Articles

New Synthesis of All Four Isomers of 3-Hydroxy-4-methyl-γ-butyrolactone by Stereoselective Intramolecular Lactonization. Application to Asymmetric Synthesis of Biologically Active Compounds

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A new synthesis of all four isomeric 3-hydroxy-4-methyl-γ-butyrolactones (**11**, *ent*-**11**, **12**, *ent*-**12**) has been performed. The former two were prepared *via* stereoselective iodolactonization, which favors the *cis*-3,4-disubstituted system (**16a** and *ent*-**16a**), of *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamides (*R*)- and (*S*)-**13**, readily available by resolution of the racemate by lipase-mediated transesterification; and the latter two were prepared *via* stereoselective oxylactonization, which favors the *trans*-3,4-disubstituted system [(3*R*,4*S*)-**20a** and *ent*-(3*R*,4*S*)-**20a**], of *O*-TBDMS-protected *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamides (*R*)- and (*S*)-**14**. Butyrolactones **11** and **12** have been readily transformed into biologically active compounds [(−)-blastmycinolactol (**27**), (−)-NFX-2 (**2**), (−)-NFX-4 (**3**), lipid metabolites **9** and **10**, and the sex pheromone (−)-(2*S*,3*S*)-2,3-octanediol (**30**)].

Introduction

Functionalized chiral γ-lactones have attracted substantial attention in recent years because of their importance as chiral building blocks, for the synthesis of compounds such as alkaloids, macrocyclic antibiotics, lignan lactones, pheromones, antileukemics, and flavor components.[1] The lactones have been prepared by means of a variety of methods, including the transformation of chiral natural products,[2] microbial reduction of γ-keto acids,[3] enzymatic resolution,[4] and chiral induction with chiral chemical reagents.[5] Our interest in this field has focused on the synthetic utilization of oxidative heterocyclization,[6] and this method has been employed powerfully for the stereoselective construction of oxygen- and nitrogen-heterocycles leading to biologically active compounds.[7]

The 2-alkyl or -alkylidene 3-hydroxy-4-methyl-γ-butyrolactones and their *O*-acyl derivatives for example, polyketides (+)-blastmycinone (**1**),[8] (−)-NFX-2 (**2**),[9] (−)-NFX-4 (**3**),[9] (−)-litsenolide B1, B2, C1, C2 (**4-7**),[10] and (−)-isodihydromahubanolide B (**8**)[11] and unusual lipid metabolites **9** and **10**,[12] are widespread as metabolites from different natural sources (Chart 1). Herein we describe a new synthesis of all four stereoisomers of 3-hydroxy-4-methyl-γ-butyrolactone (**11**, *ent*-**11**, **12**, and *ent*-**12**) by stereoselective intramolecular lactonization (either iodolactonization or oxylactonization) of homochiral *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamides **13** and *O*-TBDMS derivatives **14** as shown in Scheme 1 and the use of these isomers for expeditious synthesis of biologically active compounds such as those mentioned above.

Results and Discussion

Preparation of Both Enantiomers of *N*-Benzyl-*N*-methyl-3-hydroxy-4-pentenamide (13). The physi-

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0022-3263/94/1959-7201$04.50/0

Scheme 1

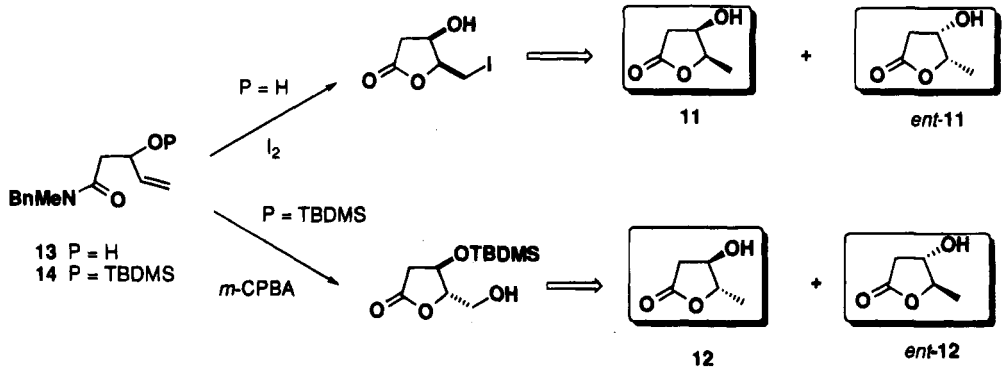
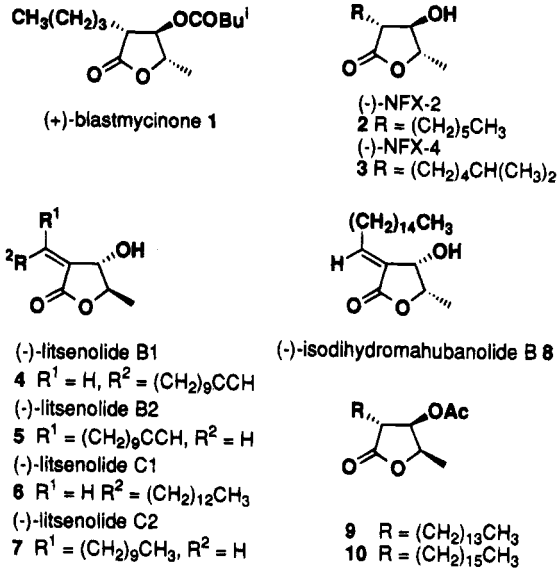
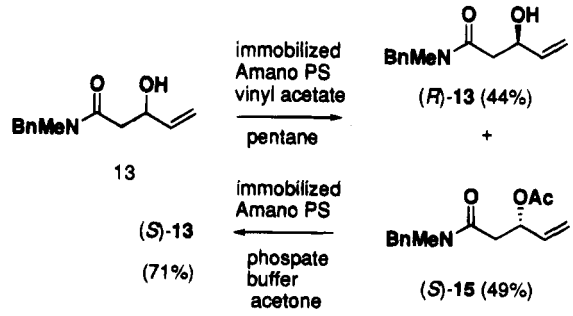


Chart 1

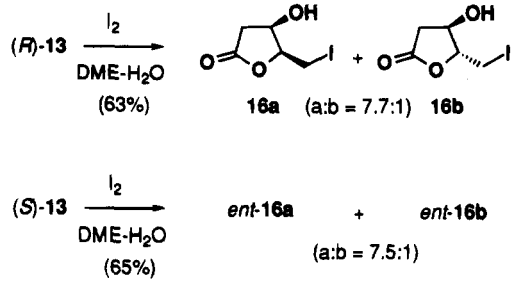


ological activity of γ-lactones often depends on both the optical purity and absolute configuration;[13] for example the presence of even a small amount of the counter enantiomer of a lactone can greatly reduce its biological activity.[14] The use of enzymes in organic synthesis has provided a new and powerful tool for the synthesis of enantiomerically pure educts.[15] Transesterification-based enzymatic resolution of secondary alcohols is now widely regarded as a method of choice for the synthesis of either enantiomer of an alcohol with high enantiomeric purity.[16] Recently we enzymatically resolved *N,N*-dialkyl-3-hydroxy-4-pentenamides that could not be resolved by the Katsuki–Sharpless asymmetric epoxidation.[17] Transesterification of racemic **13** with vinyl acetate catalyzed by the immobilized lipase from Amano PS[18] in pentane at 30 °C provided (*R*)-**13** (>99% ee)[19] in 44% yield and acetate (*S*)-**15** (>98% ee) in 49% yield.

Scheme 2



Scheme 3



Acetate (*S*)-**15** was hydrolyzed by the immobilized lipase (Amano PS) in acetone and phosphate buffer (0.1 N, pH 7) at 30 °C to give (*S*)-**13** (>99% ee)[19] in 71% yield (Scheme 2).

Stereoselective Intramolecular Lactonization. With both the enantiomerically pure secondary allylic alcohols [(*R*)- and (*S*)-**13**] thus prepared, we turned our attention to the stereoselective construction of functionalized γ-butyrolactones. The protocol based on the diastereoselective intramolecular addition of heteronucleophiles, directed by an allylic hydroxyl, has proven to be useful for the synthesis of heterocyclic compounds with defined stereochemistry.[20] The iodine-induced lactonization[21] of (*R*)-**13** was performed with iodine in DME–H_2O (1:1) at room temperature to give a mixture (7.7:1) of γ-lactones **16a** and **16b** with high cis selectivity in 63% yield (Scheme 3).[22] Similar iodolactonization of (*S*)-**13** provided a diastereomeric mixture (7.5:1) of *ent*-**16a** and *ent*-**16b** in 65% yield.[22]

Next, the iodolactonization of **13** was effected with the opposite stereoselectivity by oxylactonization of *O*-pro-

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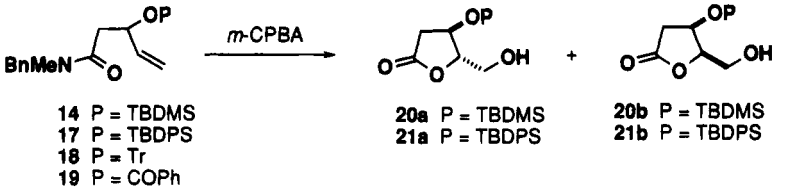
(19) Analysis by HPLC with a chiral column (Daisel AS) established the enantiomeric ratio of (*R*)- and (*S*)-**13** to be >100/1; see experimental section.
(20) For a review, see: Takahata, H. *Yakugaku Zasshi* **1992**, *112*, 229.
(21) (a) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C.; *J. Am. Chem. Soc.* **1983**, *105*, 5819.
(22) The diastereomeric ratio was determined by HPLC.

Table 1. Oxylactonization of *O*-Protected Alkenylamides 14, 17, 18, and 19



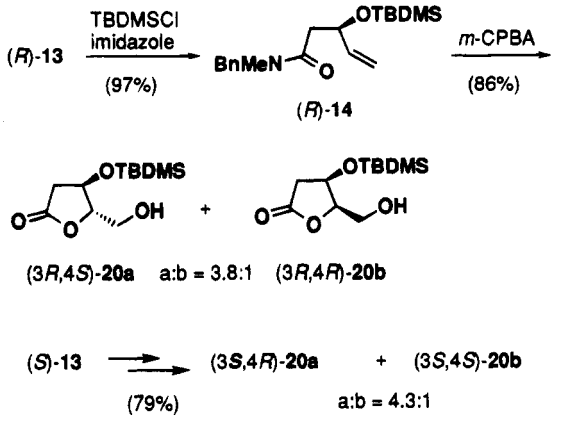
14 P = TBDMS
17 P = TBDPS
18 P = Tr
19 P = COPh

20a P = TBDMS
21a P = TBDPS

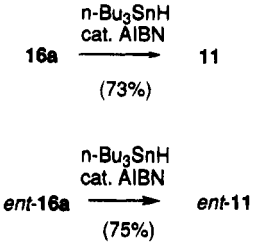
20b P = TBDMS
21b P = TBDPS

entry	amide	solvent	additive	temp. (°C)	time (h)	product	yield (%)	trans:cis (a:b)
1	**14**	benzene	none	30	24	**20a,b**	78	4.0:1
2	**17**	benzene	none	30	24	**21a,b**	78	1.8:1
3	**18**	benzene	none	30	24	-	-	-
4	**19**	benzene	none	30	24	-	-	-
5	**14**	CH_2Cl_2	none	30	24	**20a,b**	53	3.5:1
6	**14**	CH_2Cl_2	CSA	0	19	**20a,b**	14	4.1:1
7	**14**	CH_2Cl_2	BF_3-OEt_2	-30	22	**20a,b**	44	4.3:1

Scheme 4



Scheme 5



tected alkenamides with *m*-CPBA.[23] Under several conditions, oxylactonization of racemic alkenamides **14**, **17**,**18**, and **19** was examined (Table 1). The oxylactonization of **14** in benzene at 30 °C gave *trans*-γ-lactone **20a** and *cis*-γ-lactone **20b** in a 4:1 ratio (entry 1). Surprisingly, *tert*-butyldiphenylsiloxy derivative **17** gave lower stereoselectivity, though the reason remains unknown (entry 2). The oxylactonization of alkenamides **18** and **19** gave no product under the conditions shown in Table 1 (starting materials were recovered). Both the replacement of benzene by CH_2Cl_2 as a solvent and the use of an additive such as a Lewis acid reduced the yields (entries 5–7). Thus, oxylactonization of alkenamide (R)-**14** prepared by *tert*-butyldimethylsilylation of (*R*)-**13** (97%), under the conditions given in entry 1, afforded a diastereomeric mixture (3.8:1) of (3*R*,4*S*)-**20a** and (3*R*,4*R*)-**20b** in 86% yield (Scheme 4). Analogous oxylactonization of (*S*)-**14** gave (3*S*,4*R*)-**20a** and (3*S*,4*S*)-**20b** in a 4.3:1 ratio in 90% yield. Thus, both enantiomers of *trans*-**20a** were prepared with moderate stereoselectivity.

Synthesis of All of Four Isomeric 3-Hydroxy-4-methyl-γ-butyrolactones. The transformations of functionalized γ-lactones **16a**, *ent*-**16a**, (3*R*,4*S*)-**20a**, and (3*S*,4*R*-**20a** into 3-hydroxy-4-methyl γ-lactones **11**, *ent*-**11**, **12**, and *ent*-**12**, respectively, were examined. Both *cis*-γ-lactones **16a** and *ent*-**16a** were reduced with n-Bu_3SnH in the presence of cat. AIBN to give the desired γ-lactones **11** and *ent*-**11** in 73% and 75% yield, respectively (Scheme 5).

Our synthesis of **12** began with the sulfenylation of (3*R*,4*S*)-**20a**. The sulfenylation by Hata's method[24] (PhSSPh/n-Bu_3P/pyridine) provided **22** in 96% yield. Lactone **22** was desulfenylated with excess Raney-Ni (W-2) in EtOH to afford **23** in 52% yield. Finally, **23** was deprotected with PPTS to give **12** in 89% yield.[25] An alternative synthesis of **23** was performed in 62% yield by iodination of (3*R*,4*S*)-**20a** followed by radical reduction (Scheme 6). As the yield of the latter procedure was an improvement, the synthesis of *ent*-**12** was performed in 57% yield by iodination of (3*S*,4*R*)-**20a** followed by reduction and deprotection.

Asymmetric Synthesis of Biologically Active Compounds. With all four 3-hydroxy-4-methyl-γ-butyrolactones in hand, we focused our attention on their transformation into biologically active compounds. The formal synthesis of (+)-blastmycinone (**1**),[26] obtained from the degradation of (+)-antimycin A_3 (**25a**),[8] was performed by stereoselective alkylation of γ-butyrolactone **12** at the C2 position (Scheme 7). The lithium enolate of **12** was alkylated with butyl iodide to give (−)-blastmycinolactol

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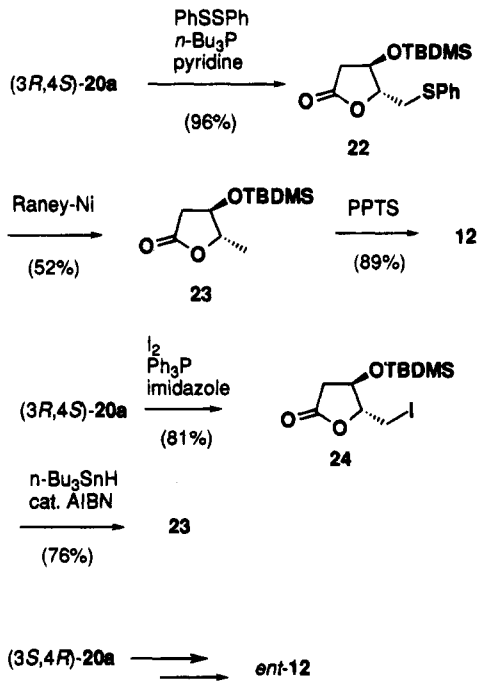
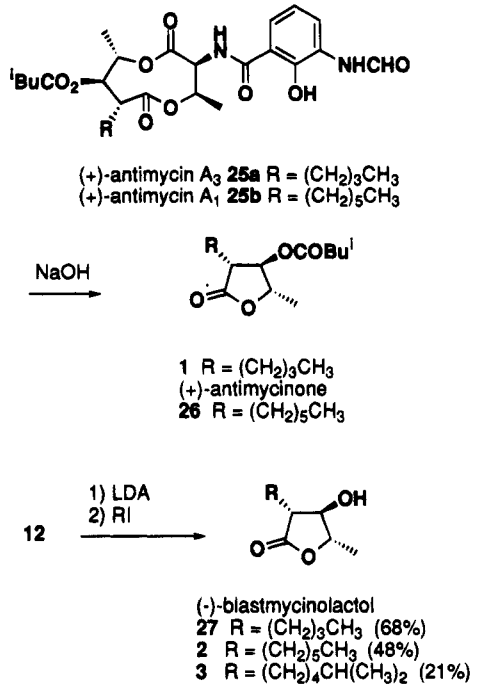
Scheme 6

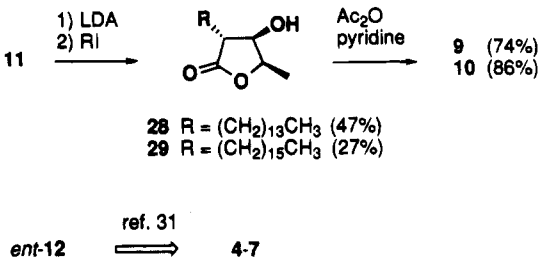


Scheme 7

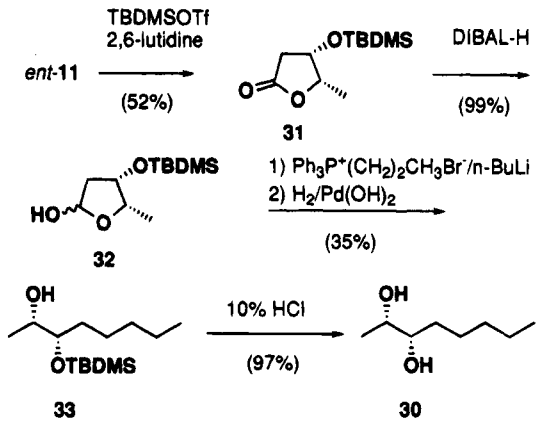


(**27**)[27] in 68% yield; the spectral data and optical rotation of **27** were identical to those reported.[28] Isovalerylation of **27** had previously been achieved to give **1**.[28] Very recently, Yamada *et al.* isolated new virginiamycin inducing factors, NFX-2 (**2**) and NFX-4 (**3**), from the culture broth of *Streptomyces antbiotics* NF-18 and determined their structures.[9] In addition, NFX-2 (**2**) has also been obtained from degradation of (+)-antimycin A_1 (**25b**).[29] So far, only one synthesis of **2** has been reported,[29] and the synthesis of **3** has never been performed. By means of the method used for **27**, the alkylations of **12** with hexyl iodide and 5-methylhexyl iodide were performed to afford NFX-2 (−)-**2** and NFX-4 (−)-**3** in 48 and 21% yields, respectively. Spectral data for **2** and **3** were completely identical to those reported.[9,29]

Scheme 8



Scheme 9



Next, we turned our attention to the synthesis of unusual lipid metabolites **9** and **10** produced from the Gorgonian coral *Plexaura flava*.[12] Font *et al.* had already synthesized *ent*-**9** and *ent*-**10** by means of stereoselective alkylation at C2 of *ent*-**11**.[30] With this method in mind, a similar procedure for *cis*-γ-butyrolactone **11** gave alkylated products **28** and **29**, which were acetylated to afford desired metabolites **9** and **10**, respectively, as shown in Scheme 8. Thus the absolute configurations of **9** and **10** were unequivocally determined to be 2*R*,3*R*,4*R* (Scheme 8). Lactone *ent*-**12** has been converted by alkylidenation into the naturally occurring Lauraceae lactones, (−)-litsenolides B1 (**4**), B2(**5**), C1(**6**), and C2 (**7**), by Joullié *et al.*[31]

It was expected that ring-opening of γ-butyrolactone *ent*-**11** would lead to *threo* diols of biological interest. Indeed, male-produced sex pheromone (2*S*,3*S*)-2,3-octanediol (**30**), extracted from the grape borer *Xylotrechus pyrrhoderus*,[32,33] was obtained by a stereocontrolled transformation of *ent*-**11** as shown in Scheme 9. Our synthesis of **30** began with protection of the hydroxyl in *ent*-**11**. *tert*-Butyldimethylsilylation of *ent*-**11** with TBDMSOTf gave **31**, which was reduced with DIBAL-H to

(27) For recent synthesis (−)-blastmycinolactol (**27**), Mikami, K.; Terada, M.; Nakai, T. *J. Chem. Soc. Chem. Commun.* **1993**, 343. (b) Nishide K.; Aramata, A.; Kamanaka, T.; Node, M. *Heterocycles* **1993**, *36*. 2237.

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lactol **32** in 51% yield from *ent*-**11**. Wittig reaction of **32** provided the ring-opened product, which was reduced to give **33** in 35% overall yield from **32**. Finally, deprotection of **33** gave diol **30** (97%), whose spectral data and optical rotation were completely identical to those reported.[32]

Conclusion

A new synthesis of all four 3-hydroxy-4-methyl-γ-butyrolactones (**11**, *ent*-**11**, **12**, *ent*-**12**), potentially chiral building blocks for biologically active compounds, has been performed by stereoselective intramolecular lactonization (iodolactonization and oxylactonization) of both enantiomers of *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamide, readily available from lipase-mediated transesterification. The transformation of lactones **11** and **12** into biologically active compounds such as polyketides and pheromones has been demonstrated. With highly functionalized γ-butyrolactones **16a**, *ent*-**16a**, (3*R*,4*S*)-**20a**, and *ent*-(3*R*,4*S*)-**20a** in hand, we can now turn our attention to further elaboration that will lead to an asymmetric synthesis of a variety of naturally occurring products.[34]

Experimental Section

Melting points are uncorrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No 9385) with a medium pressure apparatus and a mixture of ethyl acetate/hexane was used as eluant unless otherwise specified. Extracts were dried over Na_2SO_4 unless otherwise specified.

(*R*)-*N*-Benzyl-*N*-methyl-3-hydroxy-4-pentenamide [(*R*)-13] and (*S*)-*N*-Benzyl-*N*-methyl-3-acetoxy-4-pentenamide [(*S*)-15]. A suspension of *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamide (**13**) (220 mg, 1 mmol), vinyl acetate (0.463 mL, 5 mmol), and immobilized Amano PS (500 mg), prepared by Bianchi's procedure,[35] in pentane (5 mL) was stirred for 15 h at 30 °C.[36] The insoluble material was filtered off, and the filtrate was concentrated and chromatographed with a mixture of CCl_4 and ethyl acetate to give (*R*)-**13** (97 mg, 44%) and (*S*)-**15** (128 mg, 49%) as oils.

[(*R*)-**13**]: bp 116–120 °C (0.5 mmHg); $[\alpha]^{25}_D$ +24.27 (*c* 1.425, $CHCl_3$) (99% ee by HPLC using DAICEL CHIRALPAC AS; 40 °C; hexane:2-propanol = 9:1; flow 0.7 mL/min); IR (neat) 3420, 1625, 1496, 1453, 1404, 1244, 700 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.50 (1H, dd, *J* = 16.5, 8.8 Hz), 2.61 (1H, dd, *J* = 16.5, 3.3 Hz), 2.89 and 2.95 (3H, s), 4.46–4.51 (1H, m), 4.53–4.65 (1H, m), 4.58–4.60 (2H, m), 5.08–5.17 (1H, m), 5.25–5.37 (1H, m), 5.80–5.98 (1H, m), 7.13–7.39 (5H, m). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.27; H, 7.80; N, 6.27.

[(*S*)-**15**]: bp 125–130 °C (0.4 mmHg); $[\alpha]^{25}_D$ +19.77 (*c* 1.825, $CHCl_3$) (98% ee by HPLC using DAICEL CHIRALPAC AS; 40 °C; hexane:2-propanol = 9:1; flow 0.7 mL/min); IR (neat) 2932, 1739, 1650, 1453, 1372, 1240 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.03 and 2.05 (3H, s), 2.57–2.65 (1H, m), 2.81–2.90 (1H, m), 2.94 (3H, s), 4.48–4.70 (2H, m), 5.17–5.35 (2H, m), 5.73–5.80 (1H, m), 5.84- 6.00 (1H, m), 7.16–7.40 (5H, m, Ph). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.18; H, 7.20; N, 5.35.

(*S*)-*N*-Benzyl-*N*-methyl-3-hydroxy-4-pentenamide [(*S*)-13]. A suspension of (*S*)-**15** (7.869 g, 30.1 mmol), immobilized Amano PS (19.673 g), and phosphate buffer (0.1 N, pH 7) (164 mL) in acetone (7.87 mL) was stirred for 15 h at 30 °C. The insoluble material was filtered off. After the addition of ethyl acetate (100 mL) to the filtrate, the organic solvent was separated. The aqueous phase was extracted with ethyl acetate (100 mL) four times, and the combined extracts were washed with brine, dried, and evaporated to give the residue, which was chromatographed with a mixture of CCl_4 and ethyl acetate to provide (*S*)-**13**[37] (4.69 g, 71%) as an oil; bp 116–118 °C (0.5 mmHg); $[\alpha]^{25}_D$ −24.31 (*c* 1.09, $CHCl_3$) (99% ee by HPLC using DAICEL CHIRALPAC AS; 40 °C; hexane:2-propanol = 9:1; flow 0.7 mL/min). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.32; H, 7.99; N, 6.38.

(3*R*,4*S*)-3-Hydroxy-4-(iodomethyl)-γ-butyrolactone (16a). A solution of (*R*)-**13** (5.68 g, 25.88 mmol) and I_2 (13.19 g, 51.97 mmol) in DME–H_2O (1:1) (104 mL) was stirred for 24 h at 30 °C. After the addition of Et_2O (30 mL) and saturated $Na_2S_2O_3$ (30 mL) to the mixture, the organic solvent was separated. The aqueous phase was extracted with Et_2O (20 mL) three times, and the combined organic solvent was washed with saturated $NaHCO_3$ (30 mL) and brine, dried, and evaporated to leave a residue. The residue was chromatographed to give **16a** (3.95 g, 63%) as white crystals: mp 68–70 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ −39.61 (*c* 1.15, $CHCl_3$); IR (KBr) 3420, 1749, 1325, 1238, 1205, 1162, 1103, 1042, 1015, 967 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.65 (1H, d, *J* = 18.1 Hz), 2.85 (1H, dd, *J* = 18.1, 5.5 Hz), 3.14 (1H, d, *J* = 5.0 Hz), 3.42 (2H, d, *J* = 7.7 Hz), 4.59–4.63 (1H, m), 4.65–4.69 (1H, m); ^{13}C-NMR (300 MHz, $CDCl_3$) δ −1.38, 39.61, 68.22, 83.89, 175.98. Anal. Calcd for $C_5H_7O_3I$: C, 24.81; H, 2.92. Found: C, 25.08; H, 2.90.

(3*S*,4*R*)-3-Hydroxy-4-(iodomethyl)-γ-butyrolactone (*ent*-16a). By means of a procedure analogous to that used for **16a**, (*S*)-**13** (6.06 g, 27.6 mmol) and I_2 (14.1 g, 55.4 mmol) in DME–H_2O (1:1) (110 mL) gave *ent*-**16a**[37] (4.32 g, 65%); $[\alpha]^{25}_D$ +39.15 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_5H_7O_3I$: C, 24.81; H, 2.92. Found: C, 24.79; H, 2.87.

(*R*)-*N*-Benzyl-*N*-methyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-pentenamide [(*R*)-14]. A mixture of (*R*)-**13** (1.51 g, 6.90 mmol), imidazole (1.17 g, 17.19 mmol), TBDMSCl (1.56 g, 10.32 mmol), and DMAP (168 mg, 1.38 mmol) in DMF (9.12 mL) was stirred for 12 h at rt. The insoluble material was filtered through Celite, and the filtrate was reduced in vacuo to leave an oil. The residue was chromatographed to give (*R*)-**14** (2.234 g, 97%) as an oil: $[\alpha]^{25}_D$ +6.45 (*c* 2.25, $CHCl_3$); IR (neat) 2928, 1646, 1401, 1253, 836, 779 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 and 0.90 (9H, s), 2.36–2.49 (1H, m), 2.68–2.76 (1H, m), 2.95 (3H, s), 4.34–4.40 (1H, m), 4.72–4.86 (2H, m), 5.03–5.10 (1H, m), 5.22–5.31 (1H, m), 5.81–5.98 (1H, m), 7.16–7.38 (5H, m). Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.35; H, 9.49; N, 4.29.

(*S*)-*N*-Benzyl-*N*-methyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-pentenamide [(S)-14]. By means of a procedure similar to that described for the preparation of (*R*)-**14**, a mixture of (*S*)-**13** (1.91 g, 8.69 mmol), imidazole (1.48 g, 21.68 mmol), TBDMSCl (1.96 g, 13.02 mmol), and DMAP (212 mg, 1.74 mmol) in DMF (11.5 mmol) gave (*S*)-**14**[37] (2.556 g, 88%) as an oil: $[\alpha]^{25}_D$ −6.36 (*c* 2.92, $CHCl_3$). Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.39; H, 9.48; N, 4.06.

(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(hydroxymethyl)-γ-butyrolactone [(3*R*,4*S*)-20a] and (3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(hydroxymethyl)-γ-butyrolactone [(3*R*,4*R*)-20b]. A mixture of (*R*)-**14** (2.184 g, 6.55 mmol) and *m*-CPBA (5.64 g, 26.2 mmol) in benzene (46 mL) was stirred for 24 h at 30 °C. After the addition of saturated Na_2CO_3 (20 mL) and 10% K_2CO_3 (20 mL), the organic solvent was separated. The aqueous layer was extracted with Et_2O (20 mL) three times, and the combined organic solvents were washed with 10% K_2CO_3 (20 mL) and brine (20 mL), dried, and evaporated. The residue was chromatographed to give (3*R*,4*S*)-**20a** (1.097 g, 68%) and (3*R*,4*R*)-**20b** (292 mg, 18%).

(3*R*,4*S*)-**20a**: mp 72–74 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ −36.69 (*c* 1.05, $CHCl_3$); IR (KBr) 3258, 2956, 1770, 1175, 1076, 1000, 933, 832, 785 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.09 (6H, s),

(34) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123.
(35) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531.
(36) The present procedure can be scaled up (to 20 g of **13**).
(37) Spectral data were identical to those of its enantiomer.

0.89 (9H, s), 1.83 (1H, br s), 2.47 (1H, dd, J = 17.6, 4.4 Hz), 2.86 (1H, dd, J = 17.8, 7.1 Hz), 3.73 (1H, dd, J = 11.7, 1.5 Hz), 3.93 (1H, dd, J = 12.2, 2.0 Hz), 4.34 (1H, sext), 4.52 (1H, sext); ^{13}C-NMR (300 MHz, $CDCl_3$) δ −4.72, −4.58, 18.08, 25.80, 39.15, 61.80, 69.16, 88.11, 175.72. Anal. Calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00. Found: C, 53.60; H, 8.88.

(3*R*,4*R*)-**20b**: mp 96−97 °C (hexane−CH_2Cl_2); $[\alpha]^{25}_D$ +8.62 (*c* 1.21, $CHCl_3$); IR (KBr) 3375, 2930, 1748, 1168, 1034, 946 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.89 (9H, s), 1.83 (1H, br s), 2.53 (1H, dd, J = 17.6, 3.4 Hz), 2.77 (1H, dd, J = 17.6, 6.4 Hz), 3.88 (1H, dd, J = 11.7, 1.5 Hz), 4.00 (1H, dd, J = 12.2, 2.0 Hz), 4.52 (1H, sext), 4.67 (1H, m). Anal. Calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00. Found: C, 53.67; H, 9.13.

(3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(hydroxymethyl)-γ-butyrolactone [*ent*-(3*R*,4*S*)-20a] and (3*S*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-(hydroxymethyl)-γ-butyrolactone [*ent*-(3*R*,4*R*)-20b]. By means a procedure analogous to that described for the preparation of (3*R*,4*S*)-**20a** and (3*R*,4*R*)-**20b**, a mixture of (*S*)-**13** (6.962 g, 20.85 mmol) and *m*-CPBA (18 g, 83.5 mmol) in benzene (165.3 mL) gave *ent*-(3*R*,4*S*)-**20a**[37] (3.763 g, 73%) and *ent*-(3*R*,4*R*)-**20b**[37] (865 mg, 17%).

[*ent*-(3*R*,4*S*)-**20a**] : $[\alpha]^{25}_D$ +37.33 (*c* 3.405, $CHCl_3$). Anal. Calcd for $C_{11}H_{22}O4Si$: C, 53.63; H, 9.00. Found: C, 53.67; H, 8.94.

[*ent*-(3*R*,4*R*)-**20b**]: $[\alpha]^{25}_D$ −8.73 (*c* 1.805, $CHCl_3$). Anal. Calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00. Found: C, 53.58; H, 8.74.

(3*R*,4*R*)-3-Hydroxy-4-methyl-γ-butyrolactone (11). A mixture of **16a** (518 mg, 2.14 mmol), Bu_3SnH (0.87 mL, 3.23 mmol), and AIBN (70.9 mg, 0.43 mmol in toluene (27.2 mL) was refluxed for 12 h. After evaporation of the solvent, CH_3CN (5 mL) was added to the residue. The mixture was washed with hexane (5 mL) three times and chromatographed to give **11** (181 mg, 73%) as an oil: bp 103−105 °C (3 mmHg); $[\alpha]^{25}_D$ +72.02 (*c* 2.915, EtOH), lit.[3a] $[\alpha]^{20}_D$ +73.2 (*c* 1.1, EtOH); IR (neat) 3433, 2938, 1772, 1173, 1058 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.41 (3H, d, J = 6.0 Hz), 2.54 (1H, d, J = 18.1 Hz), 2.79 (1H, dd, J = 17.6, 5.5 Hz), 3.12 (1H, br s), 4.40−4.45 (1H, m), 4.53−4.61 (1H, m); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 13.81, 39.53, 69.46, 81.51, 176.75; HRMS calcd for $C_5H_8O_3$ 116.0472, found 116.0437.

(3*S*,4*S*)-3-Hydroxy-4-methyl-γ-butyrolactone (*ent*-11). By means of a procedure analogous to that described for the preparation of **11**, a mixture of *ent*-**16a** (1.226 g, 5.06 mmol), Bu_3SnH (2.04 mL, 7.65 mmol), and AIBN (168 mg, 1.02 mmol) in toluene (30 mL) gave *ent*-**11**[37] (442 mg, 75%); $[\alpha]^{25}_D$ −75.22 (*c* 2.935, EtOH), lit.[38] $[\alpha]^{20}_D$ −73.7 (*c* 1.6, EtOH).

(3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-[(phenylthio)methyl]-γ-butyrolactone (22). Bu_3P (1.55 mL, 6.22 mmol) was added to a mixture of (3*R*,4*S*)-**20a** (1.018 g, 4.13 mmol), pyridine (4.13 mL), and PhSSPh (1.355 g, 6.22 mmol), and the reaction mixture was stirred for 3 h at rt. After the addition of H_2O (20 mL) and AcOEt (20 mL) to the mixture, the organic phase was separated. The organic solvent was washed with saturated citric acid (20 mL), dried, and evaporated to leave a residue, which was chromatographed to yield **22** (1.345 g, 96%) as an oil: $[\alpha]^{25}_D$ −14.24 (*c* 1.47, $CHCl_3$); IR (neat) 2929, 1786, 1164, 1087, 838 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 2.44 (1H, dd, J = 17.6, 3.3 Hz), 2.82 (1H, dd, J = 17.6, 6.0 Hz), 3.02 (1H, dd, J = 14.3, 7.1 Hz), 3.24 (1H, dd, J = 14.4, 4.9 Hz), 4.41−4.47 (2H, m), 7.22−7.41 (5H, m). Anal. Calcd for $C_{17}H_{26}O_3SSi$: C, 60.31; H, 7.74. Found: C, 60.44; H, 7.81.

(3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(iodomethyl)-γ-butyrolactone (24). A mixture of (3*R*,4*S*)-**20a** (1.916 g, 7.69 mmol), PPh_3 (3.1 g, 11.53 mmol), imidazole (784 mg, 11.53 mmol), and I_2 (2.924 g, 11.53 mmol) in Et_2O−CH_3CN (3:1) (27.5 mL) was stirred for 2 h at rt. After addition of H_2O (10 mL) and Et_2O (30 mL) to the mixture, the organic solvent was separated. The aqueous layer was extracted with Et_2O (20 mL) three times, and the combined organic extracts were dried and evaporated. The residue was chromatographed to yield **24** (2.211 g, 81%) as a solid: mp 34−35 °C (hexane); $[\alpha]^{25}_D$ −10.97 (*c* 3.14, $CHCl_3$); IR (KBr) 2929, 1792, 1160, 1088, 838, 779 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (6H, d, J = 7.1 Hz), 0.89 (9H, s), 2.48 (1H, dd, J = 18.1, 4.4 Hz), 2.87 (1H, dd, J = 18.1, 7.1 Hz), 3.27 (1H, dd, J = 11.0, 6.6 Hz), 3.34 (1H, dd, J = 11.0, 4.4 Hz), 4.26- 4.30 (1H, m), 4.37−4.42 (1H, m). Anal. Calcd for $C_{11}H_{21}O_3SiI$: C, 37.08; H, 5.94. Found: C, 37.02; H, 5.87.

(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-γ-butyrolactone (23). (a) A mixture of **22** (1.226 g, 3.62 mmol) and Raney-Ni (W-2) (20.4 mL) in EtOH (12.7 mL) was stirred for 15 min at rt. The insoluble material was filtered through Celite, and the filtrate was evaporated to leave the residue, which was chromatographed to yield **23** (436 mg, 52%) as a solid: mp 54−55 °C (hexane); $[\alpha]^{25}_D$ −36.66 (*c* 1.2, $CHCl_3$); IR (KBr) 2930, 1753, 1183, 1073, 1014, 935, 834 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.89 (9H, s, t-Bu), 1.35 (3H, d, J = 6.6 Hz), 2.45 (1H, dd, J = 17.6, 5.1 Hz), 2.77 (1H, dd, J = 17.6, 6.6 Hz), 4.11 (1H, sext), 4.38 (1H, sext). Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.36; H, 9.63. Found: C, 57.18; H, 9.60.

(b) A mixture of **24** (2.739 g, 7.68 mmol), Bu_3SnH (3.13 mL, 11.6 mmol), and AIBN (255 mg, 1.55 mmol) in toluene (98 mL) was refluxed for 12 h. After evaporation of the solvent, CH_3CN (30 mL) was added to the residue. The mixture was washed with hexane (20 mL) three times and evaporated. The residue was chromatographed to give **23** (1.348 g, 76%) as solid, whose spectral data were identical to those of a sample obtained by procedure a.

(3*R*,4*S*)-3-Hydroxy-4-methyl-γ-butyrolactone (12). A mixture of **23** (600 mg, 2.61 mmol) and PPTS (195 mg, 0.8 mmol) in EtOH (13 mL) was refluxed for 12 h. After evaporation, the residue was chromatographed to give **12** (269 mg, 89%) as an oil: bp 95−97 °C (0.25 mmHg); $[\alpha]^{25}_D$ −10.83 (*c* 1.21, $CHCl_3$), lit.[38] $[\alpha]^{25}_D$ −10.81 (*c* 1.85, $CHCl_3$); IR (neat) 3425, 2938, 1771, 1208, 1173, 1137, 1058, 994, 944 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.35 (1H, d, J = 6.6 Hz), 2.50 (1H, dd, J = 18.1, 3.8 Hz), 2.83 (1H, dd, J = 18.1, 6.6 Hz), 3.35 (1H, br s), 4.19−4.25 (1H, m), 4.50 (1H, dq, J = 2.7 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.65, 37.53, 72.92, 84.44, 175.83. Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.78; H, 6.98.

(3*S*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(iodomethyl)-γ-butyrolactone (*ent*-24). By means of a procedure analogous to that described for **24**, a mixture of (3*S*,4*R*)-**20a** (611 mg, 2.48 mmol), Ph_3P (1.005 g, 3.72 mmol), imidazole (253 mg, 3.72 mmol), and I_2 (944 mg, 3.72 mmol) in Et_2O-CH_3CN (1:1) (8.88 mL) gave *ent*-**24**[37] (689 mg, 78%); $[\alpha]^{25}_D$ +11.04 (*c* 2.795, $CHCl_3$).

(3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-γ-butyrolactone (*ent*-23). By means of procedure b described for **23**, a mixture of *ent*-**24** (212 mg, 0.595 mmol), Bu_3SnH (0.242 mL, 0.899 mmol), and AIBN (19.7 mg, 0.12 mmol) in toluene (7.56 mL) gave *ent*-**23**[37] (100 mg, 73.2%); $[\alpha]^{25}_D$ +36.23 (*c* 1.235, $CHCl_3$).

(3*S*,4*R*)-4-Hydroxy-5-methyl-γ-butyrolactone (*ent*-12). By means of a procedure analogous to that described for **12**, a mixture of *ent*-**23** (306 mg, 1.32 mmol) and PPTS (98.8 mg, 0.4 mmol) in EtOH (6.6 mL) gave *ent*-**12** (124 mg, 80%); $[\alpha]^{25}_D$ +10.91 (*c* 1.27, $CHCl_3$), lit.[31] $[\alpha]^{20}_D$ +10.87 (*c* 2.42, $CHCl_3$). Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.42; H, 6.73.

(2*R*,3*R*,4*S*)-2-Butyl-3-hydroxy-4-methyl-γ-butyrolactone [(−)-blastmycinolactol] (27). A solution of **12** (51 mg, 0.44 mmol) in THF (0.42 mL) was added to a solution of LDA, prepared from diisopropylamine (0.14 mL, 0.96 mmol) and BuLi (0.67 mL of 1.6 M solution in hexane, 1.07 mmol), in THF (1.39 mL) at −78 °C. After the reaction mixture stirred for 40 min, a solution of C_4H_9I (68 μL, 0.62 mmol) in HMPA (0.37 mL) and THF (0.37 mL) was added to the mixture at the same temperature. After the mixture stirred for 20 min, warmed to −40 °C and stirred for 5 h. 10% HCl (1.0 mL) and ethyl acetate (5 mL) were added to the mixture, and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (3 mL) three times, and the combined organic extracts were washed with brine, dried, and evaporated. The residue was chromatographed to yield **27** (30 mg, 68%) as a

(38) Ortuño, R. M.; Alonso, D.; Cardellach, J.; Font, J. *Tetrahedron* **1987**, *43*, 2191.

solid: mp 50–51 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ −15.32 (*c* 0.63, MeOH), lit.[27a] $[\alpha]^{25}_D$ −17.3 (*c* 1.29, MeOH); IR (KBr) 3475, 1740, 1188, 1059 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.45 (3H, d, *J* = 6.5 Hz), 1.25–1.90 (6H, m), 2.30 (1H, br s), 2.55 (1H, ddd, *J* = 8.5, 7.5, 6.0 Hz), 3.84 (1H, t, *J* = 8.0 Hz), 4.20 (1H, quintet, *J* = 6.5 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 13.83, 18.22, 22.62, 28.14, 28.84, 48.58, 79.03, 79.88, 176.06. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.58; H, 9.19.

(2*R*,3*R*,4*S*)-2-Hexyl-3-hydroxy-4-methyl-γ-butyrolactone [(−)-antimycinolactol, NFX-2] (2). By means of a procedure similar to that described for **27**, the reaction of the lithium enolate of **12** (103 mg, 0.89 mmol) in THF 0.84 mL) with a solution of $C_6H_{13}I$ (204 μL, 1.24 mmol) in HMPA (0.75 mL) and THF (0.75 mL) gave **2** (85 mg, 48%) as a solid: mp 63–64 °C (hexane–CH_2Cl_2), lit.[29] mp 57–58.5 °C; $[\alpha]^{25}_D$ −13.58 (*c* 1.23, MeOH), lit.[29] $[\alpha]^{21}_D$ −11.9 (*c* 0.986, MeOH); IR (KBr) 3471, 1732, 1061 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.9 Hz), 1.45 (3H, d, *J* = 6.5 Hz), 1.24–1.87 (10H, m), 2.59 (1H, ddd, *J* = 8.7, 7.5, 6.0 Hz), 3.33 (1H, br s), 3.83 (1H, t, *J* = 8.7 Hz), 4.21 (1H, quintet, *J* = 6.5 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.02, 18.23, 22.54, 26.68, 28.45, 29.18, 31.55, 48.61, 79.05, 79.87, 176.01. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.09; H, 10.28.

(2*R*,3*R*,4*S*)-3-Hydroxy-2-isoheptyl-4-methyl-γ-butyrolactone (NFX-4) (3). By means of the method described for **27**, the reaction of the lithium enolate of **12** (226 mg, 1.95 mmol) in THF (1.50 mL) with $(CH_3)_2CH(CH_2)_4I$ (662 mg, 2.93 mmol) in HMPA (1.56 mL, 8.97 mmol) and THF (3.12 mL) provided **3** (86 mg, 21 %) as a solid: mp 63–64 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ −12.12 (*c* 1.825, MeOH); IR (KBr) 3425, 1734, 1055 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (6H, d, *J* = 7.0 Hz), 1.47 (3H, d, *J* = 6.5 Hz), 1.18–1.88 (9H, m), 2.13 (1H, d, *J* = 5.5Hz, OH), 2.57 (1H, ddd, *J* = 8.5, 7.5, 5.5 Hz), 3.86 (1H, ddd, *J* = 8.5, 7.5, 5.5 Hz), 4.21 (1H, dq, *J* = 7.0, 6.5 Hz); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 18.43, 22.75, 22.79, 27.19, 27.48, 28.03, 28.69, 38.87, 48.82, 79.31, 79.97, 176.05. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.13; H, 10.35.

(2*R*,3*R*,4*R*)-3-Hydroxy-4-methyl-2-tetradecyl-γ-butyrolactone (28). A solution of **11** (131 mg, 1.14 mmol) in THF (2.18 mL) was added to a solution of LDA prepared from diisopropylamine (0.35 mL, 2.49 mmol) and BuLi (1.75 mL of a 1.6 M solution in hexane, 2.80 mmol) in THF (3.06 mL) at −78 °C. After the reaction mixture stirred for 40 min, a solution of $C_{14}H_{29}I$ (427 mg, 1.32 mmol) in HMPA (1.32 mL) and THF (2.60 mL) was added to the reaction mixture at the same temperature. After being stirred for 20 min, the reaction temperature was warmed to −35 °C and then stirred for 5 h. After addition of 10% HCl (2.8 mL) and ethyl acetate (10 mL), the organic phase was separated. The aqueous layer was extracted with ethyl acetate (5 mL) three times, and the combined organic solvents were washed with brine, dried, and evaporated. The residue was chromatographed to yield **28** (166 mg, 47%) as a solid: mp 67–68 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ +36.02 (*c* 0.65, CH_2Cl_2), lit.[30] $[\alpha]^{20}_D$ −43.2 (*c* 1.2, CH_2Cl_2) for *ent*-**28**; IR (KBr) 3530, 2918, 2850, 1760, 1736, 1048 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.0 Hz), 1.40 (3H, d, *J* = 7.0 Hz), 1.25–1.75 (26H, m), 2.10 (1H, br s), 2.52–2.53 (1H, m), 4.19–4.20 (1H, m), 4.60–4.65 (1H, m); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 14.06, 14.30, 22.86, 27.44, 28.61, 29.54, 29.56, 29.73, 29.79, 29.83, 29,85, 29.86, 32.10, 49.45, 74.24, 78.46, 177.99. Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.14; H, 11.81.

(2*R*,3*R*,4*R*)-2-Hexadecyl-3-hydroxy-4-methyl-γ-butyrolactone (29). By means of a procedure analogous to that described for **28**, the reaction of the lithium enolate of **11** (114 mg, 0.99 mmol) in THF (2.66 mL) using LDA prepared from diisopropylamine (0.304 mL, 2.17 mmol) and BuLi (1.52 mL of a 1.6 M solution in hexane, 2.43 mmol), with $C_{16}H_{33}I$ (414 mg, 1.14 mmol) in HMPA (1.14 mL, 8.97 mmol) and THF (2.28 mL), provided **29** (90 mg, 27%) as a solid: mp 76–77 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ +35.90 (*c* 1.355, dioxane), lit.[30] $[\alpha]^{25}_D$ −38.0 (*c* 1.42, dioxane) for *ent*-**29**; IR (KBr) 3531, 2918, 2850, 1762, 1736, 1050 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.6 Hz), 1.40 (3H, d, *J* = 6.6 Hz), 1.25–1.77 (30H, m), 2.02 (1H, br s), 2.50–2.56 (1H, m), 4.20 (1H, s), 4.59–4.67 (1H, m); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.07, 14.31, 22.87, 27.45, 28.64, 29.55, 29.58, 29.73, 29.81, 29.84, 29,88, 29.99, 32.11, 49.44, 74.29, 78.37, 177.82. Anal. Calcd for $C_{21}H_{40}O_3$: C, 74.06; H, 11.84. Found: C, 73.64; H, 11.69.

(2*R*,3*R*,4*R*)-3-Acetoxy-4-methyl-2-tetradecyl-γ-butyrolactone (8). Acetic anhydride (244 μL, 2.55 mmol) was added to a solution of **28** (61 mg, 0.196 mmol) and DMAP (5 mg, 0.04 mmol) in pyridine (2.94 mL). After the reaction mixture stirred for 12 h at rt, H_2O (3 mL) was added to the mixture. The organic solvent was separated, and the aqueous layer was extracted with ethyl acetate (5 mL) three times. The combined organic solvents were washed with brine, dried, and evaporated. The residue was chromatographed to yield **8** (51 mg, 74%) as a solid: mp 31.5–32.5 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ +36.70 (*c* 1.79, CH_2Cl_2), lit.[12] $[\alpha]^{20}_D$ +36.1 (*c* 1.9, CH_2Cl_2); IR (KBr) 2918, 2849, 1773, 1745, 1474, 1463, 1376, 1232, 1202, 1044 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.9 Hz), 1.34 (3H, d, *J* = 6.6 Hz), 1.22–1.72 (26H, m), 2.12 (3H, s), 2.60 (1H, m), 4.77 (1H, dq, *J* = 6.6, 4.8 Hz), 5.17 (1H, dd, *J* = 5.1, 2.7 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.29, 14.36, 20.87, 22.86, 27.18, 28.69, 29.45, 29.53, 29.70, 29.77, 29.81, 32.09, 47.28, 75.70, 77.30, 176.78. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.13; H, 10.46.

(2*R*,3*R*,4*R*)-3-Acetoxy-2-hexadecyl-4-methyl-γ-butyrolactone (9). By means of a procedure similar to that described for **8**, a mixture of **29** (31 mg, 0.09 mmol), Ac_2O (89.9 μL, 0.94 mmol), DMAP (9.7 mg, 0.08 mmol), and pyridine (1.08 mL) gave **9** (30 mg, 86%) as a solid: mp 43–44 °C (hexane–CH_2Cl_2); $[\alpha]^{25}_D$ +32.30° (*c* 1.75, CH_2Cl_2), lit.[12] $[\alpha]^{20}_D$ +31.9 (*c* 1.3, CH_2Cl_2); IR (KBr) 2918, 2849, 1773, 1745, 1474, 1464, 1377, 1236, 1198, 1051 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.6 Hz), 1.33 (3H, d, *J* = 6.6 Hz), 1.25–1.81 (30H, m), 2.11 (3H, s), 2.60 (1H, m), 4.76 (1H, dq, *J* = 6.6, 4.9 Hz), 5.16 (1H, dd, *J* = 4.9, 2.7 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.31, 14.37, 20.88, 22.87, 27.20, 28.70, 29.46, 29.49, 29.55, 29.72, 29.79, 29.84, 29.88, 32.11, 47.29, 75.71, 77.63, 170.30, 176.80. Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.20; H, 11.07. Found: C, 72.02; H, 10.96.

(3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-γ-butyrolactone (31). TBDMSOTf (2.07 mL, 9.08 mmol) and 2,6-lutidine (2.11 mL, 18.85 mmol) were successively added to a solution of *ent*-**11** (1.003 g, 8.64 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After being warmed to rt, the reaction mixture was stirred for 40 h. After addition of MeOH , the solvent was evaporated. The residue was chromatographed to yield **31** (1.029 g, 52%) as a solid: mp 75–76 °C (hexane); $[\alpha]^{25}_D$ −16.30 (*c* 1.3, $CHCl_3$); IR (KBr) 1758, 1169, 1067, 1029, 837 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 1.36 (3H, d, *J* = 6.6 Hz), 2.45 (1H, dd, *J* = 17.6, 1.6 Hz), 2.73 (1H, dd, *J* = 17.0, 5.5 Hz), 4.36–4.40 (1H, m), 4.50–4.58 (1H, m). Anal. Calcd for $C_{11}H_{22}O_3Si$; C, 57.36; H, 9.63. Found: C, 57.09; H, 9.53.

(2*S*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-octanol (33). DIBAL-H (1.41 mL of a 0.93 M solution in hexane, 1.32 mmol) was added to a solution of **31** (303 mg, 1.32 mmol) in Et_2O (5 mL) at −78 °C. After the mixture stirred for 30 min, MeOH (0.5 mL) was added. The reaction mixture was warmed to rt and 30% sodium potassium tartarate (3 mL) was added. The organic layer was separated, and the aqueous layer was extracted CH_2Cl_2 (3 mL) three times. The combined organic solvents were washed with 30% sodium potassium tartarate, dried, and evaporated. The residue was chromatographed to yield **32** (304 mg, 99%) as an oil. Compound **32** was used without further purification in the next step. BuLi (0.574 mL of a 1.6 M solution in hexane, 0.918 mmol) was added to a suspension of $PPh_3{}^+CH_2CH_2CH_3Br^-$ (420 mg, 1.09 mmol) in THF (2.7 mL) at 0 °C. After the mixture stirred for 30 min, **32** (115 mg, 0.495 mmol) in THF (1 mL) was added at −78 °C. The mixture was warmed to 0°C and stirred for 3 h. After the addition of saturated NH_4Cl, the organic layer was separated. The aqueous layer was extracted with Et_2O (5 mL) three times, and the combined organic solvents were washed with brine, dried, and evaporated. The residue was chromatographed to give a mixture of (*E*)- and (*Z*)-(2*S*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-5-octen-2-ol (62 mg, 47%). A suspension of the oil thus prepared (62 mg, 0.24 mmol) and $Pd(OH)_2$

(6 mg) in EtOH (1 mL) was stirred under hydrogen atmosphere for 12 h. The insoluble material was filtered through celite and the filtrate was evaporated to yield **33** (48 mg, 77%) as an oil: bp 90–93 °C (5 mmHg); $[\alpha]^{25}_D$ +4.77 (*c* 1.36, $CHCl_3$); IR (neat) 3854, 3650, 2932, 1458, 1255, 1075, 836, 776 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.14 (3H, d, J = 6.0 Hz), 1.19–1.52 (11H, m), 2.37 (1H, d, J = 4.9 Hz), 3.26–3.29 (1H, m), 3.60–3.64 (1H, m); ^{13}C-NMR (300 MHz, $CDCl_3$) −4.446, −3.975, 14.205, 18.303, 19.851, 22.780. 24.616, 26.073, 32.340, 33.828, 69.142; HRMS calcd for $C_{10}H_{23}O_2Si$ (M^+ − t-Bu) 203.1466, found 203.1424.

(2S,3S)-2,3-Octanediol (30). A solution of **33** (48 mg, 0.184 mmol) and 36% HCl (43.4 mg) in EtOH (0.5 mL) was stirred for 1.5 h. After evaporation of the solvent, saturated $NaHCO_3$ (2.3 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 mL) three times. The combined extracts were washed with brine, dried, and evaporated. The residue was chromatographed to yield **30** (26 mg, 97%) as an oil: bp 95–97 °C (8 mmHg); $[\alpha]^{25}_D$ −19.23 (*c* 1.06, $CHCl_3$), lit.[32] $[\alpha]^{23}_D$ −19.2 (*c* 0.48, $CHCl_3$); IR (neat) 3385, 2932, 2860, 1458, 1066 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 6.6 Hz), 1.19 (3H, d, J = 6.6 Hz), 1.25–1.62 (8H, m), 2.07–2.13 (2H, br), 3.34–3.36 (1H, m), 3.57–3.61 (1H, m); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.22, 19.71, 22.78, 25.42, 32.04, 33.54, 71.10, 76.44; HRMS calcd for $C_8H_{18}O_2$ (M^+ − H) 145.1227, found 145.1196.

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Supplementary Material Available: Various ^{1}H and ^{13}C NMR spectra (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.