in improved diastereoselectivities by these sequential aldol reactions via titanium dianion **26**. Only one stereoisomer **D** was obtained in cases when aliphatic α-bromo ketones were used (Entries 2–3 and 6–9) whereas two stereoisomers **D** and **B** were obtained in the ratios of $>$ 85/15 when benzaldehyde was used as one of the two aldehydes in the sequential aldol reactions (Table 4, Entry 4 and 5).

Conclusion

Thus, convenient methods for the synthesis of unsymmetrical double aldols according to three different types of reactions were developed. The $Sn(OTf)_2$-mediated aldol reaction of aldehydes with mono-aldols afforded double aldols in good yields with high diastereoselectivities. The SmI_2-mediated aldol reaction of aldehydes with alkyl or aryl oxiranyl ketones afforded the desired double aldols in good to high yields, which was applied to the synthesis of small and medium-sized carbocyclic compounds whose ring skeletons contained double aldol structure. In the third method, highly diastereoselective double aldol synthesis was achieved by way of two sequential aldol reactions: that is, after the first aldol reaction of α-bromo ketones with aldehydes gave α-bromo-β-stannyloxy ketones which were then converted to β-titaniumoxy titanium enolates on successive treatment with $TiCl_4$ and low-valent titanium. Double aldols were formed stereoselectively by the subsequent reaction between the above titanium enolates with aldehydes in one-pot procedure.

Experimental

General. All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and are not corrected. Infrared (IR) spectra were recorded on a Horiba FT300 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM EX270L (270 MHz), JEOL JNM LA300 (300 MHz), JEOL JNM LA400 (400 MHz) or JEOL JNM LA500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a JEOL JNM LA400 (100 MHz) or JEOL JNM LA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0 ppm). High resolution mass spectra (HRMS) were reported on a JEOL LC-Mate. Analytical high performance liquid chromatography (HPLC) was performed on a Hitachi LC-Organizer (L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator) equipped with a column of Shodex SIL-5B (ϕ 4.6 $\times$ 250 mm). Analytical TLC was performed on Merck preparative TLC plates (silica gel 60 GF254, 0.25 mm). Column chromatography was carried out on Merck silica gel 60 (0.063–0.200 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. Dry solvents were prepared by distillation under appropriate drying agents. Powder molecular sieves 3A, 4A, 5A (purchased

from Aldrich) and Drierite (purchased from W. A. HAMMOND DRIERITE COMPANY) were dried in vacuo (13.3 Pa) at 260 °C for 5 h before use. Aldehydes and ketones were purified by distillation or recrystallization. Titanium tetrachloride was purified by distillation. Sodium iodide and potassium iodide (purchased from Kanto Kagaku) were dried in vacuo (13.3 Pa) at 100 °C for 6 h and kept under an argon atmosphere. Zinc powder was activated according to the reported procedure and kept under an argon atmosphere. Copper powder (purity 99.999%; purchased from Soekawa Kagaku) was dried in vacuo at 100 °C for 1 h and kept under an argon atmosphere. Titanium dichloride and $Sn(OTf)_2$ were prepared according to the reported procedures.[22,23]

Typical Procedure for $Sn(OTf)_2$-Mediated Aldol Reaction between Mono-Aldols and Aldehydes (Table 1, entry 4). Under an argon atmosphere, DBU (0.15 mL, 1.02 mmol) was added to a suspension of $Sn(OTf)_2$ (220 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After the mixture was stirred for 15 min at the same temperature, a solution of 3-hydroxy-4-methyl-1-phenylpentan-1-one (98.0 mg, 0.51 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture, and the mixture was stirred for 1 h at −78 °C and for 10 min at 0 °C. After 3-phenylpropionaldehyde (80.5 mg, 0.6 mmol) was added to the above mixture at −78 °C, the resulting reaction mixture was stirred for 1 h, and then the reaction was quenched with phosphate buffer solution (pH = 7). The mixture was filtered through a short pad of Celite, and the filtrate was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 3-hydroxy-2-(1-hydroxy-3-phenylpropyl)-4-methyl-1-phenylpentan-1-one (**9b**) (129.9 mg, 81%) as colorless oil. The structure of the obtained double aldol was determined by converting it to the corresponding acetonide. That is, to a solution of double aldol **9b** and acetone dimethyl acetal (0.3 mL, 2.4 mmol) in CH_2Cl_2 (2 mL) was added camphor-10-sulfonic acid (CSA) (5 mg, 0.02 mmol) at 0 °C. After the reaction mixture was stirred for 10 h at room temperature, it was quenched with Et_3N (0.3 mL, 2.2 mmol). The solvent was evaporated, the crude product was purified by PTLC (5% hexane–EtOAc, or 5% hexane–Et_2O) to give [(4*RS*,5*RS*,6*SR*)-4-isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]phenylmethanone (**9bAc-D**) (121.2 mg, 78%) as colorless oil.

[(4*RS*,5*RS*,6*SR*)-4-Isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]phenylmethanone (9bAc-D). IR (neat, cm^{-1}) 2962, 1673, 1597, 1450, 1373, 1196, 918, 733; ^1H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2H), 7.54–7.39 (m, 3H), 7.27–7.05 (m, 5H), 3.99 (dt, J = 3.0, 6.1 Hz, 1H), 3.52 (t, J = 3.0 Hz, 1H), 3.49 (t, J = 3.0 Hz, 1H), 2.78–2.52 (m, 2H), 1.75–1.55 (m, 5H), 1.61 (s, 3H), 1.42 (s, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.5, 141.2, 139.4, 132.6, 128.8, 128.6, 128.6, 128.3, 128.3, 128.1, 128.0, 126.8, 125.6, 99.0, 70.0, 44.5, 35.5, 31.4, 30.3, 29.6, 19.6, 19.3, 18.9; HRMS *m/z* calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389. 2092.

[(4*RS*,5*SR*,6*RS*)-4-Isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]phenylmethanone (9bAc-B). IR (neat, cm^{-1}) 2931, 1666, 1589, 1450, 1373, 1227, 733; ^1H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2H), 7.58–7.43 (m, 3H), 7.21–7.02 (m, 5H), 4.11 (dd, J = 6.8, 8.6 Hz, 1H), 4.01 (ddd, J = 3.0, 6.8, 10.5 Hz, 1H), 3.81 (dd, J = 5.9, 8.6 Hz, 1H), 2.82–2.72 (m, 1H), 2.53–2.42 (m, 1H), 1.73–1.49 (m, 5H), 1.54 (s, 3H), 1.36 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.4, 141.3, 138.1, 130.0, 128.7, 128.7, 128.4, 128.2, 128.2, 128.1, 128.1, 127.9, 125.7, 101.0, 68.5, 51.4, 33.4, 33.4, 32.7, 25.0, 23.9, 18.3; HRMS *m/z* calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389.2090.

Typical Procedure for the Synthesis of Epoxy Ketones. To a solution of cyclohex-2-en-1-one (9.9 g, 0.10 mol) in MeOH (100 mL), hydrogen peroxide (30%, 10 mL, 0.31 mol) and 1.0 M (= 1 mol dm^{-3}) aqueous NaOH (pH > 12) were successively added at 0 °C. After the completion of the reaction was confirmed by TLC analysis, the reaction mixture was extracted with Et_2O (100 mL). The combined organic extracts were washed with H_2O, aqueous sodium thiosulfate and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude product by distillation under reduced pressure gave (1*RS*,6*SR*)-7-oxabicyclo[4.1.0]heptan-2-one (**13e**) (9.2 g, 80%) as colorless oil.

(1*RS*,6*SR*)-7-Oxabicyclo[4.1.0]heptan-2-one (13e).[24] IR (neat, cm^{-1}) 2939, 1712, 1412, 1335, 1242; ^1H NMR ($CDCl_3$) δ 3.60 (br, 1H), 3.20 (d, J = 4.2 Hz, 1H), 2.57–2.49 (m, 1H), 2.35–1.85 (m, 4H), 1.77–1.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 205.6, 55.6, 54.8, 54.8, 36.1, 22.5, 16.6; HRMS *m/z* calcd for $C_6H_7O_2$ $[M - H]^-$ 111.0446, found 111.0433.

[(2*RS*,3*SR*)-3-Methyloxiran-2-yl]phenylmethanone (13a).[25] IR (neat, cm^{-1}) 1689, 1589, 1450, 1234, 941; ^1H NMR ($CDCl_3$) δ 8.03–8.00 (m, 2H), 7.72–7.28 (m, 3H), 3.99 (d, J = 1.6 Hz), 3.20 (dq, J = 1.6, 4.6 Hz, 1H), 1.49 (d, J = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 194.1, 135.1, 133.4, 128.4, 127.8, 57.7, 55.5, 17.1; HRMS *m/z* calcd for $C_{10}H_{10}O_2Na$ $[M + Na]^+$ 185.0579, found 185.0611.

[(2*RS*,3*SR*)-3-Propyloxiran-2-yl]phenylmethanone (13b).[26] IR (neat, cm^{-1}) 2939, 1689, 1597, 1450, 1234, 903; ^1H NMR ($CDCl_3$) δ 8.04–8.00 (m, 2H), 7.64–7.29 (m, 3H), 4.03 (d, J = 1.9 Hz, 1H), 3.14 (dq, J = 1.9, 4.3 Hz, 1H), 1.83–1.49 (m, 4H), 1.00 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 194.6, 133.7, 128.7, 128.1, 59.8, 57.2, 33.8, 19.1, 13.7; HRMS *m/z* calcd for $C_{12}H_{14}O_2Na$ $[M + Na]^+$ 213.0892, found 213.0901.

1-[(2*RS*,3*SR*)-3-Isopropyloxiran-2-yl]ethanone (13c).[26] IR (neat, cm^{-1}) 2970, 1712, 1466, 1427, 1365, 1250, 872; ^1H NMR ($CDCl_3$) δ 3.20 (d, J = 1.9 Hz, 1H), 2.86 (dd, J = 1.9, 6.2 Hz, 1H), 2.04 (s, 3H), 1.67–1.56 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 204.5, 115.8, 63.0, 58.9, 30.3, 24.2, 18.7, 18.0.

1-[(2*RS*,3*SR*)-3-Phenyloxiran-2-yl]ethanone (13d).[27] IR (neat, cm^{-1}) 3032, 1705, 1442, 1342, 1241, 1095, 841; ^1H NMR ($CDCl_3$) δ 7.90–7.19 (m, 5H), 4.00 (d, J = 1.8 Hz, 1H), 3.49 (d, J = 1.8 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.1, 135.0, 129.0, 128.7, 125.7, 63.4, 57.7, 24.8; HRMS *m/z* calcd for $C_{10}H_{10}O_2Na$ $[M + Na]^+$ 185.0579, found 185.0613.

Typical Procedure for SmI_2-Mediated Aldol Reaction between Epoxy Ketones and Aldehydes (Table 2, entry 3). To a solution of epoxy ketone **13a** (162.2 mg, 1.0 mmol) and 3-phenylpropionaldehyde (147.6 mg, 1.1 mmol) in THF (10 mL) was added dropwise a solution of SmI_2 in THF (0.1 M, 22 mL, 2.2 mmol) over 1 h at −78 °C under an argon atmosphere. After the reaction mixture was stirred for 1 h at −78 °C and for 5 h at −45 °C, the reaction was quenched by adding MeOH–H_2O (1:9) (0.1 mL). After having been diluted with EtOAc, the mixture was filtered through silica gel that had been deactivated with H_2O, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (deactivated silica gel, 25% hexane–EtOAc) to give the corresponding double aldol (280.9 mg, 83%) as colorless oil. The structure of the obtained double aldol was determined by converting it to the corresponding phenyl(2,2,4-trimethyl-6-phenethyl-1,3-dioxan-5-yl)methanone **14cAc** (**B/D** = 61/39) according to the procedure described above.

Phenyl[(4*RS*,5*RS*,6*RS*)-2,2,4-trimethyl-6-phenethyl-1,3-dioxan-5-yl]methanone (14cAc-B). IR (neat, cm^{-1}) 2947, 1673, 1450, 1373, 1211, 995; ^1H NMR ($CDCl_3$) δ 7.90–7.89 (m, 2H), 7.58–7.42 (m, 3H), 7.24–7.02 (m, 5H), 4.40 (dt, J = 6.2, 9.0 Hz, 1H), 4.06 (dq, J = 2.9, 6.8 Hz, 1H), 3.70 (dd, J = 6.8, 9.0 Hz, 1H), 2.80–2.71 (m, 1H), 2.53–2.46 (m, 1H), 1.80–1.70 (m, 2H), 1.54 (s, 3H), 1.38 (s, 3H), 1.16 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.6, 141.3, 138.4, 133.2, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 125.8, 101.0, 68.1, 37.0, 55.5, 33.3, 32.0, 24.8, 24.4, 20.8; HRMS *m*/*z* calcd for $C_{22}H_{26}O_3Na$ $[M + Na]^+$ 361.1780, found 361.1786.

Phenyl[(4*RS*,5*SR*,6*SR*)-2,2,4-trimethyl-6-phenethyl-1,3-dioxan-5-yl]methanone (14cAc-D). IR (neat, cm^{-1}) 2947, 1682, 1450, 1373, 1203, 995; ^1H NMR ($CDCl_3$) δ 7.92–7.89 (m, 2H), 7.55–7.41 (m, 3H), 7.24–7.05 (m, 5H), 4.26 (dq, J = 3.1, 6.6 Hz, 1H), 4.06 (ddd, J = 3.1, 3.4, 3.5 Hz, 1H), 3.40 (t, J = 3.1 Hz, 1H), 2.78–2.69 (m, 1H), 2.63–2.53 (m, 1H), 1.90–1.77 (m, 2H), 1.62–1.51 (m, 2H), 1.62 (s, 3H), 1.48 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.7, 141.3, 139.8, 132.6, 128.6, 128.5, 128.2, 127.8, 125.7, 99.0, 69.5, 66.8, 47.1, 35.1, 31.4, 29.7, 19.6, 19.0; HRMS *m*/*z* calcd for $C_{22}H_{26}O_3Na$ $[M + Na]^+$ 361.1780, found 361.1783.

Phenyl[(4*RS*,5*RS*,6*SR*)-2,2,4-trimethyl-6-phenyl-1,3-dioxan-5-yl]methanone (14aAc-B). IR (neat, cm^{-1}) 2978, 1689, 1458, 1373; ^1H NMR ($CDCl_3$) δ 7.50–6.90 (m, 10H), 5.26 (d, J = 7.0 Hz, 1H), 4.64 (dq, J = 6.2, 9.0 Hz, 1H), 4.02 (dd, J = 7.0, 9.0 Hz, 1H), 1.64 (s, 3H), 1.46 (s, 3H), 1.27 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.1, 132.3, 128.5, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 126.5, 126.1, 101.5, 71.0, 66.4, 57.6, 24.6, 24.3, 21.0; HRMS *m*/*z* calcd for $C_{20}H_{22}O_3Na$ $[M + Na]^+$ 333.1467, found 333.1468.

Phenyl[(4*RS*,5*SR*,6*RS*)-2,2,4-trimethyl-6-phenyl-1,3-dioxan-5-yl]methanone (14aAc-D). IR (neat, cm^{-1}) 2978, 1689, 1458, 1373; ^1H NMR ($CDCl_3$) δ 7.50–7.00 (m, 10H), 5.30 (d, J = 3.3 Hz, 1H), 4.49 (dq, J = 6.4, 3.3 Hz, 1H), 3.74 (t, J = 3.3 Hz, 1H), 1.72 (s, 3H), 1.61 (s, 3H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.2, 140.0, 139.3, 131.9, 128.1, 128.0, 127.4, 127.3, 126.9, 125.9, 99.4, 72.9, 67.0, 49.6, 29.7, 19.7, 19.1; HRMS *m*/*z* calcd for $C_{20}H_{22}O_3Na$ $[M + Na]^+$ 333.1467, found 333.1465.

[(4*RS*,5*SR*,6*RS*)-4-Ethyl-2,2,6-trimethyl-1,3-dioxan-5-yl]-phenylmethanone (14bAc-B). IR (neat, cm^{-1}) 2976, 1666, 1450, 1373; ^1H NMR ($CDCl_3$) δ 7.95–7.91 (m, 2H), 7.60–7.44 (m, 3H), 4.42 (dq, J = 6.2 , 9.2 Hz, 1H), 4.00 (dt, J = 3.7, 6.6 Hz, 1H), 3.74 (dd, J = 6.6, 9.2 Hz, 1H), 1.52 (s, 3H), 1.39 (s, 3H), 1.45–1.20 (m, 2H), 1.20 (d, J = 6.2 Hz, 3H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.6, 138.5, 133.1, 128.7, 128.3, 128.1, 100.9, 70.8, 66.8, 55.6, 25.0, 24.5, 24.3, 20.8, 10.7; HRMS *m*/*z* calcd for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467, found 285.1468.

[(4*RS*,5*SR*,6*SR*)-4-Ethyl-2,2,6-trimethyl-1,3-dioxan-5-yl]-phenylmethanone (14bAc-D). IR (neat, cm^{-1}) 2978, 1681, 1450, 1373, 1196; ^1H NMR ($CDCl_3$) δ 7.95–7.92 (m, 2H), 7.57–7.43 (m, 3H), 4.34 (dq, J = 3.1 , 6.4 Hz, 1H), 4.02 (dt, J = 3.1, 5.5 Hz, 1H), 3.51 (t, J = 3.1 Hz, 1H), 1.59 (s, 3H), 1.51 (s, 3H), 1.51–1.36 (m, 2H), 1.14 (d, J = 6.4 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.7, 139.9, 132.6, 128.5, 127.8, 98.8, 72.7, 66.8, 46.8, 29.7, 16.6, 19.7, 19.0, 10.1; HRMS *m*/*z* calcd for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467, found 285.1467.

[(4*RS*,5*SR*,6*RS*)-4-Isopropyl-2,2,6-trimethyl-1,3-dioxan-5-yl]phenylmethanone (14dAc-B). IR (neat, cm^{-1}) 2954, 1673, 1458, 1373, 1227, 995; ^1H NMR ($CDCl_3$) δ 7.98–7.96 (m, 2H), 7.59–7.44 (m, 3H), 4.05 (dq, J = 6.4, 9.9 Hz, 1H), 3.84 (dd, J = 5.7, 8.8 Hz, 1H), 3.55 (dd, J = 5.7, 9.9 Hz, 1H), 1.78–1.67 (m, 1H), 1.50 (s, 3H), 1.37 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H), 0.60 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.5, 138.6, 133.0, 128.7, 128.1, 128.0, 101.3, 53.4, 37.3, 28.8, 24.0, 23.8, 19.8, 18.8, 18.7, 13.7; HRMS *m*/*z* calcd for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1617.

[(4*RS*,5*RS*,6*SR*)-4-Isopropyl-2,2,6-trimethyl-1,3-dioxan-5-yl]phenylmethanone (14dAc-D). IR (neat, cm^{-1}) 2978, 1682, 1458, 1373, 1196, 987; ^1H NMR ($CDCl_3$) δ 7.97–7.94 (m, 2H), 7.58–7.36 (m, 3H), 4.32 (dq, J = 3.0, 6.6 Hz, 1H), 3.61–3.57 (m, 2H), 1.74–1.55 (m, 1H), 1.59 (s, 3H), 1.49 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.5, 139.7, 132.5, 128.6, 127.8, 98.9, 67.1, 45.2, 30.4, 29.7, 20.1, 19.6, 18.9, 18.3; HRMS *m*/*z* calcd for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1620.

[(4*RS*,5*SR*,6*RS*)-2,2-Dimethyl-4-phenethyl-6-propyl-1,3-dioxan-5-yl]phenylmethanone (14eAc-B). IR (neat, cm^{-1}) 2954, 1674, 1458, 1373, 1227, 995; ^1H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2H), 7.59–7.44 (m, 3H), 7.26–7.02 (m, 5H), 4.28 (dt, J = 3.5, 9.0 Hz, 1H), 4.05 (ddd, J = 2.6, 6.4, 10.3 Hz, 1H), 3.72 (dd, J = 6.4, 9.0 Hz, 1H), 2.81–2.71 (m, 1H), 2.52–2.42 (m, 1H), 1.76–1.64 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.50–1.20 (m, 5H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.9, 133.7, 128.5, 128.3, 125.7, 101.7, 100.8, 71.1, 68.4, 37.4, 24.5, 14.0; HRMS *m*/*z* calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389.2093.

[(4*RS*,5*RS*,6*SR*)-2,2-Dimethyl-4-phenethyl-6-propyl-1,3-dioxan-5-yl]phenylmethanone (14eAc-D). IR (neat, cm^{-1}) 2954, 1682, 1450, 1373, 1196, 941; ^1H NMR ($CDCl_3$) δ 7.92–7.89 (m, 2H), 7.54–7.40 (m, 3H), 7.24–7.05 (m, 5H), 4.07–4.04 (m, 2H), 3.40 (t, J = 3.0 Hz, 1H), 2.77–2.54 (m, 2H), 1.87–1.74 (m, 1H), 1.62 (s, 3H), 1.46 (s, 3H), 1.70–1.20 (m, 5H), 0.76 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.9, 141.3, 139.7, 132.6, 128.1, 127.8, 125.7, 99.0, 70.8, 69.6, 46.4, 35.5, 35.2, 31.4, 29.7, 19.0, 18.7, 13.4; HRMS *m*/*z* calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389.2095.

[(4*RS*,5*SR*,6*RS*)-4-Isopropyl-2,2-dimethyl-6-propyl-1,3-dioxan-5-yl]phenylmethanone (14fAc-B). IR (neat, cm^{-1}) 2985, 1674, 1450, 1373, 1227, 980; ^1H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2H), 7.59–7.44 (m, 3H), 7.26–7.02 (m, 5H), 4.28 (dt, J = 3.5, 9.0 Hz, 1H), 4.05 (ddd, J = 2.6, 6.4, 10.3 Hz, 1H), 3.72 (dd, J = 6.4, 9.0 Hz, 1H), 2.81–2.71 (m, 1H), 2.52–2.42 (m, 1H), 1.76–1.64 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.50–1.20 (m, 5H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.5, 138.6, 133.0, 128.7, 128.1, 128.0, 101.3, 72.1, 53.4, 37.3, 28.8, 24.0, 23.8, 13.7, 19.8, 18.8, 13.7; HRMS *m*/*z* calcd for $C_{19}H_{28}O_3Na$ $[M + Na]^+$ 327.1936, found 327.1944.

[(4*RS*,5*RS*,6*SR*)-4-Isopropyl-2,2-dimethyl-6-propyl-1,3-dioxan-5-yl]phenylmethanone (14fAc-D). IR (neat, cm^{-1}) 2962, 1682, 1458, 1373, 1196, 949; ^1H NMR ($CDCl_3$) δ 7.98–7.96 (m, 2H), 7.59–7.27 (m, 3H), 4.05 (m, 1H), 3.84 (dd, J = 5.7, 8.9 Hz, 1H), 3.56 (dd, J = 5.7, 9.9 Hz, 1H), 1.76–1.65 (m, 1H), 1.60–1.20 (m, 5H), 1.49 (s, 3H), 1.37 (s, 3H), 0.91 (t, J = 6.4 Hz, 3H), 0.82 (t, J = 7.0 Hz, 3H) , 0.60 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.7, 139.6, 132.5, 128.5, 128.0, 98.9, 71.1, 44.8, 36.0, 30.4, 29.6, 19.6, 18.9, 18.8, 18.4, 13.4; HRMS *m*/*z* calcd for $C_{19}H_{28}O_3Na$ $[M + Na]^+$ 327.1936, found 327.1936.

1-[(4*RS*,5*SR*,6*RS*)-4-Ethyl-2,2-dimethyl-6-isopropyl-1,3-dioxan-5-yl]ethanone (14gAc-B). IR (neat, cm^{-1}) 2985, 1697, 1465, 1373; ^1H NMR ($CDCl_3$) δ 3.85–3.73 (m, 2H), 2.79 (dd, J = 5.7, 8.4 Hz, 1H), 2.25 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.64–1.27 (m, 3H), 0.84 (t, J = 6.9 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 210.1, 99.2, 74.0,

70.1, 59.9, 32.9, 30.9, 24.6, 24.5, 23.5, 18.2, 17.7, 10.8; HRMS *m/z* calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$ 251.1623, found 251.1627.

1-[(4*RS*,5*RS*,6*SR*)-4-Ethyl-2,2-dimethyl-6-isopropyl-1,3-dioxan-5-yl]ethanone (14gAc-D). IR (neat, cm^{-1}) 2978, 1689, 1465, 1365, 1257; ^1H NMR ($CDCl_3$) δ 3.85–3.79 (m, 2H), 3.46 (dd, J = 3.1, 9.9 Hz, 1H), 2.46 (t, J = 3.1 Hz, 3H), 2.34 (s, 3H), 1.60–1.30 (m, 3H), 0.97–0.84 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 210.2, 99.2, 76.2, 72.0, 54.9, 32.7, 31.2, 29.7, 26.6, 19.7, 18.9, 17.9, 9.9; HRMS *m/z* calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$ 251.1623, found 251.1622.

1-[(4*RS*,5*SR*,6*RS*)-4-Isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]ethanone (14hAc-B). IR (neat, cm^{-1}) 2931, 1704, 1458, 1373,1227; ^1H NMR ($CDCl_3$) δ 7.26–7.13 (m, 5H), 3.84 (ddd, J = 3.4, 5.6, 9.3 Hz, 1H), 3.77 (dd, J = 7.1, 8.6 Hz, 1H), 2.84–2.77 (m, 1H), 2.73 (dd, J = 5.6, 8.6 Hz, 1H), 2.55–2.48 (m, 2H), 2.21 (s, 3H), 1.74–1.57 (m, 3H), 1.44 (s, 3H), 1.30 (s, 3H), 0.87 (d, J = 7.2 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 209.8, 141.3, 128.5, 128.4, 125.9, 101.0, 74.1, 67.7, 59.8, 33.0, 32.9, 32.2, 31.2, 24.9, 23.5, 18.3, 17.7; HRMS *m/z* calcd for $C_{19}H_{28}O_3Na$ $[M + Na]^+$ 327.1936, found 327.1937.

1-[(4*RS*,5*RS*,6*SR*)-4-Isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]ethanone (14hAc-D). IR (neat, cm^{-1}) 2938, 2877, 1697, 1450, 1373, 1265, 1188, 987; ^1H NMR ($CDCl_3$) δ 7.26–7.12 (m, 5H), 3.83 (ddd, J = 3.2, 4.4, 7.8 Hz, 1H), 3.38 (dd, J = 2.9, 10.0 Hz, 1H), 2.75–2.59 (m, 2H), 2.35 (dd, J = 2.9, 3.2 Hz, 1H), 2.34 (s, 3H), 1.77–1.57 (m, 2H), 1.56–1.47 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 209.9, 141.1, 128.5, 128.3, 125.9, 98.3, 74.3, 68.9, 61.9, 55.3, 36.2, 33.3, 32.6, 31.5, 29.5, 19.6, 17.8; HRMS *m/z* calcd for $C_{19}H_{28}O_3Na$ $[M + Na]^+$ 327.1936, found 327.1938.

1-[(4*RS*,5*RS*,6*SR*)-2,2-Dimethyl-4-phenethyl-6-phenyl-1,3-dioxan-5-yl]ethanone (14iAc-B). IR (neat, cm^{-1}) 2939, 1697, 1442, 1373, 1219, 1110, 710; ^1H NMR ($CDCl_3$) δ 7.31–7.16 (m, 10H), 5.10 (d, J = 9.0 Hz, 1H), 4.15–4.08 (m, 1H), 3.13 (dd, J = 6.4, 9.0 Hz, 1H), 2.85–2.52 (m, 2H), 2.09 (s, 3H), 1.83–1.57 (m, 2H), 1.55 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.3, 138.9, 128.6, 128.5, 128.4, 127.9, 126.0, 124.8, 101.7, 71.8, 67.7, 62.6, 57.8, 33.1, 32.6, 32.2, 31.2, 29.8, 24.1, 19.1; HRMS *m/z* calcd for $C_{22}H_{26}O_3Na$ $[M + Na]^+$ 361.1780, found 361.1786.

1-[(4*RS*,5*SR*,6*RS*)-2,2-Dimethyl-4-phenethyl-6-phenyl-1,3-dioxan-5-yl]ethanone (14iAc-D). IR (neat, cm^{-1}) 2962, 1689, 1458, 1365, 1265, 1196, 980; ^1H NMR ($CDCl_3$) δ 7.32–7.16 (m, 10H), 5.18 (d, J = 3.4 Hz, 1H), 4.15–4.08 (m, 1H), 2.80–2.58 (m, 2H), 2.72 (t, J = 3.4 Hz, 1H), 2.14 (s, 3H), 1.83–1.70 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.4, 141.0, 138.8, 128.6, 128.4, 128.3, 128.3, 128.2, 127.3, 125.9, 124.7, 99.8, 70.5, 68.9, 57.9, 35.1, 32.7, 31.4, 29.9, 19.2; HRMS *m/z* calcd for $C_{22}H_{26}O_3Na$ $[M + Na]^+$ 361.1780, found 361.1783.

(4*RS*,4a*SR*,8a*SR*)-2,2-Dimethyl-4-phenethyl-4,4a,6,7,8,8a-hexahydro-5*H*-1,3-benzodioxin-5-one (14jAc-A). IR (neat, cm^{-1}) 2970, 1712, 1442, 1373, 1195, 1026, 810; ^1H NMR (C_6D_6) δ 7.21–7.08 (m, 5H), 3.76 (brd, J = 2.7 Hz, 3H), 3.40 (dt, J = 2.7, 9.8 Hz, 1H), 3.12–3.05 (m, 2H), 3.07 (t, J = 2.7 Hz, 1H), 2.84–2.79 (m, 1H), 2.66–2.60 (m, 1H), 2.29–2.27 (m, 1H), 2.11–2.00 (m, 1H), 1.86–1.65 (m, 3H), 1.49 (s, 3H), 1.40–1.33 (m, 2H), 1.23 (s, 3H), 1.23–1.13 (m, 1H); ^{13}C NMR (C_6D_6) δ 205.7, 142.3, 128.8, 128.2, 125.7, 99.6, 71.9, 70.2, 50.2, 42.4, 34.7, 32.4, 30.3, 29.9, 21.2, 19.1; HRMS *m/z* calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$ 311.1623, found 311.1610.

(4*RS*,4a*SR*,8a*RS*)-2,2-Dimethyl-4-phenethyl-4,4a,6,7,8,8a-hexahydro-5*H*-1,3-benzodioxin-5-one (14jAc-B). IR (neat, cm^{-1}) 2938, 1704, 1450, 1373, 1227, 1103; ^1H NMR (C_6D_6) δ 7.18–7.058 (m, 5H), 4.55–4.48 (m, 1H), 4.15 (m, 1H), 2.97–2.86 (m, 1H), 2.75–2.64 (m, 1H), 2.26–2.20 (m, 1H), 1.95–1.60 (m, 4H), 1.80 (dd, J = 3.5, 7.8 Hz, 1H), 1.40–1.22 (m, 2H), 1.31 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (C_6D_6) δ 208.9, 142.4, 128.8, 128.6, 126.0, 100.6, 67.6, 66.4, 55.8, 41.2, 38.8, 32.3, 29.3, 26.1, 24.0, 20.6; HRMS *m/z* calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$ 311.1623, found 311.1620.

2-(4-Bromobutoxy)tetrahydro-2*H*-pyran (18a). A mixture of 4-bromobutan-1-ol (5 g, 33 mmol), 3,4-dihydro- 2*H*-pyran (3.6 g, 36 mmol) and Amberlite® (3 g) in CH_2Cl_2 (120 mL) was stirred for 2 h at room temperature. After filtration, the filtrate was concentrated and the obtained crude product was purified by distillation to afford (**18a**) (7.1 g, 30 mmol, 90%) as colorless oil (bp 84–90 °C/400 Pa) ^1H NMR ($CDCl_3$) δ 4.57–4.55 (m, 1H), 3.89–3.72 (m, 2H), 3.51–3.34 (m, 4H), 2.02–1.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 98.8, 66.4, 62.3, 33.7, 30.7, 29.8, 28.3, 25.4, 19.6.

2-(5-Bromopentyloxy)tetrahydro-2*H*-pyran (18b). Colorless oily substance **18b** (7.5 g, 30 mmol, 91%) was prepared from 5-bromopentan-1-ol according to the procedure described above (bp 101–102 °C/200 Pa): ^1H NMR ($CDCl_3$) δ 4.57–4.55 (m, 1H), 3.87–3.71 (m, 2H), 3.53–3.37 (m, 4H), 1.92–1.43 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 98.9, 67.2, 62.3, 33.7, 32.6, 30.7, 28.8, 25.4, 24.9, 19.6.

(*E*)-1-Phenyl-9-(tetrahydro-2*H*-pyran-2-yloxy)non-3-en-5-ol (20a). To a mixture of activated magnesium (620 mg, 25.5 mmol) in THF (20 mL) was added dropwise a solution of **18a** (5.5 g, 23.2 mmol) in THF (20 mL). After the reaction mixture was refluxed for 6 h, this solution was added dropwise to a solution of 5-phenylhept-2-en-1-al (2.5 g, 15.5 mmol) in THF (20 mL) at 0 °C. After the reaction mixture was stirred for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 30% hexane–EtOAc) to give **20a** (3.7 g, 11.6 mmol, 75%) as colorless oil: IR (neat, cm^{-1}) 2916, 1450, 1134, 1026, 980; ^1H NMR ($CDCl_3$) δ 7.30–7.15 (m, 5H), 5.69–5.40 (m, 2H), 4.58–4.56 (m, 1H), 4.04–3.35 (m, 5H), 2.71–2.66 (m, 2H), 2.39–2.32 (m, 2H), 1.85–1.25 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 141.6, 133.8, 130.9, 128.4, 128.2, 125.8, 98.8, 73.0, 67.6, 62.3, 37.2, 35.6, 33.9, 30.7, 29.7, 29.3, 26.2, 25.5, 25.3, 19.6; HRMS *m/z* calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2102.

(*E*)-1-Phenyl-10-(tetrahydro-2*H*-pyran-2-yloxy)dec-3-en-5-ol (20b). Colorless oily substance **20b** (4.0 g, 12.1 mmol, 81%) was prepared from bromo ether **18b** according to the procedure described above: IR (neat, cm^{-1}) 2915, 1720, 1442, 1358, 1265, 1126, 1034; ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 5.70–5.60 (m, 1H), 5.45 (dd, J = 7.0, 15.4 Hz, 1H), 4.57–4.54 (m, 1H), 4.04–3.97 (m, 1H), 3.88–3.82 (m, 1H), 3.76–3.68 (m, 1H), 3.51–3.33 (m, 2H), 2.71–2.66 (m, 2H), 2.37–2.30 (m, 2H), 1.86–1.22 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 141.6, 133.7, 130.9, 128.4, 128.2, 125.8, 98.8, 72.9, 67.5, 62.3, 37.2, 35.6, 33.9, 30.7, 29.6, 26.2, 26.1, 25.4, 25.2, 25.2, 19.7; HRMS *m/z* calcd for $C_{21}H_{32}O_3Na$ $[M + Na]^+$ 355.2249, found 355.2254.

(*E*)-9-Phenylnon-6-ene-1,5-diol (21a). Camphor-10-sulfonic acid (172 mg, 0.74 mmol) was added to a solution of **20a** (2.4 g, 7.4 mmol) in MeOH (20 mL) and the mixture was stirred for 4 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified

by column chromatography (silica gel, 30–50% hexane–EtOAc) to give **21a** (1.6 g, 6.8 mmol, 92%) as colorless oil: IR (neat, cm^{-1}) 3448, 2900, 1442, 1350, 1057; ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 5.70–5.60 (m, 1H), 5.45 (dd, J = 6.8, 15.4 Hz, 1H), 4.05–3.98 (m, 1H), 3.59 (t, J = 6.3 Hz, 2H), 2.71–2.66 (m, 2H), 2.38–2.30 (m, 4H), 1.60–1.22 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 141.6, 133.6, 130.9, 128.4, 128.2, 125.8, 72.7, 62.5, 36.7, 35.5, 33.8, 32.3, 21.5; HRMS *m/z* calcd for $C_{15}H_{22}O_2Na$ $[M + Na]^+$ 257.1518, found 257.1526.

(*E*)-10-Phenylnon-7-ene-1,6-diol (21b). Colorless oily substance **21b** (1.9 g, 7.8 mmol, quantitative yield) was prepared from allyl alcohol **20b** according to the procedure described above: IR (neat, cm^{-1}) 2978, 1689, 1458, 1373; ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 5.70–5.60 (m, 1H), 5.44 (dd, J = 7.0, 15.4 Hz, 1H), 4.03–3.97 (m, 1H), 3.59 (t, J = 6.5 Hz, 2H), 2.71–2.66 (m, 2H), 2.38–2.30 (m, 2H), 2.09 (brs, 2H), 1.54–1.22 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 141.6, 133.7, 130.9, 130.9, 128.4, 128.2, 125.8, 72.8, 62.6, 37.1, 35.5, 33.8, 32.5, 25.6, 25.1; HRMS *m/z* calcd for $C_{16}H_{24}O_2Na$ $[M + Na]^+$ 271.1674, found 271.1669.

1-(3-Phenethyloxiran-2-yl)pentane-1,5-diol (22a). To a solution of diol **21a** (1.5 g, 6.4 mmol) in CH_2Cl_2 (30 mL) was added *m*-CPBA (2.2 g, 12.8 mmol) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched with 0.5 M aqueous NaOH, and the mixture was extracted with chloroform. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 40–80% hexane–EtOAc) to give **22a** (1.5 g, 6.0 mmol, 94%) as colorless oil (mixture of 2 isomers, ratio = 3/7): IR (neat, cm^{-1}) 3463, 3378, 2916, 1450, 1057, 845; ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 3.66 (br, 0.3H), 3.62–3.58 (m, 2H), 3.36 (br, 0.7H), 2.99 (br, 0.3H), 2.93–2.90 (m, 0.7H), 2.79–2.64 (m, 2H), 2.20–1.41 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.4, 128.3, 126.1, 71.0, 68.6, 62.4, 62.0, 61.2, 56.2, 54.7, 33.7, 33.2, 33.2, 32.9, 32.3, 32.1, 32.1, 21.5, 21.4; HRMS *m/z* calcd for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ 273.1467, found 273.1459.

1-(3-Phenethyloxiran-2-yl)hexane-1,6-diol (22b). Colorless oily substance **22b** (1.6 g, 5.9 mmol, 92%) was prepared from diol **21b** according to the procedure described above (mixture of 2 isomers, ratio = 3/7): IR (neat, cm^{-1}) 3433, 3379, 2924, 1450, 1049, 895; ^1H NMR ($CDCl_3$) δ 7.29–7.15 (m, 5H), 3.67 (br, 0.3H), 3.61 (t, J = 6.3 Hz, 2H), 3.37 (br, 0.7H), 2.99 (dt, J = 2.4, 5.7 Hz, 0.3H), 2.91 (dt, J = 2.4, 5.7 Hz, 0.7H), 2.88–2.64 (m, 3H), 1.90–1.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.5, 128.3, 126.1, 71.0, 62.7, 62.0, 56.2, 34.1, 33.3, 32.5, 32.1, 25.6, 25.0; HRMS *m/z* calcd for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ 287.1623, found 287.1621.

5-Oxo-5-(3-phenethyloxiran-2-yl)pentanal (15a). To a solution of $(COCl)_2$ (0.86 mL, 10 mmol) in CH_2Cl_2 (40 mL) was added DMSO (1.42 mL, 20 mmol) at −78 °C. After the reaction mixture was stirred for 30 min, a solution of epoxy diol **22a** (500 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After the mixture was stirred for 30 min, Et_3N (3.9 mL, 28.0 mmol) was added dropwise and the reaction mixture was warmed up to 0 °C. After this mixture was stirred for 30 min, the reaction was quenched with saturated aqueous NH_4Cl, and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 40% hexane–EtOAc) to give **15a** (459 mg, 1.9 mmol, 93%) as colorless oil: IR (neat, cm^{-1}) 2723, 1712, 1442, 1373; ^1H NMR ($CDCl_3$) δ 9.19 (t, J = 1.2 Hz, 1H), 7.29–7.06 (m, 5H), 3.02 (d, J = 1.8 Hz, 1H), 2.78 (dt, J = 1.8, 5.5 Hz, 1H), 2.64–2.44 (m, 2H), 2.14–1.58 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 206.6, 201.6, 140.3, 128.5, 128.2, 126.2, 65.7, 59.4, 57.8, 42.6, 35.9, 33.3, 31.8, 17.7, 15.2; HRMS *m/z* calcd for $C_{15}H_{18}O_3Na$ $[M + Na]^+$ 269.1154, found 269.1140.

6-Oxo-6-(3-phenethyloxiran-2-yl)hexanal (15b). Colorless oily substance **15b** (469 mg, 1.8 mmol, 88%) was prepared from epoxy diol **22b** according to the procedure described above: IR (neat, cm^{-1}) 2746, 1712, 1442, 1095; ^1H NMR ($CDCl_3$) δ 9.17 (t, J = 1.2 Hz, 1H), 7.50–6.90 (m, 10H), 5.26 (d, J = 7.0 Hz, 1H), 4.64 (dq, J = 6.2, 9.0 Hz, 1H), 4.02 (dd, J = 7.0, 9.0 Hz, 1H), 1.64 (s, 3H), 1.46 (s, 3H), 1.27 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.8, 202.0, 128.5, 128.2, 126.2, 65.7, 59.5, 57.7, 43.4, 36.8, 33.4, 33.3, 31.8, 31.8, 22.2, 21.3, 15.1; HRMS *m/z* calcd for $C_{16}H_{20}O_3Na$ $[M + Na]^+$ 283.1310, found 283.1307.

2-(6-Bromo-5,5-dimethylhexyloxy)tetrahydro-2*H*-pyran (18c). 3,4-Dihydro-2*H*-pyran (2.2 g, 26 mmol) and CSA were added to a solution of 6-bromo-5,5-dimethylhexan-1-ol in CH_2Cl_2 (30 mL) at 0 °C (pH < 5), and the mixture was stirred for 1 h. The reaction was quenched by adding Et_3N (pH > 8), and the mixture was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 5–20% hexane–EtOAc) to give **18c** (4.5 g, 70% for 4 steps) as colorless oil: IR (neat, cm^{-1}) 2947, 1458, 1365, 1257, 1126,1034; ^1H NMR ($CDCl_3$) δ 4.52 (brs, 1H), 3.89–3.69 (m, 2H), 3.50–3.27 (m, 1H), 3.26 (s, 2H), 1.85–1.21 (m, 10H), 0.98 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 99.0, 67.4, 62.4, 46.7, 39.8, 34.5, 30.7, 30.3, 25.7, 25.7, 25.5, 20.7, 19.7; HRMS *m/z* calcd for $C_{13}H_{25}O_2BrNa$ $[M + Na]^+$ 315.0936, found 315.0944.

(*E*)-7,7-Dimethyl-1-phenyl-11-(tetrahydro-2*H*-pyran-2-yloxy)undec-3-en-5-ol (20c). To a solution of **18c** (860 mg, 2.9 mmol) in Et_2O was added *t*-BuLi (1.62 M in pentane, 3.6 mL, 5.9 mmol) at −78 °C, and the reaction mixture was stirred for 1 h, and then 5-phenyl-2-pentenal (470 mg, 2.9 mmol) was added to it. After the mixture was further stirred for 2 h, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 40% hexane–EtOAc) to give **20c** (590 mg, 1.8 mmol, 61%) as colorless oil: IR (neat, cm^{-1}) 2931, 1450, 1365, 1079,1034; ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 5.68–5.59 (m, 1H), 5.48 (dd, J = 6.9, 15.4 Hz, 1H), 4.56 (brs, 1H), 3.59 (dt, J = 6.9, 11.9 Hz, 1H), 3.89–3.82 (m, 1H), 3.77–3.69 (m, 1H), 3.50–3.45 (m, 1H), 3.42–3.34 (m, 1H), 2.71–2.66 (m, 2H), 2.33 (dt, J = 7.0, 14.9 Hz, 2H), 1.87–1.22 (m, 14H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.7, 135.5, 129.9, 128.4, 128.3, 125.8, 98.9, 70.5, 67.6, 62.4, 48.7, 42.6, 35.5, 33.9, 32.6, 30.8, 30.5, 30.5, 27.8, 25.5, 20.6, 19.7.

(*E*)-5,5-Dimethyl-11-phenylundec-8-ene-1,7-diol (21c). Camphor-10-sulfonic acid (172 mg, 0.74 mmol) was added to a solution of **20c** (1.8 g, 4.9 mmol) in MeOH (20 mL) and the mixture was stirred for 4 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 30–50% hexane–EtOAc) to give **21c** (1.3 g, 6.8 mmol, 90%) as colorless oil: IR (neat, cm^{-1}) 3371, 3348, 3309, 2924, 1450, 1373, 1057; ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 5.63 (dt, J = 6.3, 15.3 Hz, 1H), 5.48 (dd, J = 6.9, 15.3 Hz, 1H), 4.20–4.12 (m, 1H), 3.66–3.61 (m, 2H), 2.71–2.65 (m, 2H), 2.37 (dt, J = 7.2, 15.0 Hz, 2H), 1.55–1.15 (m, 12H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.4, 129.9, 128.4, 128.3, 125.8, 62.6, 48.3, 42.0,

35.5, 33.9, 33.3, 32.7, 28.0, 27.9, 20.0; HRMS *m/z* calcd for $C_{24}H_{38}O_3Na$ $[M + Na]^+$ 397.2719, found 397.2722.

3,3-Dimethyl-1-[(2*RS*,3*SR*)-3-phenethyloxiran-2-yl]heptane-1,7-diol (22c). To a solution of **21c** (1.3 g, 4.4 mmol) in CH_2Cl_2 (30 mL) was added *m*-CPBA (1.5 g, 8.8 mmol) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched with 0.5 M aqueous NaOH, and the mixture was extracted with chloroform. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 30–80% hexane–EtOAc) to give **22c** (1.3 g, 97%) as colorless oil (mixture of 2 isomers, ratio = 3/7): IR (neat, cm^{-1}) 3487, 3425, 3263, 2931, 1458, 1381, 1257, 1057, 895; ^1H NMR ($CDCl_3$) δ 7.30–7.16 (m, 5H), 3.84 (br, 0.3H), 3.63 (t, J = 6.3 Hz, 2H), 3.47 (br, 0.7H), 3.00 (dt, J = 2.2, 5.7 Hz, 0.3H), 2.90 (dt, J = 2.2, 5.7 Hz, 0.7H), 2.85–2.62 (m, 3H), 1.96–1.07 (m, 10H), 0.89 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 128.5, 128.4, 128.4, 126.1, 69.1, 63.2, 62.6, 56.8, 45.1, 33.2, 33.2, 32.5, 32.2, 27.8, 27.8, 20.0; HRMS *m/z* calcd for $C_{19}H_{30}O_3$ Na $[M + Na]^+$ 329.2093, found 329.2097.

5,5-Dimethyl-7-oxo-7-[(2*SR*,3*RS*)-3-phenethyloxiran-2-yl]-heptanal (15c). To a solution of $(COCl)_2$ (518 mg, 4.1 mmol) in CH_2Cl_2 (15 mL) was added DMSO (637 mg, 8.2 mmol) at −78 °C. After the reaction mixture was stirred for 30 min, a solution of **22c** (206 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After the mixture was stirred for 30 min, Et_3N (1.16 g, 11.4 mmol) was further added dropwise to it and the mixture was warmed up to 0 °C. After this mixture was further stirred for 30 min, the reaction was quenched with saturated aqueous NH_4Cl, and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by PTLC (40% hexane–EtOAc) to give **15c** (193 mg, 95%) as colorless oil: IR (neat, cm^{-1}) 2954, 1712, 1450, 1381, 1057; ^1H NMR ($CDCl_3$) δ 9.19 (t, J = 1.3 Hz, 1H), 7.39–7.23 (m, 5H), 3.19 (d, J = 1.8 Hz, 1H), 2.78 (dt, J = 1.8, 5.4 Hz, 1H), 2.95–2.75 (m, 2H), 2.47 (dt, J = 1.3, 7.0 Hz, 1H), 2.35 (d, J = 15.1 Hz, 1H), 2.12 (d, J = 15.1 Hz, 1H), 2.04–1.96 (m, 2H), 1.68–1.56 (m, 2H), 1.41–1.29 (m, 2H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.7, 202.6, 140.4, 128.5, 128.2, 126.2, 60.2, 57.6, 47.1, 44.4, 41.4, 33.9, 33.5, 32.0, 27.2, 16.9; HRMS *m/z* calcd for $C_{19}H_{26}O_3$ Na $[M + Na]^+$ 325.1780, found 325.1777.

Typical Procedure for SmI_2-Mediated Intramolecular Cyclization Using 3.0 Molar Amounts of Water (Table 3, entry 2). To a solution of **15a** (305 mg, 1.2 mmol) in THF (5 mL) and water (0.07 mL, 3.7 mmol) was added dropwise a solution of SmI_2 (0.1 M in THF, 26.7 mL, 2.67 mmol) at −90 °C under an argon atmosphere. After the reaction mixture was stirred for 30 min at −90 °C and for 30 min at −78 °C, the reaction was quenched by adding MeOH–H_2O (1:9) (0.1 mL). After having been diluted with EtOAc, the mixture was filtered through silica gel that had been deactivated with H_2O, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (deactivated silica gel, 40% hexane–EtOAc) to give 3-hydroxy-2-(1-hydroxy-3-phenylpropyl)cyclohexanone (**17a**) as colorless oil. The structure of the obtained cyclic double aldol **17a** was determined by converting it to the corresponding (4*RS*,4a*RS*,8a*SR*)-2,2-dimethyl-4-phenethyl-4,4a,6,7,8,8a-hexahydro-5*H*-1,3-benzodioxin-5-one [**17aAc-B** (*cis-anti*)] and (4*RS*,4a*SR*,8a*RS*)-2,2-dimethyl-4-phenethyl-4,4a,6,7,8,8a-hexahydro-5*H*-1,3-benzodioxin-5-one. [**17aAc-D** (*cis-syn*)] according to the procedure described above.

(4*RS*,4a*RS*,8a*SR*)-2,2-Dimethyl-4-phenethyl-4,4a,6,7,8,8a-hexahydro-5*H*-1,3-benzodioxin-5-one (17aAc-B, *cis-anti* = 14jAc-B).

(4*RS*,4a*SR*,8a*RS*)-2,2-Dimethyl-4-phenethyl-4,4a,6,7,8,8a-hexahydro-5*H*-1,3-benzodioxin-5-one (17aAc-D, *cis-syn*). IR (neat, cm^{-1}) 2900, 1712, 1442, 1373, 1257, 1111; ^1H NMR (C_6D_6) δ 7.30–7.15 (m, 5H), 3.97 (m, 1H), 3.40 (dt, J = 3.6, 10.7 Hz, 1H), 2.86–2.60 (m, 2H), 2.33 (t, J = 10.7 Hz, 1H), 2.33–1.55 (m, 8H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (C_6D_6) δ 205.7, 142.3, 128.8, 128.2, 125.7, 99.6, 71.9, 70.2, 50.2, 42.4, 34.7, 32.4, 30.3, 29.9, 21.2, 19.1; HRMS *m/z* calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$ 311.1623, found 311.1621.

(4*RS*,4a*SR*,9a*RS*)-2,2-Dimethyl-4-phenethyl-4,4a,7,8,9,9a-hexahydrocyclohepta[*d*][1,3]dioxin-5(6*H*)-one (17bAc-B, *cis-syn*). IR (neat, cm^{-1}) 2947, 1697, 1442, 1381, 1257, 1196, 1119; ^1H NMR (C_6D_6) δ 7.18–7.06 (m, 5H), 3.68–3.62 (m, 1H), 3.52 (dd, J = 3.3, 7.2 Hz, 1H), 3.17–3.03 (m, 1H), 2.72–2.66 (m, 2H), 2.40–1.83 (m, 4H), 1.72 (t, J = 3.3 Hz, 1H), 1.26 (br, 1H), 1.47 (s, 3H), 1.31–1.16 (m, 3H), 1.17 (s, 3H), 1.02–0.93 (m, 1H); ^{13}C NMR (C_6D_6) δ 211.8, 142.1, 128.7, 128.0, 126.1, 98.9, 70.0, 65.5, 55.9, 44.5, 35.6, 33.2, 31.8, 30.1, 26.6, 22.1, 19.2; HRMS *m/z* calcd for $C_{19}H_{26}O_3Na$ $[M + Na]^+$ 325.1780, found 325.1785.

(4*RS*,4a*RS*,9a*SR*)-2,2-Dimethyl-4-phenethyl-4,4a,7,8,9,9a-hexahydrocyclohepta[*d*][1,3]dioxin-5(6*H*)-one (17bAc-D, *cis-anti*). IR (neat, cm^{-1}) 2931, 1697, 1442, 1373, 1227, 1103; ^1H NMR (C_6D_6) δ 7.16–7.03 (m, 5H), 4.20 (dt, J = 3.0, 9.5 Hz, 1H), 3.86 (ddd, J = 2.9, 7.6, 9.7 Hz, 1H), 2.90–2.87 (m, 1H), 2.65–2.58 (m, 1H), 2.60 (dd, J = 7.6, 9.5 Hz, 1H), 2.31–2.25 (m, 1H), 1.99–1.73 (m, 3H), 1.59–1.44 (m, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.33–1.17 (m, 3H); ^{13}C NMR (C_6D_6) δ 209.9, 142.2, 128.6, 128.2, 126.1, 100.6, 67.5, 65.6, 60.7, 42.6, 36.9, 32.3, 31.7, 24.5, 24.4, 24.4, 22.3; HRMS *m/z* calcd for $C_{19}H_{26}O_3Na$ $[M + Na]^+$ 325.1780, found 325.1784.

(4*RS*,4a*SR*,10a*RS*)-2,2,7,7-Tetramethyl-4-phenethyl-4,4a,6,-7,8,9,10,10a-octahydro-5*H*-cycloocta[*d*][1,3]dioxin-5-one (17cAc-B, *cis-syn*). IR (neat, cm^{-1}) 2947, 1689, 1450, 1373, 1227, 1103; ^1H NMR (C_6D_6) δ 7.17–7.04 (m, 5H), 3.61–3.55 (m, 3H), 2.67 (t, J = 7.3 Hz, 2H), 1.92–1.82 (m, 2H), 1.77 (t, J = 3.2 Hz, 1H), 1.76–1.60 (m, 4H), 1.50 (s, 3H), 1.39–1.10 (m, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (C_6D_6) δ 213.2, 142.2, 128.5, 128.2, 126.4, 99.5, 70.3, 69.9, 57.6, 51.7, 40.7, 36.3, 36.1, 35.1, 31.9, 31.7, 30.2, 29.3, 19.3, 18.1; HRMS *m/z* calcd for $C_{22}H_{32}O_3Na$ $[M + Na]^+$ 367.2249, found 367.2241.

(4*RS*,4a*RS*,10a*SR*)-2,2,7,7-Tetramethyl-4-phenethyl-4,4a,6,-7,8,9,10,10a-octahydro-5*H*-cycloocta[*d*][1,3]dioxin-5-one (17cAc-D, *cis-anti*). IR (neat, cm^{-1}) 2931, 1682, 1450, 1373, 1265, 1134; ^1H NMR (C_6D_6) δ 7.15–7.03 (m, 5H), 4.24–4.20 (m, 1H), 3.97–3.94 (m, 1H), 2.91–2.85 (m, 1H), 2.62–2.56 (m, 1H), 2.55 (dd, J = 6.4, 9.2 Hz, 1H), 2.35 (d, J = 12.0 Hz, 1H), 1.85 (d, J = 12.0 Hz, 1H), 1.85–1.75 (m, 3H), 1.56–1.50 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H), 1.36–1.20 (m, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (C_6D_6) δ 211.1, 142.2, 128.7, 128.0, 126.1, 100.9, 68.7, 68.6, 62.5, 54.2, 39.4, 37.5, 35.0, 32.4, 32.1, 28.0, 25.0, 24.3, 19.5; HRMS *m/z* calcd for $C_{22}H_{32}O_3Na$ $[M + Na]^+$ 367.2249, found 367.2251.

Preparation of Low-Valent Ti Solution Using TiI_4 and Cu. To a stirring suspension of TiI_4 (2.5 g, 4.5 mmol) and Cu (0.72 g, 11.2 mmol) in CH_2Cl_2 (45 mL) was added *t*-BuCN (1.97 mL, 18 mmol) at room temperature. The reaction mixture was stirred for 6 h and was kept standing for 1 h. The supernatant of this mixture was used as a 0.1 M CH_2Cl_2 solution of low-valent Ti.

Typical Procedure for Synthesis of Double Aldol by Way of Consecutive Aldol Reaction (Method A) (Table 4, entry 1). To a suspension of $Sn(OTf)_2$ (330 mg,0.79 mmol) in CH_2Cl_2 (8

mL) was added Et_3N (0.11 mL, 0.75 mmol) at −78 °C under an argon atmosphere, and the mixture was stirred for 15 min. Then, bromoacetone (103 mg, 0.76 mmol) was added to it, and the mixture was stirred for 1 h. 3-Phenylpropionaldehyde (96.5 mg, 0.72 mmol) was added to it at −78 °C, and then the mixture was stirred for 1 h. To the above mixture were added dropwise the above-mentioned low-valent Ti solution (0.1 M, 8.6 mL, 0.86 mmol) at −90 °C, and then ^{i}PrCHO (62 mg, 0.86 mmol). After the mixture was stirred for 3 h, the reaction was quenched with phosphate buffer solution (pH = 7), and diluted with EtOAc. It was filtered through a short pad of Celite, and the filtrate was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by PTLC (40% hexane–EtOAc) to give 4-hydroxy-3-(1-hydroxy-3-phenylpropyl)-5-methylhexan-2-one (**14h**) as colorless oil. The structure of thus formed double aldol was determined by converting it to the corresponding acetonide; 1-[(4*RS*,5*SR*,6*RS*)-4-isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]ethanone (**14hAc-B**) and 1-[(4*RS*,5*RS*,6*SR*)-4-isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]ethanone (**14hAc-D**) according to the procedure described above.

Typical Procedure for Synthesis of Double Aldol by Way of Consecutive Aldol Reaction (Method B) (Table 4, entry 4). To a suspension of $Sn(OTf)_2$ (330 mg, 0.79 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (0.11 mL, 0.76 mmol) at −78 °C under an argon atmosphere, and the mixture was stirred for 15 min. Then, bromoacetone (103 mg, 0.75 mmol) was added to this mixture. After this mixture was stirred for 1 h, 3-phenylpropionaldehyde (96.5 mg, 0.72 mmol) was added at −78 °C, and then $TiCl_4$ (0.16 mg, 0.86 mmol) was added at −90 °C. After the mixture was stirred for 1 h, the above-mentioned low-valent Ti solution (0.1 M, 8.6 mL, 0.86 mmol) and benzaldehyde (92 mg, 0.86 mmol) were added to the reaction mixture, and this was again stirred for 1 h at −90 °C and for 3 h at −78 °C. The reaction was quenched with phosphate buffer solution (pH = 7), and diluted with EtOAc. The mixture was filtered through a short pad of Celite, and the filtrate was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by PTLC (40% hexane–EtOAc) to give 4-hydroxy-3-[hydroxy(phenyl)methyl]-6-phenylhexan-2-one (**14i**) as colorless oil. The structure of thus obtained bis-aldol was determined by converting it to the corresponding acetonide 1-[(4*RS*,5*SR*,6*SR*)-2,2-dimethyl-4-phenethyl-6-phenyl-1,3-dioxan-5-yl]ethanone (**14iAc-D**) according to the procedure described above.

1-[(4*RS*,5*SR*,6*SR*)-4-Isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]propan-1-one (14kAc-D). IR (neat, cm^{-1}) 2978, 1689, 1458, 1373, 1265, 1196, 987; ^{1}H NMR ($CDCl_3$) δ 7.28–7.138 (m, 5H), 3.83 (ddd, J = 3.2, 5.1, 8.6 Hz, 1H), 3.37 (dd, J = 3.0, 10.0 Hz, 1H), 2.80–2.55 (m, 4H), 2.40 (dd, J = 3.0, 3.2 Hz, 1H), 1.69–1.47 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 212.3, 141.6, 129.0, 128.7, 126.3, 99.7, 76.6, 69.3, 55.5, 37.9, 35.4, 31.7, 31.5, 30.2, 20.0, 19.4, 18.3, 7.5; HRMS m/z calcd for $C_{20}H_{30}O_3Na$ [M + Na]$^+$ 341.2093, found 341.2092.

1-[(4*RS*,5*SR*,6*RS*)-4-Isopropyl-2,2-dimethyl-6-phenethyl-1,3-dioxan-5-yl]-2-methylpropan-1-one (14lAc-D). IR (neat, cm^{-1}) 2970, 1689, 1458, 1373, 1265, 1188, 1126, 987; ^{1}H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5H), 3.86–3.81 (m, 1H), 3.42–3.27 (m, 3H), 2.80–2.60 (m, 2H), 2.44 (dd, J = 2.4, 2.7 Hz, 1H), 1.84–1.53 (m, 3H), 1.50 (s, 3H), 1.41 (s, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 217.3, 141.4, 128.6, 128.3, 125.8, 99.4, 76.6, 70.1, 55.2, 39.3, 35.2, 31.4, 31.0, 29.6, 19.7, 19.1, 19.1, 18.9, 18.0; HRMS m/z calcd for $C_{21}H_{32}O_3Na$ [M + Na]$^+$ 355.2249, found 355.2252.

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