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Facile and Efficient Synthesis of Lactols by a Domino Reaction of 2,3-Epoxy Alcohols with a Hypervalent Iodine(III) Reagent and Its Application to the Synthesis of Lactones and the Asymmetric Synthesis of (+)-Tanikolide

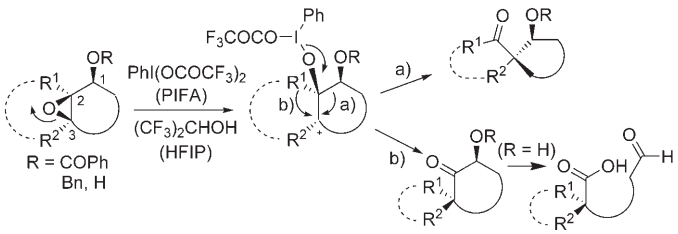
Hiromichi Fujioka, Satoshi Matsuda, Mai Horai, Eri Fujii, Maiko Morishita, Natsuko Nishiguchi, Kayoko Hata, and Yasuyuki Kita*[a]

Abstract: The domino reaction of 2,3-epoxy-1-alcohol derivatives, namely tetrasubstituted 2,3-epoxy-1-alcohols and 2- or 3-alkyl trisubstituted 2,3-epoxy-1-alcohols, with $PhI(OCOCF_3)_2$ in the presence of H_2O is described in detail. In this reaction, several types of lactol derivatives can be directly obtained from the 2,3-epoxy-1-alcohol derivatives in a single operation. The obtained lactols were successively converted into the corresponding lactones. This reaction is applicable to the construction of optically active lactone compounds. The asymmetric total synthesis of (+)-tanikolide, an antifungal marine natural product, has been effectively achieved by using this reaction.

Keywords: alcohols · domino reactions · iodine · lactols · lactones

Introduction

Domino reactions have attracted much attention from the viewpoint of 'green' chemistry because they can save reaction steps, reagents, and solvents.[1] Therefore, the development of an efficient and practical domino reaction is one of the important issues in the field of modern synthetic organic chemistry. On the other hand, hypervalent iodine(III) reagents have received much attention due to their low toxicity, ready availability, easy handling, and reactivity which is similar to those of heavy metal reagents.[2] We have developed many kinds of novel reactions by using hypervalent iodine(III) reagents[3] and have applied them to the total synthesis of biologically active natural products, such as the discorhabdin alkaloids,[4] which show potent antitumor activity. Hypervalent iodine(III) reagents have an interesting dual reactivity comprising oxidation activity and Lewis acidity. We have examined the reaction of 2,3-epoxy-1-alcohol derivatives and hypervalent iodine(III) reagents, and we recently reported that hypervalent iodine(III) reagents act as Lewis acids (LA) to give rearranged products from 2,3-epoxy-1-alcohol derivatives. Furthermore, subsequent oxidative ring cleavage occurs when the rearranged product contains a structural subunit, such as an α-hydroxy ketone (Scheme 1).[5] Although there have been a few reports about the reaction of a simple epoxide with hypervalent iodine(III) reagents,[6] there has been no report on the reaction of 2,3-epoxy-1-alcohol derivatives with hypervalent iodine(III) reagents except for ours.[5]



Scheme 1. The reactions of epoxy alcohol derivatives with PIFA in HFIP. Bn = benzyl; HFIP = $(CF_3)_2CHOH$; PIFA = $PhI(OCOCF_3)_2$.

We next examined the reaction of the 2,3-epoxy-1-alcohol derivatives, bicyclic epoxy alcohols, and trisubstituted 3-alkyl-2,3-epoxy-1-alcohols with hypervalent iodine(III) reagents in the presence of an oxygen nucleophile. We reported that the domino-type reaction proceeded to give the lactols in the presence of water by attack at the C3 position followed by C–C bond cleavage. This reaction was successfully

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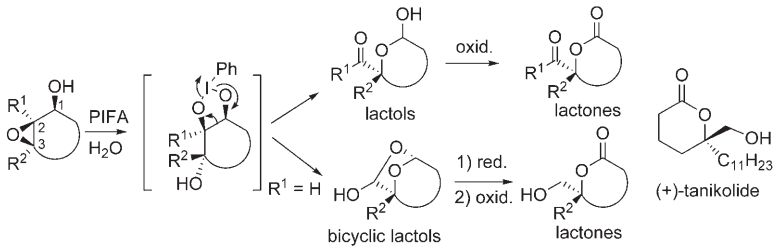
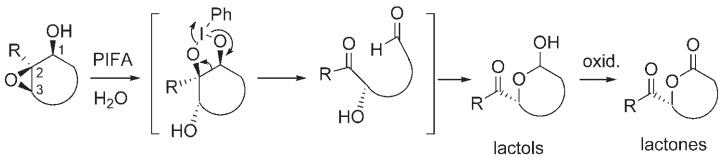
applied to the total asymmetric synthesis of (+)-tanikolide, an antifungal marine natural product (Scheme 2).[7]



Scheme 2. The reactions of tetrasubstituted or 3-alkyl trisubstituted epoxy alcohols with PIFA in the presence of water and the successive lactone formation. The structure of (+)-tanikolide is also shown.

The reactions, especially those in the presence of water, provided a very useful domino reaction for producing lactols. We examined this domino reaction in detail and found that trisubstituted 2-alkyl-2,3-epoxy-1-alcohols gave a different type of lactols, which were converted into the corresponding lactones (Scheme 3). We now report a full account of our study.



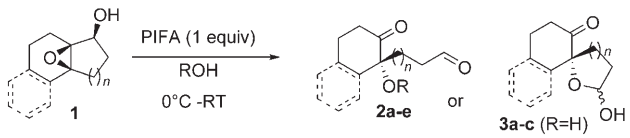
Scheme 3. The reactions of 2-alkyl trisubstituted epoxy alcohols with PIFA in the presence of water and the successive lactone formation.

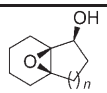
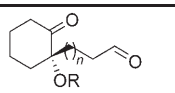
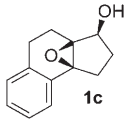
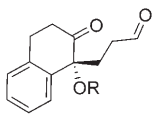
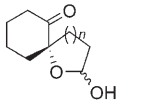
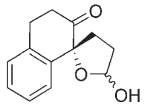
Results and Discussion

Reaction of 2,2,3,3-tetrasubstituted 2,3-epoxy-1-alcohols and phenyliodine(III) bis(trifluoroacetate): The reactions of 2,3-epoxy-1-alcohol derivatives in bicyclic and tricyclic systems with phenyliodine(III) bis(trifluoroacetate) (PIFA) in the presence of an alcohol were first examined (Table 1, entries 1–5). α-Alkoxy keto aldehydes **2a–e** were directly obtained from each of the 2,3-epoxy-1-alcohols **1a–c** in moderate yield. A plausible reaction mechanism with **1b** as the substrate is depicted in Scheme 4. In the first instance, the alcohol attacks the epoxide at the C3 position, which is activated by PIFA, to produce the *cis*-1,2-diol. Subsequently, oxidative cleavage of the 1,2-diol with PIFA proceeded smoothly to afford the α-alkoxy keto aldehyde. Cleavage of the 1,2-diol is one of the popular reactions in the field of hypervalent iodine chemistry.[8] In this reaction, PIFA first acted as a Lewis acid to accelerate the nucleophilic ring opening of the epoxide by the alcohol, and it then acted as an oxidant to cleave the 1,2-diol. Therefore, this reaction clearly shows the interesting dual character of PIFA, that is, it acts not only as an oxidizing agent, but also as a Lewis acid. Recently, several groups reported domino reactions with 2,3-epoxy-1-alcohols.[9] However, most of their studies focused on the rearrangement and subsequent reaction. We then became interested in this type of reaction and examined several kinds of substrates and oxygen nucleophiles to reveal its generality.

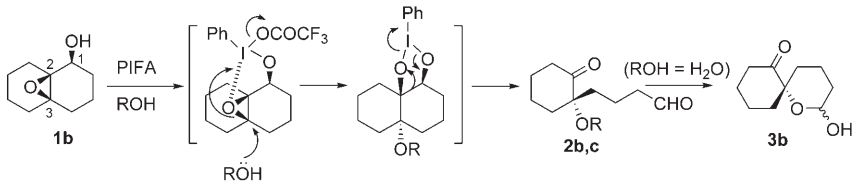
After several investigations, we used water as a nucleophile instead of the alcohol and found a novel domino-type lactol formation reaction (Table 1, entries 6–8). Namely, the 5,6-membered spiro lactol **3a** was obtained from **1a** in 66% yield (Table 1, entry 6), and the 6,6-membered spiro lactol **3b** was obtained from **1b** in 49% yield (Table 1, entry 7). In the case of **1c**, the tricyclic spiro lactol **3c** was obtained in 78% yield (Table 1, entry 8). The most plausible reaction mechanism is considered to be the same as that with the alcohol nucleophiles for part of the reaction (Scheme 4).

Table 1. Nucleophilic addition of oxygen nucleophiles to 2,3-epoxy alcohols and subsequent PIFA-mediated oxidative cleavage of the 1,2-diol.



Entry	Substrate		ROH	Product	Yield [%][c]
1[a]		**1a** ($n=1$)	MeOH	 **2a** ($n=1$, R = Me)	41
2[a]		**1b** ($n=2$)	MeOH	**2b** ($n=2$, R = Me)	67
3[a]		**1b** ($n=2$)	EtOH	**2c** ($n=2$, R = Et)	52
4[a]			MeOH	 **2d** (R = Me)	46
5[a]		**1c**	EtOH	**2e** (R = Et)	51
6[b]		**1a** ($n=1$)	H_2O	 **3a** ($n=1$)	66[d]
7[b]		**1b** ($n=2$)	H_2O	**3b** ($n=2$)	49[d]
8[b]		**1c**	H_2O	 **3c**	78[d]

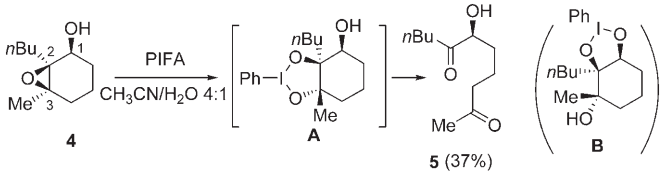
[a] Reactions were carried out in alcohol. [b] Reactions were carried out in CH_3CN/H_2O 4:1. [c] Yield of isolated product. [d] Product was obtained as a diastereomeric mixture.



Scheme 4. Plausible reaction mechanism for the formation of α-alkoxy keto aldehydes **2b** and **2c** and spiro lactol **3b** from **1b**.

Thus, nucleophilic ring opening of the epoxide by water and subsequent oxidative cleavage of the 1,2-diol occurred to give the α-hydroxy keto aldehyde, as in the cases with the alcohols. In these cases, however, an intramolecular nucleophilic attack of the hydroxy group on the aldehyde occurred immediately, to afford the spiro lactol derivatives as shown in Table 1.

In the case of the monocyclic tetrasubstituted 2,3-epoxy-1-alcohol **4**, the 1,6-diketone **5** was obtained by oxidative cleavage of the C2–C3 bond via intermediate **A**, rather than via intermediate **B** (Scheme 5). The factor that accelerates the reaction via intermediate **A** is not clear at this stage. In this case, no lactol formation occurred between the hydroxy function and the ketone function.

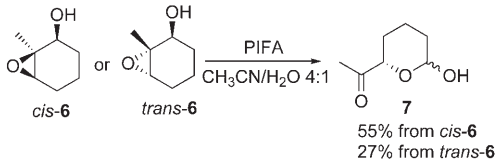


Scheme 5. Reaction of monocyclic tetrasubstituted 2,3-epoxy alcohol **4**.

Reaction of trisubstituted 2,3-epoxy-1-alcohols and PIFA: The results in the preceding section, especially the formation of lactol units, the precursors of lactones, by the reactions of the epoxy alcohols and PIFA in the presence of water, are quite interesting because many biologically active natural products contain the lactone moiety. The following examinations were then performed in the presence of water. For trisubstituted epoxy alcohols, we chose the monocyclic 2-alkyl-2,3-epoxy-1-alcohols and monocyclic 3-alkyl-2,3-epoxy-1-alcohols as the substrates of the reaction.

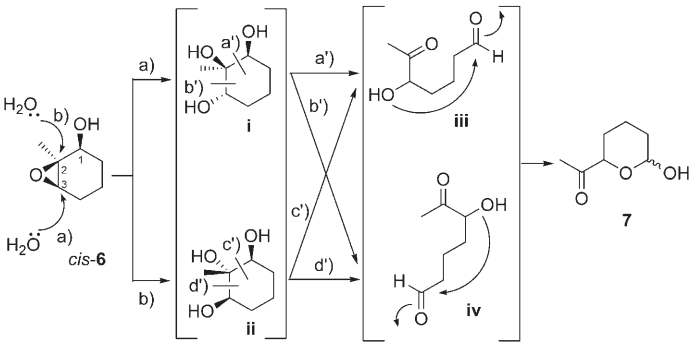
2-Alkyl-2,3-epoxy-1-alcohols: We first investigated the reaction of both the *cis* and *trans* isomers of the monocyclic 2,2,3-trisubstituted 2,3-epoxy-1-alcohols *cis*-**6** and *trans*-**6** with PIFA in the presence of water. Although both the *cis* and *trans* isomers afforded the acyl lactol **7** (with an epimeric mixture at the hemiacetal carbon atom), the *cis* isomer produced a better yield than the *trans* isomer (Scheme 6).

As described in the case of the 2,2,3,3-tetrasubstituted 2,3-epoxy-1-alcohol shown in Scheme 4, **7** was assumed to be obtained by the domino reaction that included the nucleophilic ring opening of the epoxide by water, oxidative cleavage of the 1,2-diol by PIFA, and lactol formation. However, the carbon atoms at both the C2 and C3 positions were supposed to be susceptible to the nucleophilic addition of water. The formation of two triol intermediates, **i** and **ii**, is



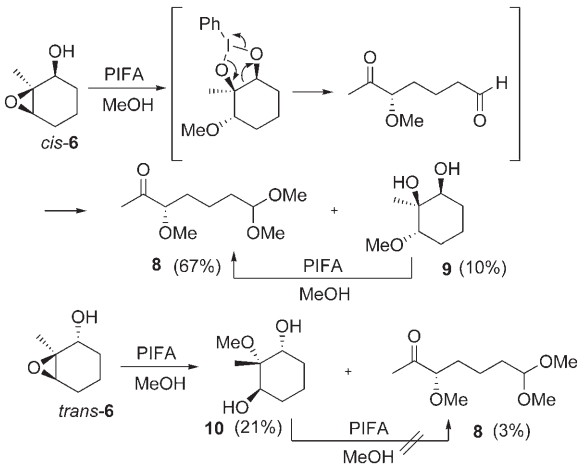
Scheme 6. Reaction of both the *cis* and *trans* isomers of the monocyclic 2,2,3-trisubstituted-2,3-epoxy-1-alcohols in the presence of water to form lactol **7**.

then possible (Scheme 7). Furthermore, vicinal diol cleavage at the C1 and C2 (a′ or c′) or C2 and C3 (b′ or d′) positions is possible. It is extremely difficult to assume the reaction mechanism from product **7** because both cases, that is, the route via intermediate **iii** and the route via intermediate **iv**, are considered to afford the same product (Scheme 7).



Scheme 7. Possible reaction pathways for the transformation from *cis*-**6** to lactol **7**.

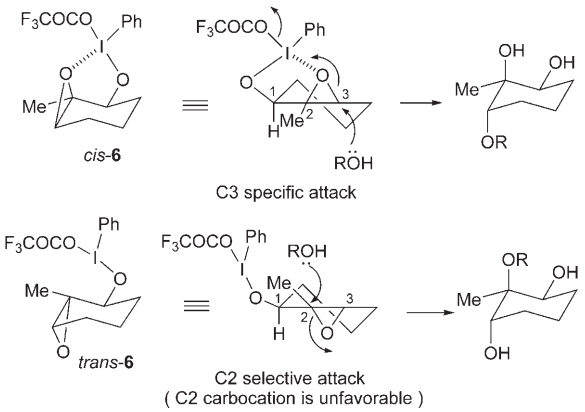
To clarify which carbon atom is susceptible to the nucleophilic addition of water, we carried out the reaction with methanol as a nucleophile (Scheme 8). As a result, in the case of *cis*-**6**, nucleophilic addition of methanol occurred at the C3 position and afforded two types of products, the acyclic keto acetal **8** and the cyclic 1,2-diol **9**. Compound **8** is the product obtained by nucleophilic addition of methanol at the C3 position followed by oxidative cleavage of the 1,2-diol with PIFA, and compound **9** is the 1,2-diol on the way to **8**. Indeed, treatment of **9** with PIFA afforded **8** in a quantitative yield. On the other hand, in the case of *trans*-**6**, 1,3-diol **10**, which is thought to be obtained by nucleophilic addition of methanol at the C2 position, was the major product. Compound **8**, which is supposed to be produced by oxi-



Scheme 8. Reactions of both the *cis* and *trans* isomers of the monocyclic 2,2,3-trisubstituted-2,3-epoxy-1-alcohols in the presence of methanol.

dative cleavage of the 1,2-diol with PIFA, was only obtained as a minor product.

These results suggest that the ring opening of the epoxide by water proceeds in a *trans* diaxial fashion according to the Fürst–Plattner rule,[10] as shown in Scheme 9. That is, the



Scheme 9. Stereochemistry of the nucleophilic ring opening of epoxides.

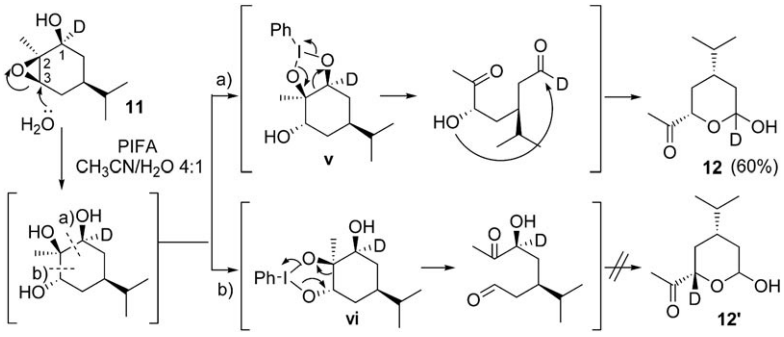
conformations of both epoxy alcohols are the chair forms, in which the hydroxy groups are located in equatorial positions. In the case of *cis* isomer, the addition of water at the C3 position then preferentially causes *trans* diaxial opening of the oxirane ring. On the other hand, the nucleophilic addition of water at the C2 position causes *trans* diaxial opening of the oxirane ring in the *trans* isomer, but the C2 carbocation is unfavorable due to the strong electron-withdrawing effect of the $OIPh(OCOCF_3)$ unit. Furthermore, the interaction between the epoxide and PIFA, which reacts with the secondary alcohol, would make the addition of water at the C3 position more favorable in the *cis* isomer and also accelerates the reaction rate compared with that with the *trans* isomer, which is without such an interaction.

As shown above, we clarified the position of the nucleophilic ring opening of the 2-methyl epoxy alcohols, *cis*-**6** and *trans*-**6**, and found that *cis*-**6** gave much better results than the *trans* isomer. We next studied the oxidative cleavage step of the 1,2-diol in Scheme 7. Scheme 10 shows the reaction of the epoxy alcohol **11**, containing deuterium, and PIFA in the presence of water. When the oxidative cleavage occurs between the C1 and C2 positions, the *cis*-2,3-epoxy-1-alcohols with deuterium at the C1 position would produce compound **12**, in which the deuterium appears on the acetal carbon atom, through path a). On the other hand, product **12′**, in which the deuterium appears on the carbon atom next to the acetyl group, would be obtained through path b) by cleavage between the C2 and C3 positions. As a result of the reaction, compound **11** exclusively afforded **12**, with the deuterium on the acetal carbon atom. This finding supports the conclusion that the reaction probably predominantly proceeds through path a).

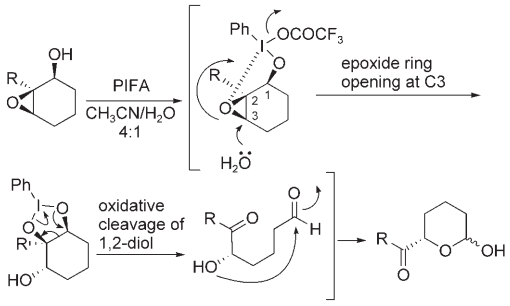
Based on the above results in Schemes 8 and 10, a plausible reaction mechanism for the 2-substituted *cis*-2,3-epoxy-1-alcohols and PIFA in the presence of water is depicted in Scheme 11. Thus, the nucleophilic addition of water causing the oxirane ring opening first occurs at the C3 position. In the reaction, PIFA reacted with the hydroxy function which accelerates the reaction rate and the nucleophilic addition at the C3 position. Cleavage at the C1−C2 bond by forming a five-membered transition state then gives the hydroxy keto aldehyde, in which automatic lactol formation occurs to produce the lactol.

The reaction has generality and various kinds of 2-substituted 2,3-epoxy-1-alcohols, **13**, are available. As shown in Table 2, all of the reactions proceeded smoothly to afford the corresponding lactol derivatives **14**.

3-Alkyl-2,3-epoxy-1-alcohols: The results of the reactions of the monocyclic 3-alkyl-2,3-epoxy-1-alcohols, **15**, have been

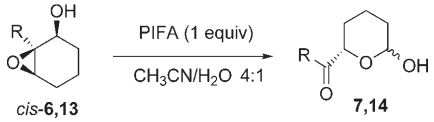


Scheme 10. The reaction of the 2,3-epoxy alcohol analogue substituted with deuterium at the C1 position (**11**).

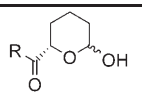
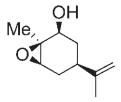
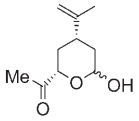
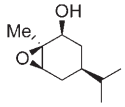
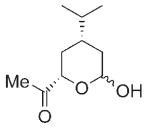


Scheme 11. Plausible reaction mechanism for the reaction of 2-substituted *cis*-2,3-epoxy-1-alcohols and PIFA in the presence of water.

Table 2. Domino-type lactol formation of 2-substituted-2,3-epoxy-1-alcohols.[a]



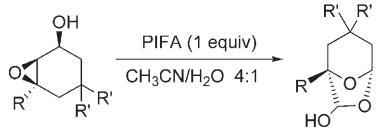
cis-**6**,**13** **7**,**14**

Entry	Substrate		Product		Yield [%][b]
1		*cis*-**6** (R = Me)		**7** (R = Me)	55
2		**13a** (R = *n*Bu)		**14a** (R = *n*Bu)	81
3		**13b**		**14b**	64
4		**13c**		**14c**	94

[a] Reactions were carried out with substrate (1 equiv) and PIFA (1 equiv) in CH_3CN/H_2O 4:1. [b] Yield of isolated product. Product was obtained as a diastereomeric mixture.

reported previously in reference [7]. This reaction proceeded in a different manner (Table 3). That is, bicyclic lactols **16** were obtained by the same type of reaction as that shown in Table 2 followed by a subsequent intramolecular lactol formation by nucleophilic attack of the hydroxy group of the lactol on the aldehyde (Scheme 12). Various epoxy alcohols were adapted to this reaction and produced bicyclic lactols in good yields. In these cases, the reaction mechanism is obvious from the structures of the products, and a plausible reaction mechanism is depicted in Scheme 12. Thus, nucleophilic ring opening of the epoxide with water at the C3 position and subsequent oxidative cleavage of the *cis*-1,2-diol at the C1–C2 bond proceeded to give a hydroxy keto aldehyde. Automatic lactol formation occurred to produce the oxacyclic lactol in the same manner as that in the reactions of the 2-alkyl-2,3-epoxy-1-alcohols (Scheme 11). However, the circumstances of the carbonyl group are different. The carbonyl groups from the 2-alkyl-2,3-epoxy-1-alcohols belong to the acetyl functions and are ketones. On the other hand, the carbonyl groups from the 3-alkyl-2,3-epoxy-1-alcohols belong to the formyl functions and are aldehydes. One more lactol formation then occurred for the 3-alkyl-2,3-epoxy-1-alcohols, probably due to the easier formation of the lactol from the alcohol and aldehyde compared to that from the alcohol and ketone.

Table 3. Domino-type lactol formation of 3-substituted-2,3-epoxy-1-alcohols.[a]



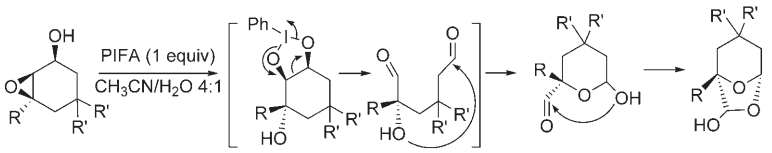
15 **16**

Entry	Substrate	R	R'	Product	Yield [%][b]
1	**15a**	Me	H	**16a**	62
2	**15b**	Et	H	**16b**	74
3	**15c**	$nC_{11}H_{23}$	H	**16c**	72
4	**15d**	CH_2CHMe_2	H	**16d**	67
5	**15e**	CH_2Ph	H	**16e**	72
6	**15f**	Ph	H	**16f**	53
7	**15g**	Me	Me	**16g**	65

[a] Reactions were carried out with substrate (1 equiv) and PIFA (1 equiv) in CH_3CN/H_2O 4:1. [b] Yield of isolated product.

Transformation of lactols to lactones: Since there are many biologically active natural products containing lactone moieties with asymmetric carbon centers, an efficient synthetic method for the construction of such a structural subunit is required for natural product synthesis. As we had developed a novel and an efficient transformation of 2,3-epoxy-1-alcohols into lactols, we next tried to convert the lactols into lactones. Table 4 shows the transformation of the monooxacyclic lactols into lactones. Bicyclic lactols **3a** and **3b** were oxidized by Jones reagent to give the corresponding lactones **17a** and **17b**, respectively. For oxidation of the monocyclic lactols **14a** and **14c**, Jones reagent gave unsuccessful results. After several trials, Ag_2CO_3/Celite[11] was proven to be an effective oxidant for this purpose and gave the corresponding lactones **17c** and **17d**. On the other hand, Table 5 shows the conversion of the bisoxacyclic lactols **16f** and **16g** into lactones **19a** and **19b**. In these cases, the conversion of the bisoxacyclic lactols **16** into the monooxacyclic lactols **18** was first conducted by reductive opening of the lactol rings. Oxidation of the hydroxy functions of the remaining lactols then gave the lactones **19**.

Asymmetric total synthesis of (+)-tanikolide: (+)-Tanikolide ((+)-**25**) is a γ-lactone metabolite of the marine cyanobacterium *Lyngbya majuscula*, which was collected on Tani-



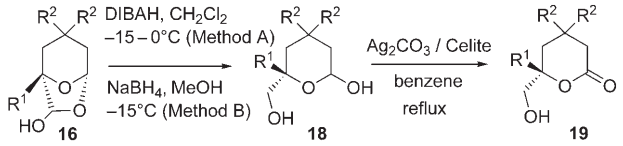
Scheme 12. Plausible reaction mechanism for the reaction of monocyclic 3-alkyl-2,3-epoxy-1-alcohols and PIFA in the presence of water.

Table 4. Transformation of lactols to lactones.

Entry	Substrate	Method of oxidation	Product	Yield [%][a]
1	**3a** ($n=1$)	Jones oxidation	**17a**	39
2	**3b** ($n=2$)	Jones oxidation	**17b**	95
3	**14a** (R = H)	Ag_2CO_3/Celite	**17c**	52
4	**14c** (R = $CHMe_2$)	Ag_2CO_3/Celite	**17d**	79

[a] Yield of isolated product.

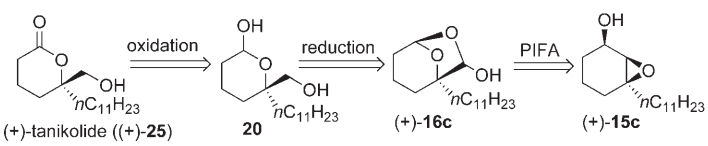
Table 5. Reductive cleavage of lactols followed by oxidation to lactones.



Entry	Substrate	R^1	R^2	Method of reduction	Product	Yield [%][b]
1	**16f**	Ph	H	DIBAH[a]	**19a**	57
2	**16g**	Me	Me	$NaBH_4$	**19b**	98

[a] DIBAH = diisobutylaluminum hydride. [b] Yield of isolated product after the two steps from **16**.

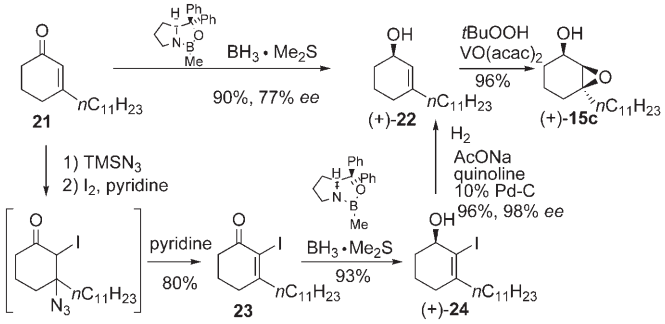
keli island, Madagascar, and its structure was determined by Gerwick and co-workers in 1999.[12] It shows brine-shrimp toxicity and antifungal activity. Although several groups have already reported its asymmetric total synthesis,[13] we planned an original and concise asymmetric total synthesis of (+)-tanikolide in order to show the usefulness of our method. The retrosynthetic analysis of (+)-tanikolide is depicted in Scheme 13. (+)-Tanikolide should be obtained by the oxidation of a six-membered ring lactol, **20**, which can be obtained by selective reduction of the bicyclic lactol (+)-**16c**. The optically active (+)-**16c** would be constructed by our domino-type lactol formation reaction with the optically



Scheme 13. Retrosynthetic analysis of (+)-tanikolide ((+)-**25**).

active 3-undecyl-2,3-epoxy-1-alcohol (+)-**15c** as the substrate.

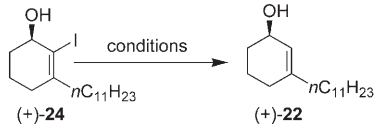
First of all, the preparation of the optically active 2,3-epoxy alcohol (+)-**15c** was studied (Scheme 14). The known enone[14] **21** was subjected to Corey's asymmetric reduction by utilizing the chiral oxazaborolidine.[15] However, the enantiomeric excess of the chiral allyl alcohol (+)-**22** proved to be 77% *ee* by chiral HPLC analysis. Knochel and co-workers reported that the enone containing the iodine atom at the C2 position could be converted into the chiral allyl alcohol with high enantiomeric excess.[16] By taking their report into account, we then prepared



Scheme 14. Preparation of optically active 2,3-epoxy-1-alcohol (+)-**15c**. TMS: trimethylsilyl; acac: acetylacetone.

2-iodoenone **23** according to the method of Sha and Huang.[17] Thus, treatment of enone **21** with trimethylsilyl azide followed by addition of iodine and pyridine gave the iodocyclohexenone **23** via the iodoazide intermediate. Compound **23** was subjected to Corey's asymmetric reduction to give the iodoolefin alcohol (+)-**24**. Table 6 shows the selective reduction of the iodoolefin alcohol (+)-**24** to (+)-**22**. The radical conditions,[18] including the method developed by us by using V-70L,[18b] succeeded in the conversion of (+)-**24** into (+)-**22** with high yields (Table 6, entries 1 and 2). Although the catalytic hydrogenation of (+)-**24** with a Pd/C catalyst without quinoline gave a complex mixture (Table 6, entry 3), the iodine atom was reduced in the best yield by catalytic hydrogenation with the Pd/C catalyst in the presence of quinoline (Table 6, entry 4).[19] These conditions were then used for the conversion of the iodoolefin alcohol (+)-**24** into the allyl alcohol (+)-**22**. The obtained (+)-**22** was found to have an *ee* value of 98%. The *cis*-selective epoxidation of (+)-**22** according to the method of

Table 6. Selective reduction of iodoolefin ((+)-**24**).



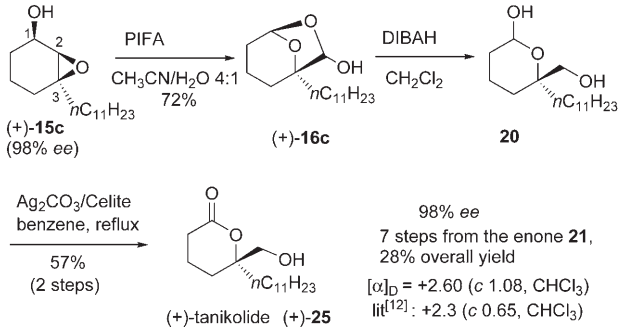
(+)-**24** (+)-**22**

Entry	Reagent	Solvent	*T*	Yield [%][a]
1	Et_3B, nBu_3SnH[18a]	toluene	0 °C–RT	84
2	V-70L,[b] nBu_3SnH[18b]	toluene	reflux	88
3	H_2, 10 % Pd/C	EtOH	RT	complex mixture
4	H_2, 10 % Pd/C,[19] quinoline, AcONa	EtOH	RT	96

[a] Yield of isolated product. [b] V-70L = 2,2′-azobis-(2,4-dimethyl-4-methoxyvaleronitrile).

Sharpless and Michaelson[20] afforded the chiral 2,3-epoxy alcohol (+)-**15c**.

The chiral 2,3-epoxy alcohol (+)-**15c** was converted into the bicyclic lactol (+)-**16c** in 72 % yield by using PIFA in the presence of water. Reduction of (+)-**16c** with DIBAH followed by chemoselective oxidation of the lactol hydroxy function with Ag_2CO_3/Celite[11] afforded (+)-tanikolide ((+)-**25**) in 57 % yield over two steps (Scheme 15). The enantiomeric excess of (+)-tanikolide was determined from the *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester of (+)-tanikolide. The absolute configuration of allyl alcohol (+)-**24** was deduced by reference to a report by Corey and co-workers[15] and was unambiguously confirmed by comparison with the optical rotation value of the natural (+)-tanikolide as reported by Gerwick and co-workers.[12] It should be noted that no racemization occurred during the synthetic process from the optically active 2,3-epoxy alcohol (+)-**15c**. This total synthesis clearly shows that our domino-type lactol formation reaction is applicable to the synthesis of lactone derivatives with asymmetric quaternary carbon centers.



Scheme 15. Asymmetric total synthesis of (+)-tanikolide ((+)-**25**).

Conclusion

We have developed a novel and efficient transformation of 2,3-epoxy-1-alcohols into lactols in a single operation by using PIFA in the presence of water. The characteristic feature of our unique methodology is that various lactol derivatives can be directly prepared from 2,3-epoxy-1-alcohols under mild and environmentally benign conditions in a simple and single operation. The lactols can be easily converted into lactones. Furthermore, this reaction can be applied to the asymmetric total synthesis of (+)-tanikolide by using optically active 2,3-epoxy alcohols. We believe this is a powerful and reliable synthetic methodology for various lactols and lactones with asymmetric quaternary carbon centers. Further extension of this reaction is currently in progress in our laboratory.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as the solvent and $SiMe_4$ as an internal standard. IR absorption spectra (cm^{-1}) were recorded from KBr pellets. PIFA is commercially available. Ag_2CO_3/Celite was purchased from Aldrich.

General procedure for the preparation of 2,3-epoxy alcohols: 2,3-Epoxy alcohols **1a**,[21] **4**,[5] *cis*-**6**,[22] **11**,[23] **13b**,[24] **13c**,[25] **15a**,[26] **15b**,[27] **15e**,[27] **15f**,[27] and **15g**[28] were prepared according to the literature methods. 2,3-Epoxy alcohols **1b**,[29] **1c**,[30] **13a**,[31] and **15d**,[32] were prepared from the corresponding known enone by synthesis according to the literature procedures in a two-step sequence: DIBAH (1.2 mmol) was added to a stirred solution of the enone (1.0 mmol) in CH_2Cl_2 (10 mmol) at 0 °C under N_2. After the reaction mixture had been stirred for 1 h at that temperature, MeOH and Rochelle's salt were added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The crude allyl alcohol was obtained. *t*BuOOH (3 mmol) was added to the solution of the allyl alcohol in benzene (10 mmol) in the presence of $VO(acac)_2$ (0.05 mmol) at 5 °C.[20] After the mixture had been stirred for 1 h, saturated aqueous $Na_2S_2O_3$ was added and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt (2:1→7:1) as the eluent, to give the *cis*-epoxy alcohol.

***cis*-1,6-Epoxybicyclo[4.4.0]decan-7-ol (1b)**: Compound **1b** was prepared from the corresponding known enone[29] by the method described in the general procedure. Colorless crystals; m.p. 68 °C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–2.22 (m, 15 H), 3.77 ppm (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7, 20.2, 20.4, 28.2, 30.4, 30.5, 30.8, 64.7, 65.6, 70.6 ppm; IR (KBr): $\tilde{\nu}$ = 3418 cm^-; elemental analysis calcd (%) for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.35, H 9.44.

***cis*-3a,9b-Epoxy-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-3-ol (1c)**: Compound **1c** was prepared from the corresponding known enone[30] by the method described in the general procedure. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69–1.86 (m, 2 H), 1.93–2.06 (m, 1 H), 2.13–2.24 (m, 1 H), 2.49–2.91 (m, 4 H), 4.22 (dd, *J* = 17.6, 7.9 Hz, 1 H), 7.11–7.37 ppm (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.08, 25.42, 26.40, 30.11, 64.43, 70.80, 75.54, 126.59, 126.57, 128.12, 128.33, 133.34, 136.54 ppm; IR (KBr): $\tilde{\nu}$ = 3383 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{14}O_2$: C 77.20, H 6.98; found: C 76.84, H, 7.03.

***trans*-2,3-Epoxy-2-methylcyclohexanol (*trans*-6)**: *p*-Nitrobenzoic acid (150 mg, 1.17 mmol) and triphenylphosphine (614 mg, 2.34 mmol) were added to a stirred solution of *cis*-**6** (150 mg, 1.17 mmol) in THF (11.7 mL) at 0 °C under N_2. After diethylazodicarboxylate (DEAD; 40 % in toluene, 1.02 g, 2.34 mmol) in THF (3.7 mL) was added dropwise, the reaction mixture was gradually warmed to room temperature and stirred for 12 h. Saturated aqueous $NaHCO_3$ solution was added and the reaction mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. After the residue had been filtered through a pad of silica gel with hexane/

AcOEt 5:1 as the eluent, the filtrate was evaporated in vacuo. The obtained crude product was dissolved in MeOH (6.0 mL), 5% NaOH (3.5 mL) was added and the mixture was stirred for 1 h at room temperature. H_2O was added and the resulting reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 1:1 as the eluent to give *trans*-**6** (114.2 mg, 76%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.57 (m, 4H), 1.38 (s, 3H), 1.77–1.90 (m, 3H), 3.03 (m, 1H), 3.97 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 19.7, 23.8, 29.0, 59.4, 60.4, 68.8 ppm; IR (KBr): $\tilde{\nu}$ = 3393, 2941, 743 cm^{-1}.

***cis*-2-Butyl-2,3-epoxycyclohexan-1-ol (13a)**: Compound **13a** was prepared from the corresponding known enone[31] by the method described in the general procedure. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.9 Hz, 3H), 1.19–1.55 (m, 9H), 1.68–1.73 (m, 1H), 1.88–2.05 (m, 3H), 3.15 (m, 1H), 3.90 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 15.8, 22.8, 24.3, 26.9, 30.3, 34.2, 61.3, 62.8, 67.3 ppm; IR (KBr): $\tilde{\nu}$ = 3445, 2936 cm^{-1}; MS (FAB): m/z: 171 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{19}O_2$: 171.1385 $[M+H]^+$; found: 171.1372.

***cis*-2,3-Epoxy-3-isobutylcyclohexan-1-ol (15d)**: Compound **15d** was prepared from the corresponding known enone[32] by the method described in the general procedure. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.17–1.35 (m, 2H), 1.40–1.90 (m, 8H), 3.10 (d, J = 3.1 Hz, 1H), 3.99 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 22.6, 23.2, 25.3, 26.4, 29.3, 46.5, 61.6, 63.6, 66.8 ppm; IR (KBr): $\tilde{\nu}$ = 3317 cm^{-1}; MS (FAB): m/z: 171 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1385; found: 171.1394.

General procedure for the reaction of 2,3-epoxy alcohols with PIFA in alcohol (Table 1, entries 1–5; Scheme 8): PIFA (1 mmol) was added to a stirred solution of 2,3-epoxy alcohol (1 mmol) in alcohol (10 mL) at 0°C and the mixture was gradually warmed to room temperature. After completion of the reaction (as checked by TLC), the reaction mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 5:1 as the eluent to give the products in the yields shown in the table.

3-(1-Methoxy-2-oxocyclohexyl)propionaldehyde (2a): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–2.38 (m, 9H), 2.40–2.52 (m, 2H), 2.61–2.75 (m, 1H), 3.15 (s, 3H), 9.80 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 23.4, 27.8, 36.8, 37.6, 39.4, 50.6, 81.8, 201.5, 211.6 ppm; IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1}; MS (EI): m/z: 184 $[M]^+$; HRMS (EI): m/z: calcd for $C_{10}H_{16}O_3$: 184.1099; found: 184.1113.

4-(1-Methoxy-2-oxocyclohexyl)butyraldehyde (2b): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–2.06 (m, 9H), 2.12–2.35 (m, 2H), 2.46–2.54 (m, 2H), 2.62–2.75 (m, 1H), 3.16 (s, 3H), 9.78 ppm (t, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 20.8, 27.9, 30.2, 36.9, 39.4, 43.9, 50.7, 82.2, 202.0, 212.4 ppm; IR (KBr): $\tilde{\nu}$ = 1717 cm^{-1}; MS (EI): m/z: 198 $[M]^+$; HRMS (EI): m/z: calcd for $C_{11}H_{18}O_3$: 198.1256; found: 198.1248.

4-(1-Ethoxy-2-oxocyclohexyl)butyraldehyde (2c): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H), 1.37–2.07 (m, 7H), 2.16–2.32 (m, 4H), 2.50 (td, J = 7.0, 1.3 Hz, 2H), 2.71 (td, J = 12.5, 5.7 Hz, 1H), 3.01–3.13 (m, 1H), 3.36–3.52 (m, 1H), 9.79 ppm (t, J = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 15.6, 20.6, 28.0, 30.6, 37.3, 39.3, 43.9, 58.3, 82.0, 202.2, 213.2 ppm; IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1}; MS (EI): m/z: 212 $[M]^+$; HRMS (EI): m/z: calcd for $C_{12}H_{20}O_3$: 212.1412; found: 212.1416.

3-(1-Methoxy-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)propionaldehyde (2d): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04–2.2 (m, 2H), 2.45–2.6 (m, 3H), 2.86–2.95 (m, 1H), 3.0–3.25 (m, 2H), 3.07 (s, 3H), 7.23–7.45 (m, 4H), 9.68 ppm (t, J = 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 32.5, 37.92, 37.95, 52.9, 83.3, 126.7, 127.2, 127.9, 128.2, 136.8, 136.9, 201.1, 209.7 ppm; IR (KBr): $\tilde{\nu}$ = 1710, 1722 cm^{-1}; MS (EI): m/z: 198 $[M]^+$; HRMS (EI): m/z: calcd for $C_{11}H_{18}O_3$: 198.1256; found: 198.1248

3-(1-Ethoxy-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)propionaldehyde (2e): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.9 Hz, 3H), 2.0–2.2 (m, 2H), 2.35–2.7 (m, 3H), 2.8–2.9 (m, 1H), 3.0–3.35 (m, 4H), 7.19–7.5 (m, 4H), 9.69 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 27.9, 32.6, 37.86, 37.87, 60.3, 82.7, 126.5, 127.0, 127.7, 128.0, 136.5, 137.5, 201.2, 209.8 ppm; IR (KBr): $\tilde{\nu}$ = 1717, 1728 cm^{-1}; MS (FAB): m/z: 255 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{14}H_{16}O_3Na$ $[M+Na]^+$: 255.0997; found: 255.1005.

General procedure for the reaction of 2,3-epoxy alcohols with PIFA in the presence of water (Tables 1 (entries 6–8), 2 and 3; Schemes 5, 6, and 10): PIFA (1 mmol) was added to a stirred solution of 2,3-epoxy alcohol (1 mmol) in CH_3CN/H_2O (v/v 4:1, 10 mL) at 0°C and the mixture was gradually warmed to room temperature. After completion of the reaction (as checked by TLC), saturated aqueous $Na_2S_2O_3$ solution was added at 0°C and the reaction mixture was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 5:1 as the eluent to give the products in the yields shown in the tables.

2-Hydroxy-1-oxaspiro[4.5]decan-6-one (3a): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–2.74 (m, 12H), 3.99 (br s, 2/5H), 4.30–4.37 (m, 3/5H), 5.55 (dd, J = 4.9, 1.9 Hz, 3/5H), 5.60 ppm (d, J = 3.8 Hz, 2/5H); IR (KBr): $\tilde{\nu}$ = 3418, 1713 cm^{-1}; MS (EI): m/z: 170 $[M]^+$; HRMS (EI): m/z: calcd for $C_9H_{14}O_3$: 170.0943; found: 170.0943.

2-Hydroxy-1-oxaspiro[5.5]undecan-7-one (3b): Colorless crystals; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41–2.69 (m, 14H), 3.71 (br s, 1H), 4.10–4.25 ppm (m, 1H); IR (KBr): $\tilde{\nu}$ = 3501, 1697 cm^{-1}; MS (EI): m/z: 184 $[M]^+$; HRMS (EI): m/z: calcd for $C_{10}H_{16}O_3$: 184.1099; found: 184.1123.

Spiro(tetrahydrofuran-2-ol-5-1′)-3′,4′-dihydro-1′*H*-naphthalene-2′-one (3c): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86–3.25 (m, 8H), 4.20 (br s, 1H), 5.81–5.89 (m, 4/5H), 5.95 (d, J = 4.4 Hz, 1/5H), 7.15–7.75 ppm (m, 4H); IR (KBr): $\tilde{\nu}$ = 3410 cm^{-1}; MS (EI): m/z: 218 $[M]^+$; HRMS (EI): m/z: calcd for $C_{13}H_{14}O_3$: 218.0943; found: 218.0958.

6-Hydroxyundecane-2,7-dione (5): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.2 Hz, 3H), 1.23–1.41 (m, 2H), 1.47–1.90 (m, 6H), 2.15 (s, 3H), 2.35–2.60 (m, 4H), 3.57 (br s, 1H), 2.35–2.60 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.1, 22.4, 25.7, 30.0, 32.8, 37.6, 42.9, 76.1, 208.3, 211.9 ppm; IR (KBr): $\tilde{\nu}$ = 3479, 1713 cm^{-1}; MS (EI): m/z: 200 $[M]^+$; HRMS (EI): m/z: calcd for $C_{11}H_{20}O_3$: 200.1412; found: 200.1405.

1-(6-Hydroxytetrahydropyran-2-yl)ethanone (7): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.41 (m, 2H), 1.52–1.65 (m, 3H), 1.75–1.93 (m, 3H), 2.11 (s, 3/2H), 2.17 (s, 3/2H), 3.88 (dd, J = 11.4, 2.4 Hz, 1/2H), 4.40 (dd, J = 12.0, 2.7 Hz, 1/2H), 4.73 (dd, J = 9.3, 2.4 Hz, 1/2H), 5.34 ppm (br s, 1/2H); IR (KBr): $\tilde{\nu}$ = 3362, 1715 cm^{-1}; MS (EI): m/z: 144 $[M]^+$; HRMS (EI): m/z: calcd for $C_7H_{12}O_3$: 144.0786; found: 144.0791.

3,7,7-Trimethoxyheptan-2-one (8): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.47 (m, 2H), 1.55–1.66 (m, 4H), 2.14 (s, 3H), 3.29 (s, 6H), 3.33 (s, 3H), 3.53 (t, J = 6.3 Hz, 1H), 4.33 ppm (t, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 25.1, 31.5, 32.1, 52.6, 52.7, 58.1, 87.2, 104.2, 211.4 ppm; IR (KBr): $\tilde{\nu}$ = 2931, 1715, 1126 cm^{-1}; MS (FAB): m/z: 227 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{20}O_4Na$: 227.1259 $[M+Na]^+$; found: 227.1261.

6-Methoxy-1-methylcyclohexane-1,2-diol (9): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09–1.26 (m, 1H), 1.13 (s, 3H), 1.46–1.71 (m, 4H), 1.89 (m, 1H), 2.29 (br s, 2H), 3.33 (m, 1H), 3.34 (s, 3H), 3.67 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.38, 25.25, 31.58, 32.23, 52.75, 58.13, 87.22, 104.16 ppm: IR (KBr): $\tilde{\nu}$ = 3416, 2937, 1101 cm^{-1}; MS (FAB): m/z: 161 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_8H_{17}O_3$: 161.1178 $[M+H]^+$; found: 161.1154.

2-Methoxy-2-methylcyclohexane-1,3-diol (10): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 3H), 1.27–1.49 (m, 2H), 1.59–1.82 (m, 4H), 3.23 (s, 3H), 3.81 (dd, J = 11.1, 4.5 Hz, 1H), 3.88 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 18.2, 28.4, 29.8, 49.0, 69.9, 71.9, 80.0 ppm; IR (KBr): $\tilde{\nu}$ = 3362, 2941, 1074 cm^{-1}; MS (EI): m/z: 160 $[M]^+$; HRMS (EI): m/z: calcd for $C_8H_{16}O_3$: 160.1122; found: 160.1099.

1-(6-Hydroxy-6-deuterio-4-isopropenyltetrahydropyran-2-yl)ethanone (12): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.37 (m, 2H),

1.73 (s, 3H), 1.84–2.06 (m, 3H), 2.20 (s, 2/3H), 2.26 (s, 1/3H), 2.67 (m, 1H), 3.97 (dd, J=12.0, 2.7 Hz, 1H), 4.51 (dd, J=12.0, 2.4 Hz, 1H), 4.73 (m, 1H), 4.77 ppm (m, 1H); IR (KBr): $\tilde{\nu}$=3369, 1715 cm^{-1}; MS (EI): m/z: 185 $[M]^+$; HRMS (EI): m/z: calcd for $C_{10}H_{15}DO_3$: 185.1161; found: 185.1183.

1-(6-Hydroxytetrahydropyran-2-yl)pentan-1-one (14a): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.83 (t, J=7.5 Hz, 3H), 1.18–1.39 (m, 4H), 1.43–1.63 (m, 4H), 1.80–1.94 (m, 3H), 2.44 (t, J=7.2 Hz, 1H), 2.53 (t, J=7.2 Hz, 1H), 3.88 (dd, J=11.4, 2.7 Hz, 1/2H), 4.40 (dd, J=11.7, 2.7 Hz, 1/2H), 4.72 (dd, J=9.3, 2.1 Hz, 1/2H), 5.34 ppm (brs, 1/2H); IR (KBr): $\tilde{\nu}$=3360, 1713 cm^{-1}; MS (FAB): m/z: 209 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{18}O_3Na$: 209.1154 $[M+Na]^+$; found: 209.1152.

(2*S,4*S**)-1-(6-Hydroxy-4-isopropenyltetrahydropyran-2-yl)ethanone (14b)**:[33] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.19–1.32 (m, 4H), 1.53 (m, 1H), 1.72 (s, 3H), 1.88 (m, 1H), 2.01 (m, 1H), 2.18 (s, 2/3H), 2.24 (s, 1/3H), 2.65 (m, 1H), 3.95 (dd, J=11.6, 2.4 Hz, 1/3H), 4.49 (dd, J=11.9, 2.43 Hz, 2/3H), 4.73 (m, 2H), 4.85 (d, J=9.2 Hz, 1/3H), 5.51 ppm (d, J=2.7 Hz, 2/3H); IR (KBr): $\tilde{\nu}$=3342, 1715 cm^{-1}.

(2*S,4*S**)-1-(6-Hydroxy-4-isopropyltetrahydropyran-2-yl)-ethanone (14c)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (d, J=6.6 Hz, 3/2H), 0.88 (d, J=6.6 Hz, 3/2H), 0.99–1.08 (m, 1H), 1.28–1.56 (m, 3H), 1.70–1.84 (m, 2H), 1.92–1.96 (m, 1H), 2.17 (s, 3/2H), 2.23 (s, 3/2H), 3.87 (dd, J=11.7, 2.4 Hz, 1/2H), 4.41 (dd, J=11.7, 2.7 Hz, 1/2H), 4.76 (dd, J=9.6, 2.4 Hz, 1/2H), 5.47 ppm (d, J=3.3 Hz 1/2H); IR (KBr): $\tilde{\nu}$=3418, 1715 cm^{-1}; MS (FAB): m/z: 209 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{18}O_3Na$: 209.1154 $[M+Na]^+$; found: 209.1168.

(1*S,5*S**)-1-Methyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16a)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (s, 3H), 1.47–1.81 (m, 6H), 3.10 (brs, 1H), 5.15 (s, 1H), 5.68 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.0, 20.1, 28.7, 32.3, 81.6, 97.3, 102.3 ppm; IR (KBr): $\tilde{\nu}$=3406 cm^{-1}; MS (FAB): m/z: 167 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_7H_{12}O_3Na$: 167.0684: $[M+Na]^+$; found: 167.0677.

(1*S,5*S**)-1-Ethyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16b)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94–1.01 (m, 3H), 1.44–1.80 (m, 8H), 3.07 (brs, 1H), 5.19 (s, 1H), 5.68 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.2, 15.8, 26.9, 28.6, 29.1, 84.2, 97.1, 102.5 ppm; IR (KBr): $\tilde{\nu}$=3406 cm^{-1}; elemental analysis calcd (%) for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.35, H 8.70.

(1*S,5*S**)-1-Undecyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16c)**: Colorless crystals; m.p. 45 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.6 Hz, 3H), 1.26 (m, 20H), 1.51–1.72 (m, 6H), 3.27 (brs, 1H), 5.17 (s, 1H), 5.67 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 15.8, 22.6, 23.8, 29.1, 29.2, 29.3, 29.5 (2C), 29.6 (2C), 30.2, 31.8, 34.0, 83.9, 97.1, 102.2 ppm; IR (KBr): $\tilde{\nu}$=3360 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{32}O_3$: C 71.79, H 11.34; found: C 71.58, H 11.09.

(1*S,5*S**)-1-Isobutyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16d)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (d, J=6.6 Hz, 3H), 0.99 (d, J=6.6 Hz, 3H), 1.47–1.95 (m, 9H), 2.92 (brs, 1H), 5.16 (s, 1H), 5.66 (s, 1H), 5.68 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.9, 23.5, 23.8, 24.0, 29.0, 29.1, 42.1, 83.8, 97.6, 102.2 ppm; IR (KBr): $\tilde{\nu}$=3412 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{18}O_3$: C 64.49, H 9.74; found: C 64.56, H 9.57.

(1*S,5*S**)-1-Benzyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16e)**: Colorless crystals; m.p. 103 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34–1.77 (m, 6H), 2.95 (A in ABq, J=13.9 Hz, 1H), 3.01 (B in ABq, J=13.9 Hz, 1H), 3.09 (brs, 1H), 5.23 (s, 1H), 5.75 (s, 1H), 7.19–7.34 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.7, 28.9, 29.2, 40.0, 83.9, 97.2, 102.8, 126.5, 128.2 (2C), 130.4 (2C), 136.5 ppm; IR (KBr): $\tilde{\nu}$=3406 cm^{-1}; MS (EI): m/z: 220 $[M]^+$; HRMS (EI): m/z: calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1116.

(1*S,5*S**)-1-Phenyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16f)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40–2.62 (m, 5H), 3.04 (t, J=7.2 Hz, 4/5H), 3.13 (s, 1/5H), 5.27 (d, J=4.8 Hz, 1/5H), 5.50 (t, J=9.9 Hz, 4/5H), 5.65 (s, 1/5H), 5.86 (s, 4/5H), 7.24–7.50 ppm (m, 5H); IR (KBr): $\tilde{\nu}$=3400 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{14}O_3$: C 69.88, H 6.84; found: C 69.73, H 6.85.

(1*S,5*S**)-1,3,3-Trimethyl-6,8-dioxabicyclo[3.2.1]octan-7-ol (16g)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (s, 3H), 1.17 (s, 3H), 1.31 (s, 3H), 1.41–1.66 (m, 4H), 2.84 (brs, 1H), 5.16 (s, 1H), 5.69 ppm (t, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.5, 27.9, 31.1, 35.6, 41.3, 46.1, 81.4, 97.0, 101.9 ppm; IR (KBr): $\tilde{\nu}$=3418 cm^{-1}; elemental analysis calcd (%) for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.59, H 9.16.

General procedure for the transformation of lactols into lactones (Tables 4 and 5)

Oxidation with Ag_2CO_3/Celite (Method A): Ag_2CO_3/Celite (10 mmol) was added to a solution of lactol (1 mmol) in benzene (10 mL) and the reaction mixture was refluxed for 1 h under an N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with AcOEt, and filtered through a pad of Celite. The filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 1:1 as the eluent to give the products in the yields shown in Tables 4 and 5.

Jones oxidation (Method B; Table 4): After H_2SO_4 (11 mmol) was added to a stirred solution of CrO_3 (7 mmol) in H_2O (1 mL), H_2O (2 mL) was to the solution (preparation of Jones reagent). The Jones reagent was added slowly to a stirred solution of lactol (10 mmol) in acetone (6 mL) with the reaction temperature kept at 20 °C. After the reaction mixture had been stirred for 3 h, $NaHSO_3$ was added slowly until the orange color of the CrO_3 had disappeared. The reaction mixture was extracted with diethyl ether. The combined organic layer was washed with brine, saturated $NaHCO_3$ solution, and brine, and then dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 1:1 as the eluent to give the products in the yields shown in Table 4.

6-Hydroxymethyl-6-phenyltetrahydropyran-2-one (19a): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.55 (m, 1H), 1.76 (m, 1H), 2.17 (dt, J=13.8, 4.2 Hz, 1H), 2.29 (dd, J=12.6, 4.2 Hz, 1H), 2.35–2.49 (m, 2H), 2.55–2.61 (m, 1H), 3.60 (A in ABq, J=12.3 Hz, 1H), 3.71 (B in ABq, J=12.3 Hz, 1H), 7.22–7.34 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.8, 27.7, 29.2, 69.9, 88.4, 125.2 (2C), 127.9, 128.8 (2C), 140.3, 171.9 ppm; IR (KBr): $\tilde{\nu}$=3333, 1715 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{14}O_3$: C 69.88, H 6.84; found: C 69.57, H 6.83.

6-Hydroxymethyl-4,4,6-trimethyltetrahydropyran-2-one (19b): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.05 (s, 3H), 1.13 (s, 3H), 1.40 (s, 3H), 1.54 (d, J=13.7 Hz, 1H), 1.96 (d, J=13.7 Hz, 1H), 2.30 (s, 2H), 2.78 (s, 1H), 3.41 (d, J=11.9 Hz, 1H), 3.56 ppm (d, J=11.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.8, 28.3, 30.5 (2C), 41.4, 43.2, 70.2, 83.6, 72.3 ppm; IR (KBr): $\tilde{\nu}$=3402, 1715, 1066 cm^{-1}; elemental analysis calcd (%) for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.74, H 9.23.

1-Oxaspiro[4.5]decane-2,6-dione (17a): The spectral data for this compound were identical to those reported in the literature.[34]

1-Oxaspiro[5.5]undecane-2,7-dione (17b): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.75–1.91 (m, 4H), 2.03–2.11 (m, 2H), 2.38 (dd, J=6.0, 5.1 Hz, 2H), 2.49 (m, 2H), 2.59 (m, 2H), 2.71 ppm (dd, J=6.3, 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0, 22.5, 24.0, 35.9, 36.1, 42.4 (2C), 201.8, 203.5 ppm; IR (KBr): $\tilde{\nu}$=2932, 1713 cm^{-1}; MS (FAB): m/z: 205 $[M+Na]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{14}O_3Na$: 205.0841 $[M+Na]^+$; found: 205.0865.

6-Acetyl-tetrahydropyran-2-one (17c): The spectral data for this compound were identical to those reported in the literature.[35]

***cis*-6-Acetyl-4-isopropyltetrahydropyran-2-one (17d)**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85 (d, J=6.6 Hz, 6H), 1.27 (m, 1H), 1.50 (m, 1H), 1.73 (m, 1H), 2.08–2.22 (m, 2H), 2.25 (s, 3H), 2.66 (ddd, J=17.8, 5.9, 1.9 Hz, 1H), 4.53 ppm (dd, J=11.9, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.2 (2C), 25.9, 28.7, 32.3, 34.0, 37.7, 83.7, 169.8, 205.8 ppm; IR (KBr): $\tilde{\nu}$=1717 cm^{-1}; MS (EI): m/z: 184 $[M]^+$; HRMS (EI): m/z: calcd for $C_{10}H_{16}O_3$: 184.1099; found: 184.1112.

Asymmetric total synthesis of (+)-tanikolide (Schemes 14 and 15): The enantiomeric excess values of optically active compounds were determined by chiral HPLC analysis by using Daicel Chiralcel OD columns with hexanes/*i*PrOH as the eluent.

2-Iodo-3-undecylcyclohex-2-enone (23): Azidotrimethylsilane (1.3 mL, 5.0 mmol) was added to a stirred solution of the known enone[14] **21** (91.6 mg, 0.36 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C under N_2. After the reaction mixture had been stirred for 2 h, I_2 (1.28 g, 5.0 mmol) in CH_2Cl_2

(0.54 mL) and pyridine (3.0 mL) were added dropwise. The reaction mixture was gradually warmed to room temperature and stirred for 24 h.[17] Saturated aqueous $Na_2S_2O_3$ solution was added to the reaction mixture and the resulting mixture was extracted with Et_2O. The organic layer was washed with 10% HCl, saturated aqueous $NaHCO_3$ solution, and brine. The layer was then dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 8:1 to give **23** (108.8 mg, 80%) as a brownish oil: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.5$ Hz, 3H), 1.24–1.31 (m, 16H), 1.47–1.52 (m, 2H), 1.89–1.98 (m, 2H), 2.46–2.60 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$, 22.3, 22.6, 26.9, 29.2, 29.3, 29.4, 29.5 (3C), 31.8, 32.5, 36.5, 44.8, 106.6, 170.2, 192.2 ppm; IR (KBr): $\tilde{\nu} = 1682$, 1583 cm^{-1}; MS (EI): *m/z*: 376 $[M]^+$; HRMS (EI): *m/z*: calcd for $C_{17}H_{29}IO$: 376.1263; found: 376.1253.

(*R*)-2-Iodo-3-undecylcyclohex-2-enol ((+)-24): (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (1M in toluene, 0.080 mL, 0.080 mmol) in THF (0.5 mL) was added dropwise to a solution of BH_3·Me_2S (2M in THF, 40 μL, 0.080 mmol) at 0°C under N_2. After the reaction mixture had been stirred for 30 min, **23** (30.0 mg, 0.080 mmol) in THF (0.25 mL) was added slowly.[15] After the resulting mixture had been stirred for a further 30 min, MeOH was added and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography with benzene/AcOEt 70:1 as the eluent to give (+)-**24** (28.0 mg, 93%) as colorless crystals. M.p. 48°C (hexane); $[\alpha]_D^{21.1} = +47.83$ ($c = 1.12$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.7$ Hz, 3H), 1.24–1.37 (m, 18H), 1.61–1.88 (m, H), 2.11–2.22 (m, 5H), 4.26 ppm (t, $J = 4.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 18.6, 22.7, 27.1, 29.3, 29.4 (2C), 29.5, 29.6, 29.6, 31.5, 31.9 (2C), 42.8, 74.0, 104.2, 146.5 ppm; IR (KBr): $\tilde{\nu} = 3441$, 1682 cm^{-1}; MS (EI): *m/z*: 378 $[M]^+$; HRMS (EI): *m/z*: calcd for $C_{17}H_{31}IO$: 378.1420; found: 378.1430.

(*R*)-3-Undecylcyclohex-2-enol ((+)-22)

By catalytic hydrogenation in the presence of quinoline:[19] 10% Pd/C (120 mg) was added to a solution of (+)-**24** (454 mg, 1.2 mmol), sodium acetate, and quinoline (catalytic amount) in MeOH (120 mL). After being stirred under a H_2 atmosphere (1 atm) for 1 h, the reaction mixture was filtered through a pad of Celite. H_2O was added to the filtrate and the mixture was extracted with CH_2Cl_2. The combined organic layer was evaporated in vacuo. The residue was purified by silica gel column chromatography with benzene/AcOEt 70:1 as the eluent to give (+)-**22** (28.0 mg, 93%).

By radical reduction:[18a] Et_3B (1M in hexane, 69.9 μL, 0.070 mmol) and Bu_3SnH (23.5 μL, 0.090 mmol) were added to a stirred solution of (+)-**24** (18.9 mg, 0.050 mmol) in toluene (0.5 mL) at 0°C under N_2.[18a] After the reaction mixture had been stirred for 3 h at room temperature, MeOH was added and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 7:1 as the eluent to give (+)-**22** (10.6 mg, 84%) as a colorless oil. $[\alpha]_D^{25.6} = +27.36$ ($c = 1.15$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.5$ Hz, 3H), 1.26–1.98 (m, 27H), 4.19 (brs, 1H), 5.48 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 19.1, 22.6, 27.5, 28.4, 29.3 (2C), 29.5, 29.6 (3C), 31.9 (2C), 37.6, 65.8, 123.5, 142.6 ppm; IR (KBr): $\tilde{\nu} = 3344$ cm^{-1}; MS (EI): *m/z*: 252 $[M]^+$; HRMS (EI): *m/z*: calcd for $C_{17}H_{32}O$; 252.2453; found: 252.2461.

(1*R*,2*R*,6*S*)-6-Undecyl-7-oxabicyclo[4.1.0]heptan-2-ol ((+)-15c): VO(acac)$_2$ (3.2 mg, 0.012 mmol) was added to a stirred solution of (+)-**22** (310 mg, 1.2 mmol) in benzene (10 mL) at 0°C under N_2. After the reaction mixture had been stirred for 1 h at room temperature, *t*BuOOH (0.4 mL, 3.7 mmol) in benzene was added at 0°C and stirred for 1.5 h at room temperature.[20] The reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 3:1 as the eluent to give (+)-**15c** (315 mg, 96%) as colorless crystals. M.p. 43°C (hexane); $[\alpha]_D^{25.6} = +21.19$ ($c = 1.56$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.7$ Hz, 3H), 1.26–1.80 (m, 26H), 2.18 (brs, 1H), 3.13 (d, $J = 2.9$ Hz, 1H), 3.98 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.1$, 18.2, 22.6, 24.7, 26.6, 29.1, 29.3, 29.5 (2C), 29.6 (3C), 31.9, 37.4, 61.4, 64.4, 66.9 ppm; IR (KBr): $\tilde{\nu} = 3418$ cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{32}O_2$: C 76.06, H 12.02; found: C 75.93, H 11.81.

(1*R*,5*R*)-1-Undecyl-6,8-dioxabicyclo[3.2.1]octan-7-ol ((+)-16c): PIFA (281.3 mg, 0.65 mmol) was added to a stirred solution of (+)-**15c** (175.6 mg, 0.65 mmol) in CH_3CN/H_2O (v/v 4:1, 6.5 mL) at 0°C. After the reaction mixture had been stirred for 12 h at room temperature, saturated aqueous $Na_2S_2O_3$ solution was added. The solution was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 5:1 as the eluent to give (+)-**16c** (134.0 mg, 72%) as colorless crystals. M.p. 45°C (hexane); $[\alpha]_D^{26.4} = +54.17$ ($c = 0.54$ in $CHCl_3$).

(+)-Tanikolide ((+)-25): DIBAH (0.94M in hexane, 1.04 mL, 0.98 mmol) was added to a stirred solution of (+)-**16c** (79.9 mg, 0.28 mmol) in CH_2Cl_2 (2.8 mL) at −15°C under N_2 and gradually warmed to 0°C. After the reaction mixture had been stirred for 30 min at the same temperature, MeOH and Rochelle's salt were added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. Ag_2CO_3 on Celite[10] (772 mg, 2.8 mmol) was added to the solution of the obtained crude lactol in benzene (2.8 mL) and the mixture was refluxed for 45 min. The cooled reaction mixture was diluted with AcOEt and filtered through a pad of Celite. The filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane/AcOEt 1:1 as the eluent to give (+)-tanikolide ((+)-**25**; 45.9 mg, 57%) as colorless crystals. M.p. 44°C (hexane); $[\alpha]_D^{25.9} = +2.60$ ($c = 1.08$ in $CHCl_3$) (lit.:[11] $[\alpha]_D^{25} = +2.3$ ($c = 0.65$ in $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (t, $J = 6.6$ Hz, 3H), 1.19 (m, 18H), 1.54–1.90 (m, 7H), 2.40 (t, $J = 6.5$ Hz, 2H), 2.57 (brs, 1H), 3.48 (d, $J = 12.0$ Hz, 1H), 3.60 ppm (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 16.6, 22.6, 23.4, 26.6, 29.3, 29.4, 29.5 (2C), 29.6, 29.7, 29.9, 31.8, 36.7, 67.4, 86.6, 171.9 ppm; IR (KBr): $\tilde{\nu} = 3396$, 1715 cm^{-1}; MS (FAB): *m/z*: 285 $[M+Na]^+$; HRMS (FAB): *m/z*: calcd for $C_{17}H_{33}O_3$: 285.2429 $[M+H]^+$; found: 285.2452.

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