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Total Synthesis of Nonactin

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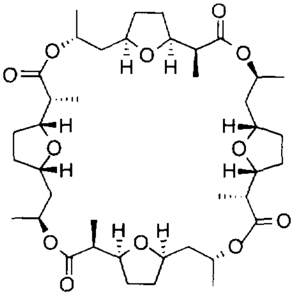
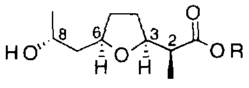
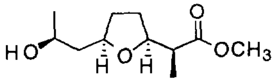
Abstract: Utilizing the efficient preparation of (+)-nonactic acid(**2a**) and (−)-methyl 8-*epi*-nonactate (**4b**) starting from optically active 2-isoxazolines **5a** and **5b**, respectively, the total synthesis of nonactin has been accomplished. Based on the high dilution version of the Yamaguchi's method, the final macrolactonization has been completed in high yield.

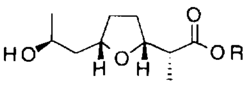
Nonactin(**1**) is the lowest homologue and most symmetrical member of the family of macrotetrolide antibiotics, which have been isolated from a variety of *Streptomyces* cultures.[1] The special feature of nonactin, and presumably others, which lend them chemical interest and potential biological importance is their ability to bind alkali metal cations, particularly potassium.[2] The antibiotic activity of nonactin can be traced to its ionophoric properties. Its constitution and configuration were first deduced by degradation and spectroscopic methods,[1b,3] and later substantiated by X-ray crystallography.[1e]

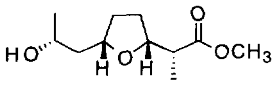

Nonactin(1)



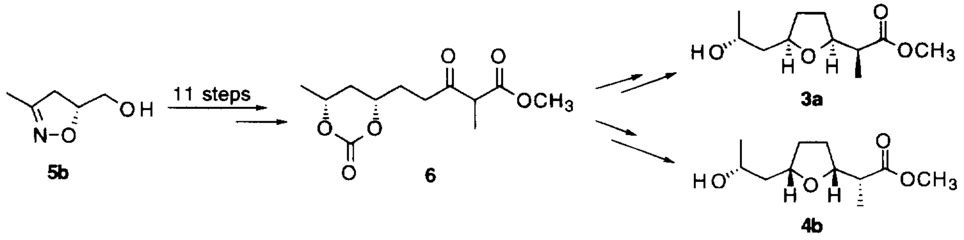
2a: R=H
3a: R=CH3


4a


2b: R=H
3b: R=CH3

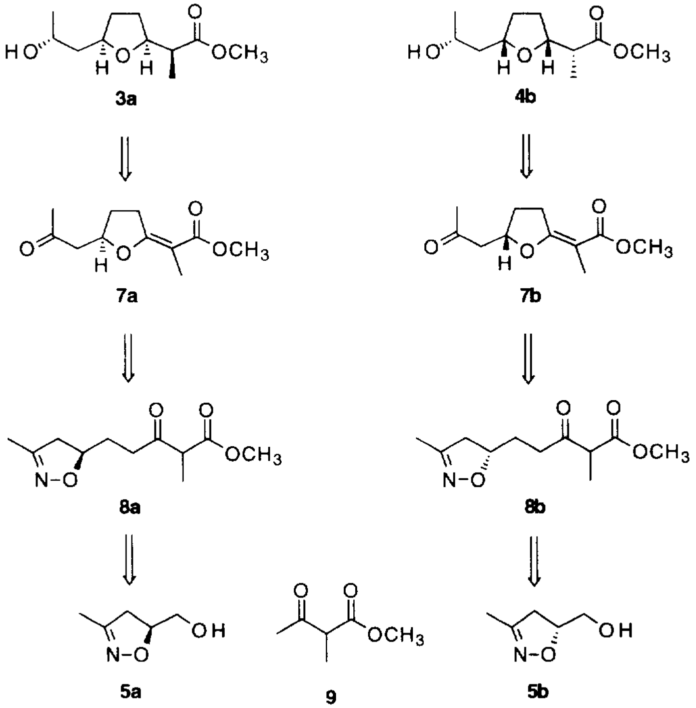

4b

Nonactin consists of two subunits of (+)-nonactic acid(**2a**) and two subunits of (−)-nonactic acid(**2b**), arranged in an alternating order. Constitution of nonactin thus requires an efficient synthesis of the two subunits, (+)-nonactic acid and (−)-nonactic acid. Many syntheses of nonactic acid(or its methyl ester) in both optically active and racemic form have been reported in recent years with varying success with respect to the stereoselectivity.[4] However, fewer syntheses of nonactin itself have been described and the overall yield from the nonactic acid esters was low in those syntheses.[5] Very recently, Fleming and Ghosh[6] reported an efficient total synthesis of nonactin employing an effective macrocyclization strategy.



Scheme 1

On the basis of Bartlett's previous work,[4n] we recently have reported the syntheses of (+)-methyl nonactate(**3a**) and (−)-methyl 8-*epi*-nonactate(**4b**)(Scheme 1).[4z] In those syntheses we have utilized the β-keto ester **6** as a common intermediate for **3a** and **4b**. In the molecular structure of β-keto ester **6**, there are β-keto ester moiety and 1,3-*syn*-dihydroxy moiety which can be used to introduce the C-2, C-3, C-6, and C-8 stereochemistry of the subunits by simple transformation. For the preparation of this molecule, we have taken advantage of versatility of 2-isoxazoline ring into β-hydroxy carbonyl group. Although those syntheses were efficient with respect to the stereoselectivity, it was required to reduce reaction steps for the



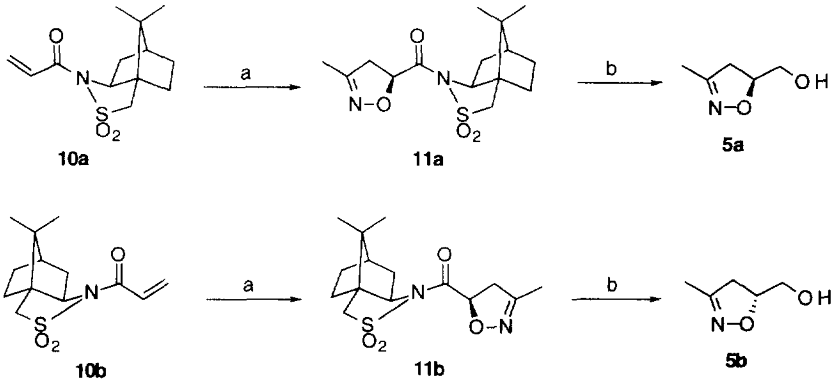
Scheme 2

more concise synthesis of nonactin. In an attempt to solve this problem we designed an alternative route as shown in Scheme 2. The compounds **8a** and **8b** which have similar structures with **6** were devised as key intermediates and prepared at the early stage. **8a** would be converted to the conjugated enol ether **7a** through the Curran's Ra-Ni-catalyzed reduction[7] and lactol formation followed by dehydration. The stereoselective reduction of **7a** followed by Rh-catalyzed hydrogenation would provide the desired (+)-methyl 8-*epi*-nonactate(**4a**). As the 2-isoxazoline ring of starting material is a protected form of *β*-hydroxy carbonyl group, no protecting group should be necessary for the synthesis of **8a**. **8a** would be prepared from optically active 2-isoxazoline **5a** and racemic methyl 2-methylacetoacetate(**9**) in only two steps; 1) replacement of hydroxy group of **5a** into a good leaving group and 2) dianion coupling reaction. This route would be also applicable to the synthesis of (−)-methyl 8-*epi*-nonactate(**4b**).

We now report a total synthesis of nonactin, which is based on the highly concise synthesis of (+)-nonactic acid and (−)-methyl 8-*epi*-nonactate using the retrosynthetic analysis in Scheme 2 and the efficient macrocyclization method.

RESULTS AND DISCUSSION

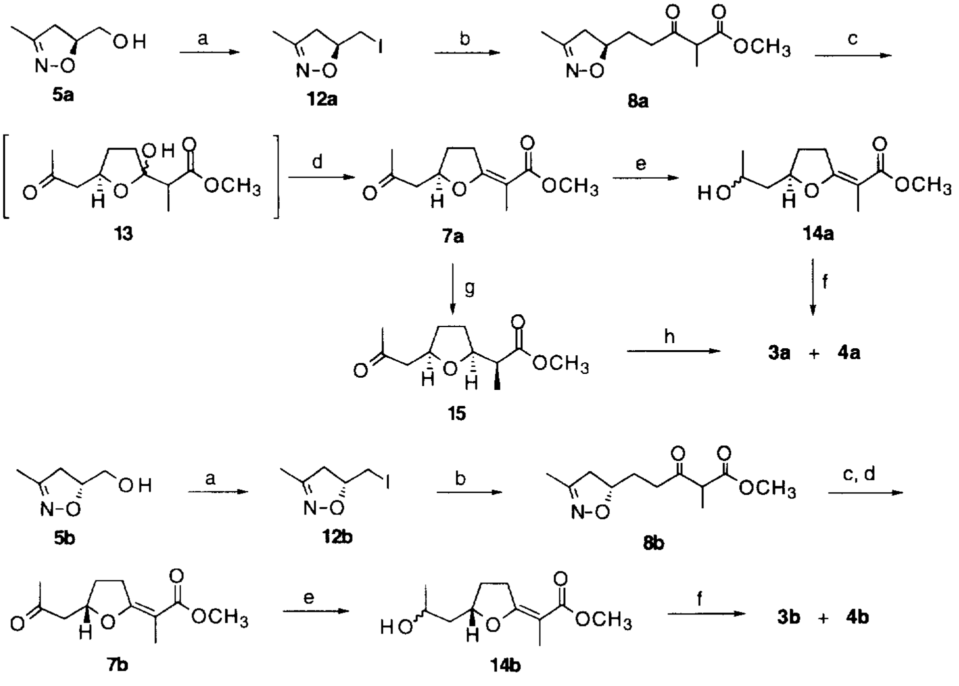
Preparation of 2-isoxazolines 5a and 5b. Optically active 2-isoxazolines **5a** and **5b** were prepared by using asymmetric silyl nitronate cycloaddition methodology[8](Scheme 3). The cycloaddition of *N*-acryloyl (2*S*)-bornane-10,2- sultam(**10a**)[9] with in situ-generated silyl nitronate from nitroethane, trimethyl silyl chloride, and triethylamine provided a mixture of *N*-trimethylsilyl isoxazolidines. Treatment of this mixture with a catalytic amount of *p*-toluenesulfonic acid afforded a 89:11 mixture of 2-isoxazoline diastereomers. Chromatographic separation of the major isomer **11a** followed by reductive cleavage with L-selectride gave the (+)-2-isoxazoline **5a**. The (−)-2-isoxazoline **5b** was also synthesized via a similar procedure using the antipodal sultam **10b**.



Reagents and conditions : (a) (1) Nitroethane, TMS Cl, Et_3N, toluene. (2) *p*-TsOH, Et_2O, **11a**(76%), **11b**(72%). (b) L-selectride, THF, **5a**(91%), **5b**(86%).

Scheme 3

*Syntheses of (+)-methyl 8-epi-nonactate(**4a**) and (−)-methyl 8-epi-nonactate(**4b**).* With both enantiomer of 2-isoxazoline, **5a** and **5b** in hand, we transformed **5a** to the iodide **12a** in 95% yield for the next dianion displacement(Scheme 4). Dianion coupling reaction[10] of **12a** with the dianion derived from methyl 2-methylacetoacetate(1.5 equiv)[NaH(1.65 equiv), n-buthyllithium(1.65 equiv), CuI(0.3 equiv.), 10% HMPA/THF, 0°C] afforded **8a** in 31% yield as an inseparable 1:1 mixture of diastereomers. When excess of the reagents(2 times than the previous) was used in the generation of dianion, yield was increased to 66%. However, **8a** was contaminated by copper species after chromagraphic separation. Thus we tried to carry out the reaction without CuI and pure **8a** was obtained in 55% yield. In this run, we observed that **12a** was all consumed in the reaction and therefore we thought the reason of low yield might be the unwanted metal-halogen exchange of **12a**. When n-butyllithium was reduced to 2.0 equiv, the yield of **8a** was improved to 81%. It also remained invariant when 2 equiv of methyl 2-methylacetoacetate, 2.2 equiv of NaH, and 1.5 equiv of n-butyllithium were used.



Reagents and conditions: (a) I_2, PPh_3, imidazole, Et_2O/CH_3CN(3/1), 95%(**12a**), 90%(**12b**). (b) Methyl 2-methylacetoacetate, NaH, n-BuLi, 10% HMPA/THF, 0°C, 81%(**8a**), 81%(**8b**). (c) Ra-Ni, H_2, $B(OH)_3$, $MeOH/H_2O$(7/1). (d) oxalic acid, CH_2Cl_2 reflux, 77% overall(**7a**), 74% overall(**7b**). (e) L-selectride, THF, -78°C, 95%(**14a**), 97%(**14b**). (f) 5% Rh/Al_2O_3, H_2, MeOH, 15%(**3a**)+62%(**4a**), 11%(**3b**)+68%(**4b**). (g) (1) 5% Rh/Al_2O_3, H_2, MeOH. (2) PCC, CH_2Cl_2, 64% overall(**15**). (h) L-selectride, THF, -78°C, 75%(**4a**).

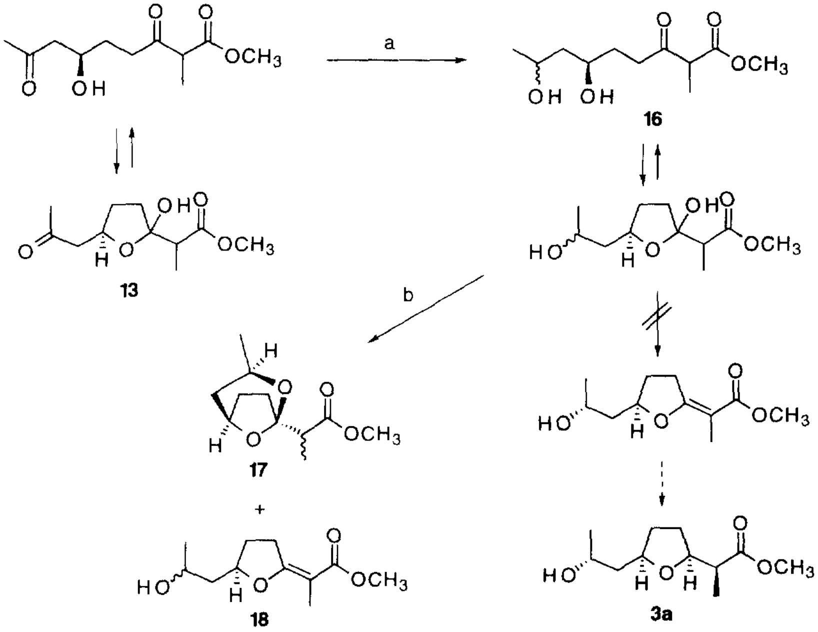
Scheme 4

Without separation of diastereomers, **8a** was subjected to the Curran's method[7] to give the lactol **13**, which was treated with oxalic acid to provide the cyclized product **7a** as a single geometric isomer in 77%

overall yield. The olefinic geometry was assigned as *E* on the basis of ample precedents.[4k,4n,11] And it would be confirmed by the subsequent conversion of **7a** to (+)-methyl 8-*epi*-nonactate(**4a**), for which high field NMR data on both natural and unnatural diastereomers has been reported.[4n] Reduction of **7a** with L-selectride gave **14a** as a 87:13 mixture of diastereomers, which were unseparable by column chromatography. Many conditions were investigated to raise the selectivity of reduction of **7a**(see below).

Stereoselective hydrogenation[4i,4n] of **14a** over 5% Rh/Al_2O_3 provided a mixture of (+)-methyl 8-*epi*-nonactate(**4a**) and (+)-methyl nonactate(**3a**) which could be separated by column chromatography. We also obtained (+)-methyl 8-*epi*-nonactate(**4a**) via another route. Rh-catalyzed hydrogenation followed by PCC oxidation gave **15** in 64% overall yield. Reduction of **15**[4r] with L-selectride provided (+)-methyl 8-*epi*-nonactate(**4a**) after separation by column chromatography.

(–)-Methyl 8-*epi*-nonactate(**4b**) was synthesized in a similar fashion to the synthesis of (+)-methyl 8-*epi*-nonactate(**4a**) starting with (–)-2-isoxazoline(**5b**) instead of (+)-**5a**. Iodination of **5b** followed by reaction with the dianion derived from methyl 2-methylacetoacetate afforded **8b**. The reductive cleavage of 2-isoxazoline ring in **8b** and oxalic acid-catalyzed dehydration gave the cyclic product **7b**. L-Selectride reduction of **7b** followed by Rh-catalyzed hydrogenation and separation by column chromatography afforded (–)-methyl 8-*epi*-nonactate(**4b**) along with (–)-methyl nonactate(**3b**). The spectroscopic data and the specific optical rotations of **4a** and **4b** were identical with those reported.[4n]



Reagents and conditions : (a) $Me_4NBH(OAc)_3$, CH_3CN/CH_3CO_2H, -40°C. (b) oxalic acid, CH_2Cl_2 reflux, 57%(**17**)+9%(**18**).

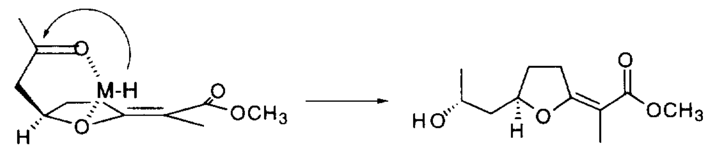
Scheme 5

Attempted preparation of methyl 8-epi-nonactate and methyl nonactate via stereoselective reduction. It would be possible to synthesize selectively methy 8-*epi*-nonactate and methyl nonactate by reducing **13**, **7a**, and **15** in diastereoselective fashion. We expected that this selective reduction might reduce the reaction steps by removing additional conversion of the C-8 center of methyl 8-*epi*-nonactate for the assembly to nonactin.

In the first case(Scheme 5), the lactol **13** which was in equilibrium with open form was reduced to the corresponding 1,3-diol **16** by Evans' reagent,[12] tetramethylammonium triacetoxyborohydride. Evans' reagent was known to reduce the β-hydroxy ketones selectively into the *anti*-1,3-diols and we expected that methyl nonactate would be provided by subsequent transformations. In addition, Bartlett[4n] reported that in the case where the stereochemistry of the 1,3-diol **16** was *syn*, oxalic acid-catalyzed dehydration resulted in the formation of the monocyclic compound in high yield. However, oxalic acid-catalyzed dehydration of the resulting 1,3-diol **16** gave the bicyclic ketal **17** , identified by ^{1}H- and ^{13}C-NMR, in 57% yield along with the monocyclic compound **18**(9%). Recently, Solladié and Dominguez[4bb] reported that the 1,3-*anti*-diol which has the same structure with **16** except *p*-tolylsulfinyl group at C-9 cyclized spontaneously into the bicyclic ketal under reduction conditions. Although we used other acids such as BF$_3$·Et$_2$O, PPTS, the same products were obtained.

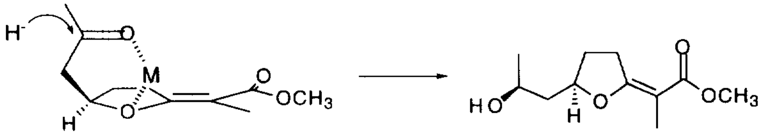
In the second case(Scheme 6), we have extensively studied the reduction of **7a**(Table 1). Reduction of **7a** with Dibal[13] which was able to chelated by the furanyl oxygen was expected to give the natural(8*R*) isomer selectively via intramolecular hydride transfer(Method A). However **7a** was reduced by Dibal and afforded the **8*S*-14a** and **8*R*-14a** in the ratio of 57:43, determined by capilliary GC. The ratio was slightly increased to 71:29(**8*S*-14a**:**8*R*-14a**) with the addition of TiCl$_4$ complexing reagent. In the case of LAH-LiI,[14] which was known to reduce the acyclic β-alkoxy ketones into the *syn* -1,3-diols with high diastereoselectivity, the reduction ratio was also very poor(**8*S*-14a**:**8*R*-14a**=52:48). A moderate selectivity(**8*S*-14a**:**8*R*-14a**=87:13) was obtained in the case of L-selectride. In order to increase the

Method A:



8*R*-14a

Method B:



8*S*-14a

Scheme 6

Table 1. Stereoselective reduction of **7a**

Entry	Reducing agent	Additive	Solvent	**8*S*-14a**:**8*R*-14a**[b]	Yield(%)[c]
1	DIBAL	-	THF	57:43	98
2	DIBAL	$ZnCl_2$	THF	65:35	93
3	DIBAL	$TiCl_4$	CH_2Cl_2	71:29	94
4	$LiAlH_4$	LiI	THF	52:48	100
5	$LiBH_4$	LiI	THF	60:40	94
6	L-selectride	-	THF	87:13	97
7	L-selectride	LiI	THF	89:11	100
8	L-selectride	$ZnCl_2$	THF	88:12	100
9	L-selectride	Et_2AlCl	Et_2O	87:13	85
10	L-selectride	-	CH_2Cl_2	90:10	100
11	L-selectride	$TiCl_2$	CH_2Cl_2	88:12	87
12	L-selectride	$Ti(OPr^i)_4$	CH_2Cl_2	88:12	94
13	L-selectride	$SnCl_4$	CH_2Cl_2	84:16	87
14	KS-selectride	-	CH_2Cl_2	87:13	74
15	LS-selectride	-	THF	92:8	83
16	LS-selectride	-	CH_2Cl_2	90:10	74

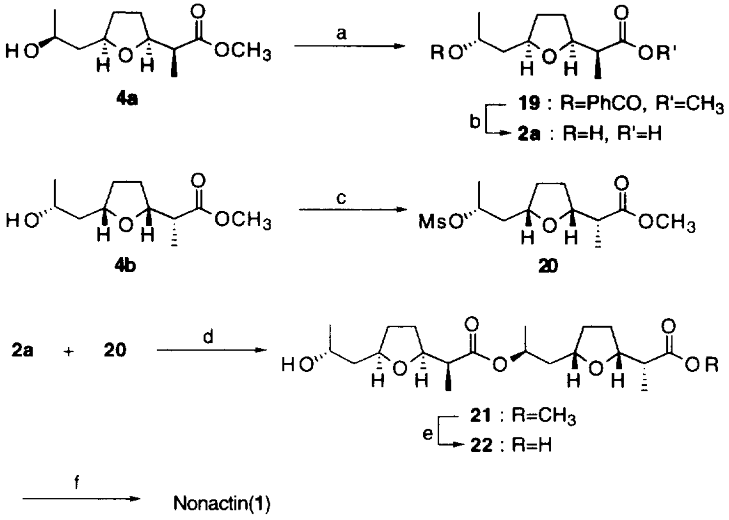
(a) Reductions were carried out at -78°C. (b) Determined by capilliary GC. (c) Combined, isolated yield of a diastereomeric mixture.

selectivity, the effect of additives such as LiI, $ZnCl_2$, $TiCl_4$, $Ti(OPr^i)_4$, $SnCl_4$ was examined(Method B). We could not observe significant complexation effect. LS-Selectride which was more bulky than L-selectride was found to be most effective(**8*S*-14a**:**8*R*-14a**=92:8) in terms of stereoselectivity.

In the last case, we examined the reduction of **15**. Vogel[4r] reported that reduction of the racemic **15** with L-selectride afforded a 1:10 mixture of methyl nonactate and its 8-epimer. Although Evans' reagent[12] and catecholborane[15] were employed to obtain methyl nonactate selectively, they gave no selectivity. In summary, we could not prepare methyl nonactate and its 8-epimer selectively by means of stereoselective reduction but only methyl 8-*epi*-nonactate was obtained as major isomer.

Assembly to nonactin. With (+)-methyl 8-*epi*-nonactate(**4a**) and its enantiomer **4b** in hand, we investigated methods for linking them to produce nonactin. To date, two methods were reported. One, described by Gerlach[5a] and Schmidt,[5b] was to assemble each nonactic acid esters into a linear tetramer and macrolactonize it to afford nonactin. The other was used by Bartlett[5c] and a linear dimer was cyclodimerized to give nonactin.

We first employed the simpler latter method and attempted to improve the yield of macrocyclization by taking advantage of an external template[16](Scheme 7). Mitsunobu esterification[17] of **4a** with benzoic acid followed by hydrolysis of **19** with 2N NaOH in MeOH furnished (+)-nonactic acid(**2a**). **4b** was mesylated to give the mesylate **20**. Displacement reaction between **20** and the potassium salt of **2a** formed in situ with KH in DMF(78%) followed by selective cleavage of the methyl ester in **21** with lithium n-propyl mercaptide



Reagents and conditions : (a) $PhCO_2H$, DEAD, PPh_3, THF, 91%. (b) 2N NaOH, MeOH, 100%. (c) MsCl, Et_3N, DMAP, CH_2Cl_2, 0°C, 97%. (d) KH, DMF, 60-70°C, 78%. (e) $LiSPr^n$, HMPA, 91%. (f) (1) $(PhO)_2POCl$, Et_3N, THF, 0°C. (2) DMAP, $KClO_4$, C_6H_6 reflux, 14%(crude).

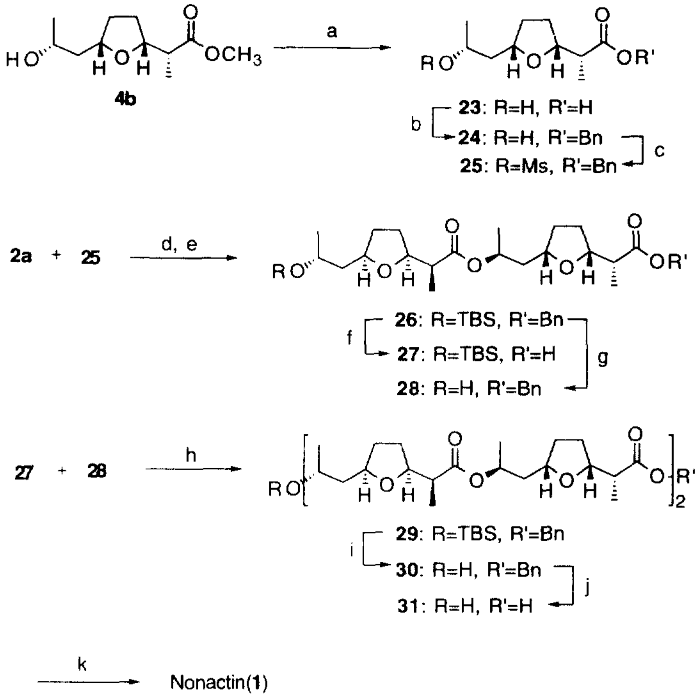
Scheme 7

afforded the hydroxy acid **22**. As reported by Bartlett,[4n] we cyclized **22** using the Masamune's macrolactonization method[18] in the presence of potassium perchlorate as an external template(nonactin chelates potassium ion well). However the inclusion of potassium perchlorate had no effect on the yield of macrolactonization and crude nonactin was obtained in 14% yield. Keck's method[19] was also not successful.

Therefore we turned our attention to the former method, macrolactonization of the linear tetramer(Scheme 8). Bartlett[4n] reported that cleavage of the methyl ester in **21** with lithium n-propyl mercaptide resulted in epimerization(up to 25%), presumably at one or both of the C-2 positions. Thus we transformed the methyl ester **4b** into the benzyl ester **24** which would be easily cleaved by catalytic hydrogenation. Hydrolysis of **4b** with 2N NaOH followed by the alkylation of **23** with benzyl bromide provided (−)-benzyl 8-*epi*-nonactate(**24**) in 95% overall yield. Mesylation of **24** followed by displacement of the mesylate **25** with the potassium salt of (+)-nonactic acid(**2a**) produced a mixture of diastereomers which were unseparable by column chromatography. *tert*-Butyldimethylsilyl ether formation in the presence of DMAP(98%) and separation by column chromatography furnished the pure dimer **26**. Without DMAP, silyl ether formation was carried out at room temperature in 42% yield and at 50-60°C in 96% yield, but under the latter conditions epimerization was observed.

Hydrogenolysis of the benzyl ester over 10% Pd/C from half of **26** gave the acid **27**, and removing the silyl protecting group with HF from the other half gave the alcohol **28**. We coupled these two compounds using Yamaguchi's mixed anhydride method[20] to give the linear tetramer **29** in 87% yield.

To complete the total synthesis of nonactin, we removed two protecting groups, *tert*-butyldimethylsilyl



Reagents and conditions : (a) 2N NaOH, 100%. (b) KOBu^t, BnBr, DMF, 60°C, 95%. (c) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C, 96%. (d) KOBu^t, DMF, 60-70°C. (e) TBSCl, imidazole, DMAP, DMF, 43% overall. (f) 5% Pd/C, H$_2$, THF, 98%. (g) 40% HF/CH$_3$CN(5/95), 96%. (h) (1) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF. (2) DMAP, C$_6$H$_6$, RT, 87%. (i) 40% HF/CH$_3$CN(5/95), 97%. (j) 5% Pd/C, H$_2$, THF, 99%. (k) (1) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF. (2) DMAP, C$_6$H$_6$ reflux, 54%.

Scheme 8

group, benzyl group, using the same methods applied to **26**, to produce the hydroxy acid **31**. Gerlach[5a] and Schmidt[5b] reported that macrolactonization of the racemic and optically active **31** using Corey-Nicolaou's method[21] afforded nonactin in 10% and 20% yield, respectively. Since the yields of both reports were low, we surveyed other methods. In 1991, Martin[22] reported that Yamaguchi's macrolactonization method[19] was very effective for the syntheses of Erythromycin antibiotics. Thus we employed the Yamaguchi method with high dilution version(1.5×10^{-3}M) and nonactin(**1**) was prepared in 54% yield after recrystallization. The ^{1}H NMR spectrum of **1** was identical with the ^{1}H NMR spectrum of nonactin kindly provided by Professor P. A. Bartlett. And other analytical data were identical in every respect with those reported.[5,23]

In conclusion, we have accomplished the total synthesis of nonactin by a route that is highly efficient. The syntheses of nonactin subunits represents one of the most effective syntheses so far explored. In addition Yamaguchi's macrolactonization method was successfully modified and nonactin was synthesized in high yield.

EXPERIMENTAL SECTION

Reactions were carried out under an argon atmosphere, except where otherwise noted. Solvents were dried by distillation shortly before use from an appropriate drying agent. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without futher purification. Analytical thin-layer chromatography(TLC) was carried out with E. Merck precoated silica gel plates(silica gel 60 F-254, layer thickness 0.25mm). Flash chromatography was carried out with E. Merck silica gel 60(230-400 mesh ASTM). Gas chromatography(GC) was performed with HP 5890 Series II(Hewllet Packard HP-1 column). Melting points were measured on a Haake Buchler apparatus and were uncorrected. Optical rotations were measured on a Jasco DIP-360 polarimeter or a Rudolph Research Autopol III digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform with a Bruker 300 MHz FT-NMR spectrometer; chemical shifts were reported in δ values relative to tetramethylsilane. Infrared spectra were recorded on a Bomem model FT-IR M100-C15 spectrophotometer. Mass spectra(MS) were obtained with a Kratos MS-25 RFA spectrometer at an ionization potential of 70eV. High-resolution mass spectra(HRMS) were obtained with a Jeol JMS-AX505WA spectrometer.

(*2R* , *5R*)-*N*-[(4,5-dihydro-3-methyl-5-isoxazolyl)carbonyl]bornane-10,2-sultam(11b). To a mixture of nitroethane(6mL, 83.55mmol) and trimethylsilyl chloride(16mL, 125.3mmol) in toluene(130mL) was added triethylamine(17.3mL, 125.3mmol) and after 15 min acryloyl camphor sultam **10b**(4.5g, 16.71mmol). The mixture was stirred at room temperature for 24 h, poured into saturated sodium bicarbonate, and extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. A solution of the residue in ether(120mL) was treated with *p*-toluenesulfonic acid(317.0mg, 1.67mmol). The mixture was stirred for 10 min, poured into brine, and extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 2.5:1) furnished a major isomer **11b** as a white solid(3.91g, 72% yield): mp 146-148°C; $[\alpha]_D^{16}$ −27.4°(*c* 0.20, $CHCl_3$); ^1H NMR($CDCl_3$) δ 0.98(3H, s), 1.31-1.45(2H, m), 1.90(3H, m), 1.99(3H, s), 2.03-2.21(2H, m), 3.20(1H, dd, J=17.6, 10.8Hz), 3.29(1H, dd, J=17.5, 6.9Hz), 3.44(1H, d, J=13.8Hz), 3.51(1H, d, J=13.8Hz), 3.91(1H, dd, J=7.7, 5.0Hz), 5.49(1H, dd, J=10.7, 6.9Hz); ^{13}C NMR($CDCl_3$) δ 12.4, 19.8, 20.8, 26.4, 32.9, 38.1, 42.4, 44.7, 47.9, 49.0, 52.9, 65.3, 76.9, 154.6, 168.7; IR(thin film) 2954, 1693, 1328, 1268, 1235, 1218, 1163, 1133, 861 cm^{-1}; MS *m/z* 326(M^+), 179, 151, 135, 107, 93, 84, 79, 67, 56. Anal. Calcd. for $C_{15}H_{23}N_2O_4S$(326.41): C, 55.20; H, 6.79; N, 8.58. Found: C, 55.63; H, 6.68; N, 8.48.

(*2S*, *5S*) -*N*-[(4,5-dihydro-3-methyl-5-isoxazolyl)carbonyl]bornane-10,2-sultam(11a). **10a** was cyclized according to the same procedure as **10b** to give **11a**(5.53g, 76% yield): ^1H NMR($CDCl_3$) δ 0.98(3H, s), 1.19(3H, s), 1.31-1.46(2H,m), 1.90(3H, m), 2.00(3H, s), 2.04-2.21(2H,m), 3.20(1H, dd, J=17.6, 10.8Hz), 3.30(1H, dd, J=17.6, 6.9Hz), 3.45(1H, d, J=13.8Hz), 3.51(1H, d, J=13.8Hz), 3.91(1H, dd, J=7.7, 5.0Hz), 5.49(1H, dd, J=10.7, 6.9Hz); ^{13}C NMR($CDCl_3$) δ 12.4, 19.8, 20.8, 26.3, 32.8, 38.0, 42.9, 44.6, 47.8, 49.0, 52.9, 65.2, 76.9, 154.6, 168.6.

(*R*)-3-Methyl-5-hydroxymethyl-2-isoxazoline(5b). To a solution of **11b**(3.9g, 11.96mmol) in THF(160mL) was added L-selectride(1M in THF, 30mL, 29.9mmol) at room temperature. The mixture was stirred for 20 min, cooled to 0°C, and quenched with water(5mL), 15% NaOH(5mL), and 35% H_2O_2(4.2mL). The resultant mixture was extracted with ether and then CH_2Cl_2, dried(Na_2SO_4), filtered, and concentrated. Flash chromatography(hexane/EtOAc, 3:1 to CH_2Cl_2/ether, 1:1) afforded **5b** as a colorless oil(1.19g, 86% yield): $[\alpha]_D^{27}$ −170.3°(c 1.1, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.97(3H, s), 2.08(1H, br. s), 2.80(1H, dd, J=16.8, 7.3Hz), 2.95(1H, dd, J=16.8, 10.6Hz), 3,54(1H, dd, J=12.2, 4.5Hz), 3.74(1H, dd, J=12.2, 3.2Hz), 4.65(1H, m): ^{13}C NMR($CDCl_3$) δ 13.0, 40.0, 63.7, 80.1, 155.9; IR(neat) 3385, 2916, 1635, 1436, 1386, 1330 cm^{-1}; MS *m/z* 115(M^+), 84, 68, 56, 51, 42, 39; HRMS *m/z* 115.0635[M^+, calcd for $C_5H_9O_2N$ 115.0634].

(*S*)-3-Methyl-5-hydroxymethyl-2-isoxazoline(5a). **11a** was reduced according to the same procedure as **11b** to give **5a**(1.71g, 91% yield): $[\alpha]_D^{28}$ +173.4°(c 1.27, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.94(3H, s), 2.61(1H, br. s), 2.79(1H, dd, J=17.1, 7.6Hz), 2.93(1H, dd, J=17.1, 10.6Hz), 3.52(1H, dd, J=12.1, 4.6Hz), 3.69(1H, dd, J=12.1, 3.4Hz), 4.61(1H, m); ^{13}C NMR($CDCl_3$) δ 12.9, 40.0, 63.5, 80.2, 155.8; IR(neat) 3376, 2913, 1635, 1436, 1054 cm^{-1}; MS *m/z* 115(M^+), 98, 96, 86, 85, 84, 83, 82, 81, 73, 70; HRMS *m/z* 115.0621[M^+, calcd for $C_5H_9O_2N$ 115.0634].

(*S*)-3-Methyl-5-iodomethyl-2-isoxazoline(12a). Triphenylphosphine(1.56g, 5.32mmol) and imidazole(408.9mg, 5.32mmol) were dissolved in ether/CH_3CN(3:1, 13mL). The mixture was cooled in an ice bath, and iodine(1.54g, 5.32mmol) was added portionwise with vigorous stirring. The resulting slurry was warmed to room temperature and stirred for 20 min and then cooled to 0°C, and a solution of **5a**(305.9mg, 2.66mmol) in ether/CH_3CN(3:1, 4mL) was added slowly. The mixture was warmed to room temperature, stirred for 10 h 30 min, and filtered through Celite. The combined mixture was concentrated and flash chromatography(hexane/EtOAc, 4:1) gave **12a** as a pale yellow solid(568.6mg, 95% yield): $[\alpha]_D^{25}$ +50.6°(c 1.31, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.99(3H, s), 2.79(1H, dd, J=17.6, 6.8Hz), 3.06-3.19(2H, m), 3.32(1H, dd, J=10.0, 4.2Hz), 4.71(1H, m); ^{13}C NMR($CDCl_3$) δ 7.8, 13.0, 44.7, 79.3, 154.5; IR(thin film) 2953, 1632, 1433, 1030 cm^{-1}; MS *m/z* 225(M^+), 167, 141, 127, 98, 88, 84, 73, 67. Anal. Calcd. for C_5H_8ONI: C, 26.69; H, 3.58; N, 6.22. Found: C, 26.77; H, 3.57;N, 6.06.

(*R*)-3-Methyl-5-iodomethyl-2-isoxazoline(12b). **5b** was converted according to the same procedure as **5a** into **12b**(284.7mg, 90% yield): $[\alpha]_D^{26}$ −49.7°(c 1.20, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.99(3H, s), 2.78(1H, dd, J=17.4, 6.8Hz), 3.05-3.18(2H, m), 3.32(1H, dd, J=10.0, 4.1Hz), 4.70(1H, m); ^{13}C NMR($CDCl_3$) δ 7.8, 13.0, 44.7, 79.3, 154.5; IR(thin film) 2953, 1631, 1433, 1196, 1030 cm^{-1}; MS *m/z* 225(M^+), 141, 127, 98, 88, 84, 73, 70, 67. Anal. Calcd. for C_5H_8NOI: C, 26.69; H, 3.58; N, 6.22. Found: C, 26.41; H, 3.72; N, 6.32.

Methyl (5*R*)- *α*,3-Dimethyl-*β*-oxo-2-isoxazoline-5-pentanoate(8a). To a solution of sodium hydride(60% oil dispersion, 586.9mg, 14.67mmol) in 10% HMPA/THF(55.5mL) at 0°C was added dropwise methyl 2-methylacetoacetate(1.56mL, 13.34mmol). The solution was stirred for 15 min and n-butyllithium(1.56M in hexane, 6.4mL, 10.0mmol) was added dropwise and stirred for 10 min. To this pale yellow solution was added slowly a solution of **12a**(1.5g, 6.67mmol) in THF(4.5mL). The mixture was stirred for 10 min and then quenched with 6mL of dil. hydrochloric acid(conc. HCl/H_2O, 2:5). The solution was diluted with water and extracted with EtOAc, and the organic phase was washed with brine, dried($MgSO_4$), filtered, and concentrated. Flash chromatography(hexane/EtOAc, 2.5:1) afforded **8a** as a colorless oil(1.22g, 81% yield): $[\alpha]_D^{23}$ +109.9°(c 2.06, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.35(3H, d, J=7.5Hz), 1.7-1.9(2H, m), 1.97(3H, s), 2.55(1H, dd, J=16.8, 7.5Hz), 2.6-2.8(2H, m), 2.95(1H, dd, J=17.4, 10.6Hz), 3.55(1H, q, J=7.5Hz), 3.73(3H, s), 4.52(1H, m); ^{13}C NMR($CDCl_3$) δ 12.6, 13.0, 29.0, 37.1, 43.9, 52.3, 52.7, 78.8, 155.1, 170.8, 204.9; IR(thin film) 2945, 1745, 1714, 1631, 1442, 1207 cm^{-1}; MS *m/z* 227(M^+), 196, 168, 154, 140, 126, 112, 98, 88, 84, 81, 71, 67; HRMS *m/z* 227.1139[M^+, calcd for $C_{11}H_{17}O_4N$ 227.1158].

Methyl (5*S*)-*α*,3-Dimethyl-*β*-oxo-2-isoxazoline-5-pentanoate(8b). **12b** was coupled according to the same procedure as **12a** to give **8b**(416.7mg, 81% yield): $[\alpha]_D^{21}$ −111.0°(*c* 2.27, CHCl$_3$); ^{1}H NMR(CDCl$_3$) δ 1.35(3H, d, J=7.5Hz), 1.7-1.9(2H, m), 1.97(3H, s), 2.55(1H, dd, J=16.8, 7.5Hz), 2.6-2.8(2H, m), 2.98(1H, dd, J=17.4, 10.6Hz), 3.54(1H, q, J=7.5Hz), 3.73(3H, s), 4.52(1H, m); ^{13}C NMR(CDCl$_3$) δ 12.7, 28.9, 37.1, 43.9, 52.3, 52.7, 78.7, 155.2, 170.8, 205.1; IR(thin film) 3458, 2943, 1747, 1714, 1630, 1443, 1204 cm^{-1}; MS *m/z* 227(M$^+$), 196, 168, 154, 140, 126, 112, 97, 88, 85, 71, 67; HRMS *m/z* 227.1186[M$^+$, calcd for C$_{11}$H$_{17}$O$_4$N 227.1158].

Methyl (6*R*)-8-Oxo-(*E*)-2,3-dehydrononactate(7a). To a solution of **8a**(818.8mg, 3.6mmol) in MeOH/H$_2$O(7:1, 19mL) was added boric acid(445.1mg, 7.2mmol) and a small amount of Ra-Ni. The mixture was stirred under a hydrogen atmosphere for 21 h and concentrated. The resultant residue was diluted with water, extracted with CH$_2$Cl$_2$, dried(MgSO$_4$), filtered, and concentrated. A solution of the resultant lactol **13** in CH$_2$Cl$_2$(45mL) was treated with oxalic acid(615.8mg, 6.84mmol) and heated at reflux for 2 h. The mixture was poured into saturated sodium bicarbonate, extracted with CH$_2$Cl$_2$, and washed with brine. The combined organic layer was dried over MgSO$_4$, filtered, and concentrated. Flash chromatography(petroleum ether/ether, 1:1) gave **7a** as a colorless oil(585.1mg, 77% yield): $[\alpha]_D^{25}$ −59.6°(*c* 1.32, CHCl$_3$); ^{1}H NMR(CDCl$_3$) δ 1.63-1.73(1H, m), 1.77(3H, t, J=1.5Hz), 2.20(3H, s), 2.28(1H, m), 2.64(1H, dd, J=16.4, 6.1Hz), 2.91(2H, m), 3.20(1H, m), 3.67(3H, s), 4.73(1H, m); ^{13}C NMR(CDCl$_3$) δ 11.3, 30.1, 30.7, 30.8, 48.6, 50.9, 78.7, 97.8, 169.4, 169.6, 205.6; IR(thin film) 2945, 1700, 1641, 1540, 1435, 1355, 1305, 1183, 1102, 918 cm^{-1}; MS *m/z* 212(M$^+$), 180, 139, 128, 122, 115, 96, 83, 70; HRMS *m/z* 212.1072[M$^+$, calcd for C$_{11}$H$_{16}$O$_4$ 212.1049].

Methyl (6*S*)-8-Oxo-(*E*)-2,3-dehydrononactate(7b). **8b** was converted according to the same procedure as **8a** into **7b**(357.9mg, 74% yield): $[\alpha]_D^{25}$ +60.7°(*c* 1.39, CHCl$_3$); ^{1}H NMR(CDCl$_3$) δ 1.61-1.72(1H, m), 1.78(3H, t, J=1.5Hz), 2.21(3H, s), 2.30(1H, m), 2.64(1H, dd, J=16.4, 6.1Hz), 2.88(1H, dd, J=16.4, 6.8Hz), 2.92(1H, m), 3.19(1H, m), 3.68(3H, s), 4.73(1H, m); ^{13}C NMR(CDCl$_3$) δ 11.3, 30.1, 30.7, 30.8, 48.6, 50.9, 78.7, 97.7, 169.4, 169.7, 205.7; IR(thin film) 2945, 1700, 1641, 1540, 1435, 1305, 1183, 1102, 918 cm^{-1}; MS *m/z* 212(M$^+$), 180, 139, 128, 122, 115, 96, 83, 70; HRMS *m/z* 212.1029[M$^+$, calcd for C$_{11}$H$_{16}$O$_4$ 212.1049].

Methyl (6*R*)-(*E*)-2,3-dehydrononactate(14a). To a solution of **7a**(273.9mg, 1.29mmol) in THF(30mL) at -78°C was added dropwise L-selectride(1M in THF, 1.48mL, 1.48mmol). The mixture was stirred for 10 min, poured into water, and extracted with ether. The combined organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. Flash chromatography(petroleum ether/ether, 1:7) afforded a 87:13 mixture of diastereomers **14a** as a colorless oil(260.4mg, 95% yield): ^{1}H NMR(CDCl$_3$) δ 1.25(3H, d, J=6.2Hz), 1.7-1.9(6H, m), 2.25(1H, m), 2.41(1H, d, J=3.1Hz), 2.92(1H, m), 3.24(1H, m), 3.69(3H, s), 4.07(1H, m), 4.54(1H, m); ^{13}C NMR(CDCl$_3$) δ 12.0, 24.0, 31.3, 44.6, 51.5, 67.3, 83.0, 98.2, 129.0, 136.0, 170.3; IR(thin film) 3421, 2937, 1681, 1647, 1444, 1313, 1189, 1102 cm^{-1}; HRMS *m/z* 214.1223[M$^+$, calcd for C$_{11}$H$_{18}$O$_4$ 214.1205].

Methyl (6*S*)-(*E*)-2,3-dehydrononactate(14b). **7b** was reduced according to the same procedure as **7a** to give **14b**(34.4mg, 97% yield): ^{1}H NMR(CDCl$_3$) δ 1.25(3H, d, J=6.2Hz), 1.8-1.9(6H, m), 2.25(1H, m), 2.36(1H, br. s), 2.92(1H, m), 3.24(1H, m), 3.69(3H, s), 4.05(1H, m), 4.54(1H, m); ^{13}C NMR(CDCl$_3$) δ 12.0, 24.1, 31.3, 44.7, 51.5, 67.3, 83.0, 98.3, 129.1, 136.1, 170.3; IR(thin film) 3420, 2934, 1681, 1647, 1444, 1313, 1101 cm^{-1}; HRMS *m/z* 214.1225[M$^+$, calcd for C$_{11}$H$_{18}$O$_4$ 214.1205].

Methyl (2*S*, 3*S*, 6*R*, 8*S*)-Nonactate(4a). Method A. A mixture of **14a**(193.7mg, 0.91mmol) and 5%

rhodium on alumina(1.49g, 0.72mmol) in MeOH(20mL) was shaken under a hydrogen atmosphere at 70 psi for 5 days. The mixture was diluted with ether, filtered through Celite, and concentrated. Flash chromatography(hexane/EtOAc, 7:1) gave **4a** as a colorless oil(121.7mg, 62% yield) and **3a** as a colorless oil(29.2mg, 15% yield).

Method B. To a solution of **15**(123.3mg, 0.58mmol) in THF(25mL) at -78°C was added dropwise L-selectride(1M in THF, 580μL, 1.16mmol). The mixture was stirred for 20 min, poured into water, and extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 7:1) gave **4a** as a colorless oil(100.8mg, 81% yield): $[\alpha]_D^{26}$ +20.7°(*c* 2.4, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ 1.05(3H, d, J=6.8Hz), 1.10(3H, d, J=6.2Hz), 1.42-1.64(4H, m), 1.88-2.05(2H, m), 2.49(1H, m), 3.29(1H, br. s), 3.64(3H, s), 3.87-4.12(3H, m); ^{13}C NMR($CDCl_3$) δ 13.3, 23.3, 28.4, 31.6, 44.6, 45.2, 51.6, 67.7, 80.1, 81.5, 175.1; IR(thin film) 3451, 2928, 1732, 1450, 1373, 1266, 1201, 1077 cm^{-1}; MS *m/z* 217(M^++1), 199, 172, 167, 157, 140, 129, 125, 117, 97, 88, 85; HRMS *m/z* 217.1437[$(M+H)^+$, calcd for $C_{11}H_{21}O_4$ 217.1440].

Methyl (2*R*, 3*R*, 6*S*, 8*R*)-Nonactate(4b). **14b** was hydrongenated according to the same procedure as **14a** to provide **4b**(96.0mg, 68% yield) and **3b**(14.6mg, 11% yield): $[\alpha]_D^{26}$ −21.3°(*c* 2.3, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ 1.03(3H, d, J=7.5Hz), 1.07(3H, d, J=6.2Hz), 1.40-1.61(4H, m), 1.86-2.01(2H, m), 2.46(1H, m), 3.61(3H, s), 3.85-4.15(3H, m); ^{13}C NMR($CDCl_3$) δ 13.3, 23.3, 28.4, 31.6, 44.6, 45.2, 51.5, 67.6, 80.0, 81.5, 175.0; IR(thin film) 3449, 2928, 1732, 1450, 1373, 1266, 1201, 1076, 853 cm^{-1}; MS *m/z* 217(M^++1), 199, 172, 167, 157, 142, 124, 116, 111, 96, 93, 87; HRMS *m/z* 217.1440[$(M+H)^+$, calcd for $C_{11}H_{21}O_4$ 217.1440].

Methyl (2*S*, 3*S*, 6*R*)-8-Oxononactate(15). A mixture of **7a**(203.0mg, 0.96mmol) and 5% rhodium on alumina(803.4mg, 0.38mmol) in MeOH(20mL) was shaken under a hydrogen atmosphere at 65 psi for 89 h. The mixture was filtered through Celite and concentrated. The residue was dissolved in CH_2Cl_2(20mL) and PCC(413.8mg, 1.92mmol) was added. The mixture was stirred for 17 h, diluted with ether, filtered, and concentrated. Flash chromatography (hexane/EtOAc, 7:1) provided **15** as a colorless oil(131.0mg, 64% yield): ^{1}H NMR($CDCl_3$) δ 1.07(3H, d, J=7.0Hz), 1.52(2H, m), 2.00(2H, m), 2.11(3H, s), 2.47(2H, dd, J=15.3, 6.7Hz), 2.70(1H, dd, J=15.6, 6.7Hz), 3.64(3H, s), 3.9-4.3(2H, m); ^{13}C NMR($CDCl_3$) δ 13.3, 28.3, 30.7, 31.0, 45.2, 49.7, 51.5, 75.4, 80.5, 175.0, 207.2.

Bicyclic compound 17. To a solution of tetramethylammonium triacetoxyborohydride(463.2mg, 1.76mmol) in CH_3CN(0.8mL) was added acetic acid(0.8mL) and the mixture was stirred at ambient temperature for 25 min. The mixture was cooled to 0°C, and a solution of the lactol **13**(51.7mg, 0.22mmol) in CH_3CN(0.6mL) was added via cannula. The mixture was stirred at 0°C for 35 min. The solution was poured into saturated sodium bicarbonate and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give the crude product **16**. To a solution of this compound in CH_2Cl_2(5mL) was added oxalic acid(36.0mg, 0.42mmol) and the mixture was heated at reflux for 3 h. The mixture was cooled, poured into water, and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 7:1 to 2:1) provided the bicyclic compound **17** as a colorless oil(26.7mg, 57% yield) and **18** as a colorless iol(4.2mg, 9% yield): ^{1}H NMR($CDCl_3$) δ 1.13(3H, d, J=6.2Hz), 1.22(3H, d, J=7.0Hz), 1.26-2.35(6H, m), 2.92(1H, q, J=7.0Hz), 3.66(3H, s), 3.93-3.99(1H, m), 4.50(1H, m); ^{13}C NMR($CDCl_3$) δ 12.6, 21.8, 27.8, 30.3, 38.6, 46.4, 51.6, 64.7, 75.3, 106.5, 173.6; IR(thin film) 2960, 1740, 1636, 1451, 1347, 1199, 1141, 950 cm^{-1}.

Methyl 8-Benzoyl-(2*S*, 3*S*, 6*R*, 8*R*)-nonactate(19). To a mixture of **4a**(150.3mg, 0.7mmol), benzoic acid(179.5mg, 1.4mmol), and triphenylphosphine(36.2mg, 1.4mmol) in THF(9mL) was slowly added DEAD(220μL, 1.4mmol). The mixture was stirred for 17 h, poured into water, and extracted with ether. The combined organic layer was dried over MgSO4, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 7:1) afforded **19** as a colorless oil(206.6mg, 92% yield): $[\alpha]_D^{28}$ −30.4°(*c* 2.2, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ 1.10(3H, d, J=6.8Hz), 1.37(3H, d, J=6.2Hz), 1.5-1.7(2H, m), 1.8-2.1(4H, m), 2.53(1H, m), 3.67(3H, s), 4.00(2H, m), 5.23(1H, m), 7.42(2H, m), 7.52(1H, m), 8.03(2H, m); ^{13}C NMR($CDCl_3$) δ 13.2, 20.7, 28.4, 31.5, 42.7, 45.3, 50.5, 70.0, 76.5, 80.5, 128.2, 129.5, 130.9, 132.6, 165.9, 175.1; IR(thin film) 3065, 2934, 1730, 1714, 1603, 1450, 1270, 1115 cm^{-1} ; MS *m/z* 321(M^++1), 289, 260, 233, 198, 183, 157, 123, 111, 105, 93, 88, 84, 77; HRMS *m/z* 321.1712[$(M+H)^+$, calcd for $C_{18}H_{25}O_5$ 321.1703].

Methyl (2*R*, 3*R*, 6*S*, 8*R*)-Nonactate Mesylate Ester(20). To a solution of **4b**(49.2mg, 0.23mmol) in CH_2Cl_2(5mL) was added 4-(dimethylamino)pyridine(5.0mg, 0.04mmol), triethylamine(104μL, 0.75mmol), and mesyl chloride(54μL, 0.69mmol). After 1h, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 3:1) gave **20** as a colorless oil(65.9mg, 97% yield):^{1}H NMR($CDCl_3$) δ 1.09(3H, d, J=7.0Hz), 1.42(3H, d, J=6.3Hz), 1.5-1.8(3H, m), 1.9-2.1(3H, m), 2.49(1H, m), 2.97(3H, s), 3.67(3H, s), 3.9-4.1(2H, m), 4.88(1H, m); ^{13}C NMR($CDCl_3$) δ 13.5, 21.1, 28.4, 31.2, 38.4, 42.8, 45.5, 51.6, 75.8, 78.0, 80.8, 175.2.

Methyl (+)-Nonactyl-(−)-nonactate(21). To a solution of **19**(115.7mg, 0.43mmol) in MeOH(4.5mL) was added 2N NaOH(2mL) and the mixture was stirred vigorously for 11 h. After concentration, the residue was diluted with brine and acidified to pH 1 with 2N HCl. The mixture was extracted with $CHCl_3$, dried($MgSO_4$), filtered, and concentrated to give **2a** quantitatively. A potassium hydride/oil suspension(62.4mg, 0.545mmol) was washed with dry hexane, a solution of **2a**(95.5mg, 0.454mmol) in DMF(3mL) was added, and the mixture was stirred for 20 min. To this solution of potassium (+)-nonactate was added a solution of **20**(89.0mg, 0.3mmol) in DMF(3mL), and the reaction mixture was stirred at 60-70°C for 43 h. The solution was cooled, saturated sodium bicarbonate (3mL) and brine(3mL) were added, and the mixture was stirred for 25 min. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was dried over $MgSO_4$ and concentrated to give the crude product. The aqueous phase was acidified to pH 1 with 2N HCl and extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated to afford (+)-nonactic acid(28mg). The crude product was purified by flash chromatography(hexane/EtOAc, 4:1 to 2:1) to give **21** as a colorless oil(97.3mg, 78% yield): ^{1}H NMR($CDCl_3$) δ 1.07(6H, d, J=6.9Hz), 1.16(3H, d, J=6.4Hz), 1.19(3H, d, J=6.2Hz), 1.5-1.7(8H, m), 1.93(4H, m), 2.50(3H, m), 3.65(3H, s), 3.8-4.2(5H, m), 4.96(1H, m); ^{13}C NMR($CDCl_3$) δ 13.2, 20.5, 23.2, 28.4, 28.5, 29.4, 30.7, 31.4, 42.5, 43.1, 45.3, 45.4, 51.5, 65.1, 69.4, 76.4, 77.0, 80.4, 80.8, 174.1, 175.2.

(+)-Nonactyl-(−)-nonactic acid(22). To **21**(97.2mg, 0.234mmol) under an argon atmosphere was added a solution of lithium n-propyl mercaptide in HMPA(1.1mL, 0.468mmol). After 2 h, the mixture was diluted with saturated sodium bicarbonate(10mL) and water(10mL), and extracted with $CHCl_3$. The aqueous layer was acidified to pH 1 with 2N HCl and extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to furnish **22** as a colorless oil(85.8mg, 91% yield): ^{1}H NMR($CDCl_3$) δ 1.08(3H, d, J=6.9Hz), 1.14(3H, d, J=7.0Hz), 1.18(3H, d, J=6.3Hz), 1.23(3H, d, J=6.3Hz), 1.5-1.8(8H, m), 2.00(4H, m), 2.46(2H, m), 3.9-4.2(5H, m), 5.02(1H, m).

Benzyl (2*R*, 3*R*, 6*S*, 8*R*)-Nonactate(24). A mixture of **4b**(146.4mg, 0.678mmol) and 2N NaOH(2mL) was stirred vigorously for 30 min. After acidification to pH 1 with 2N HCl, the mixture was extracted with $CHCl_3$ and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated to afford nonactic acid **23** quantitatively. A solution of **23**(108.1mg, 0.535mmol) in DMF(7mL) was added potassium *tert*-butoxide(72.0mg, 0.642mmol). After 30 min, benzyl bromide(76.4μL, 0.642mmol) was added slowly and the mixture was stirred for 12 h 20 min. Benzyl bromide(20μL) was added and after 1 h 10 min the mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried($MgSO_4$), filtered, and concentrated. Flash chromatography(hexane/EtOAc, 3:1) afforded **24** as a colorless oil(143.6mmol, 95% yield): $[\alpha]_D^{28}$ −16.0°(*c* 2.1, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.14(3H, d, J=7.5Hz), 1.16(3H, d, J=6.2Hz), 1.47-1.68(4H, m), 1.88-2.09(2H, m), 2.61(1H, m), 3.91-4.20(3H, m), 5.10(1H, d, J=12.5Hz), 5.17(1H, d, J=12.5Hz), 7.35(5H, m); ^{13}C NMR($CDCl_3$) δ 13.3, 23.3, 28.1, 31.7, 44.5, 45.3, 62.2, 67.7, 80.1, 81.3, 128.0, 128.2, 128.4, 136.0, 174.4; IR(thin film) 3450, 3034, 2925, 1729, 1498, 1457, 1115 cm^{-1} ; MS *m/z* 292(M^+), 274, 248, 201, 183, 158, 140, 129, 111, 98, 91, 85, 77; HRMS *m/z* 292.1629[M^+, calcd for $C_{17}H_{24}O_4$ 292.1675].

Benzyl (2*R*, 3*R*, 6*S*, 8*R*)-Nonactate Mesylate Ester(25). To a solution of **24**(117.5mg, 0.4mmol) in CH_2Cl_2(8mL) at 0°C was added mesyl chloride(93μL, 1.2mmol) and triethylamine(180μL, 1.3mmol). After 15 min, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 4:1) afforded **25** as a colorless oil(142.4mg, 96% yield): $[\alpha]_D^{27}$ −11.0°(*c* 2.0, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.14(3H, d, J=6.8Hz), 1.42(3H, d, J=6.2Hz), 1.49-1.76(3H, m), 1.96-2.09(3H, m), 2.58(1H, m), 2.93(3H, s), 3.92-4.09(2H, m), 4.87(1H, m), 5.14(1H, d, J=12.5Hz), 5.16(1H, d, J=12.5Hz), 7.35(5H, m); ^{13}C NMR($CDCl_3$) δ 13.5, 21.0, 28.4, 31.1, 38.2, 42.7, 45.6, 66.1, 75.7, 78.0, 80.8, 127.97, 128.04, 128.5, 136.1, 174.6; IR(thin film) 2942, 1732, 1498, 1457, 1350, 1170, 908 cm^{-1}; MS *m/z* 371(M^++1), 275, 236, 207, 183, 167, 149, 122, 111, 98, 91, 83, 69; HRMS *m/z* 371.1488[$(M+H)^+$, calcd for $C_{18}H_{27}O_6S$ 371.1529].

Benzyl 8-*tert*-Butyldimethylsilyl-(+)-nonactyl-(−)-nonactate(26). To a solution of **2a**(43.0mg, 0.21mmol) in DMF(1.5mL) was added potassium *tert*-butoxide(28.2mg, 0.25mmol) and the mixture was stirred for 40 min. A solution of **25**(43.9mg, 0.12mmol) in DMF(1.5mL) was added and the mixture was stirred at 60°C for 9 h 20 min and then at 70°C for 10 h. The reaction mixture was cooled, saturated sodium bicarbonate(3mL) and brine(3mL) was added, and the mixture was extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give the crude product. The aqueous layer was acidified to pH 1 with 2N HCl and extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to afford **2a**(22.7mg). The crude product was purified by flash chromatography (hexane/EtOAc, 7:1 to 2:1) to furnish a diastereomeric mixture of **28**(38.9mg, 69% yield). To this mixture(51.1mg, 0.107mmol), *tert*-butyldimethylsilyl chloride(64.5mg, 0.428mmol), imidazole(36.4mg, 0.535mmol), and 4-(dimethylamino)pyridine(13.0mg, 0.107mmol) was added DMF(0.3mL) and the mixture was stirred for 15 min. The mixture was diluted with water and extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 7:1) gave **26** as a mixture of diastereomers(61.6mg, 98% yield). The diastereomeric mixture was again purified by flash chromatography(hexane/EtOAc, 20:1) to afford **26** as a colorless oil(38.8mg, 63% yield): $[\alpha]_D^{28}$ −5.3°(*c* 1.34, $CHCl_3$); ^1H NMR($CDCl_3$) δ 0.05(6H, s), 0.87(9H, s), 1.08(3H, d, J=6.5Hz), 1.11(3H, d, J=5.9Hz), 1.12(3H, d, J=6.6Hz), 1.21(3H, d, J=6.6Hz), 1.45-1.97(12H, m), 2.46(1H, m), 2.57(1H, m), 3.85-4.06(5H, m), 4.96(1H, m), 5.13(1H, d, J=12.5Hz), 5.15(1H, d, J=12.5Hz), 7.34(5H, m); ^{13}C NMR($CDCl_3$) δ -3.4, -3.1, 13.1, 13.2, 18.0, 20.6, 24.6, 25.9, 28.4, 31.48, 31.52, 42.5, 45.4, 45.7, 46.2, 66.1, 66.3, 76.3, 76.7, 80.0, 80.3, 128.01, 128.04, 128.4, 136.2, 174.2, 174.6; IR(thin film) 2926, 1735, 1461, 1377, 1255, 1109 cm^{-1}; MS *m/z* 590(M$^+$), 558, 533, 480, 452, 427, 410, 396, 386, 379, 368, 341, 327, 275, 256, 236, 185, 167, 155, 149, 143, 137.

Benzyl 8-*tert*-Butyldimethylsilyl-(+)-nonactyl-(−)-nonactic acid(27). A mixture of **26**(7.7mg, 0.013mmol) and 5% palladium on charcol(5.9mg, 0.0026mmol) in THF(0.6mL) was stirred under a hydrogen atmosphere at 1 atm for 30 min. The mixture was filtered and concentrated to give **27** as a colorless oil(6.4mg, 98% yield): $[\alpha]_D^{26}$ −2.0°(*c* 0.98, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ 0.03(6H, s), 0.87(9H, s), 1.08(3H, d, J=6.9Hz), 1.11(3H, d, J=6.2Hz), 1.16(3H, d, J=6.9Hz), 1.24(3H, d, J=6.2Hz), 1.4-2.1(12H, m), 2.48(2H, m), 3.96(5H, m), 5.01(1H, m); ^{13}C NMR($CDCl_3$) δ -3.4, -3.1, 13.3, 18.1, 20.4, 24.6, 25.9, 28.4, 29.0, 29.7, 31.5, 42.4, 44.9, 45.6, 46.2, 68.9, 66.3, 76.5, 77.1, 80.1, 80.2, 174.3, 177.4; IR(thin film) 3600-2500, 1733, 1714, 1463, 1377, 1255, 1193, 1067 cm^{-1}; MS *m/z* 501(M$^+$+1), 443, 427, 410, 386, 368, 350, 341, 328, 279, 264, 256, 213, 185, 167, 157, 149, 143, 136, 129.

Benzyl (+)-Nonactyl-(−)-nonactate(28). To **26**(18.6mg, 0.0315mmol) was added 40% HF/CH_3CN(5/95, 0.6mL) and the solution was stirred for 10 min. After poured into water, the mixture was extracted with CH_2Cl_2 and washed with brine. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 2.5:1) gave **28** as a colorless oil(14.4mg, 96% yield): $[\alpha]_D^{26}$ +8.8°(*c* 0.73, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ 1.10(3H, d, J=5.6Hz), 1.12(3H, d, J=6.2Hz), 1.18(3H, d, J=6.2Hz), 1.20(3H, d, J=5.6Hz), 1.48-1.82(8H, m), 1.87-2.00(4H, m), 2.13(1H, br. s), 2.44-2.60(2H, m), 3.86-4.12(5H, m), 5.00(1H, m), 5.13(1H, d, J=12.5Hz), 5.15(1H, d, J=12.5Hz), 7.35(5H, m); ^{13}C NMR($CDCl_3$) δ 13.20, 13.24, 20.5, 23.3, 28.4, 28.6, 30.7, 31.4, 42.5, 43.2, 45.43, 45.47, 65.1, 66.1, 69.5, 76.5, 77.2, 80.4, 80.9, 128.0, 128.04, 128.5, 136.3, 174.1, 174.6; IR(thin film) 3483, 2940, 1731, 1458, 1068 cm^{-1} ; MS *m/z* 476(M$^+$), 313, 183, 167, 149, 129, 111, 91, 81, 69, 60; HRMS *m/z* 476.2792[M$^+$, calcd for $C_{27}H_{40}O_7$ 476.2775].

Benzyl 8-*tert*-Butyldimethylsilyl-(+)-nonactyl-(−)-nonactyl-(+)-nonactyl-(−)-nonactate(29). To a solution of **27** (18.9mg, 0.0378mmol) in THF(0.8mL) was added triethylamine(7.9μL, 0.0567mmol) and 2,4,6-trichlorobenzoyl chloride(5.9μL, 0.0378mmol). The mixture was stirred for 1 h, filtered, and concentrated under an argon atmosphere. The residue was diluted with benzene(0.8mL) and added to **28**(17.2mg, 0.0361mmol). 4-(Dimethylamino)pyridine(6.9mg, 0.0564mmol) was added and the mixture was stirred for 2 h. After poured into water, the mixture was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 5:1 to 1:1) afforded **29** as a colorless oil(30.0mg, 87% yield): $[\alpha]_D^{28}$ −2.0°(*c* 1.5, $CHCl_3$); ^{1}H NMR($CDCl_3$) δ 0.03(6H, s), 0.87(9H, s), 1.0-1.3(24H, m), 1.4-2.1(24H, m), 2.4-2.6(4H, m), 3.8-4.2(9H, m), 4.96(3H, m), 5.13(2H, s), 7.34(5H, m); IR(thin film) 2939, 1733, 1459, 1377, 1256, 1067 cm^{-1}; MS(FAB, DMSO) *m/z* 960(M$^+$+1), 958, 870, 828, 756, 686, 644, 571, 554, 459, 457, 369, 367, 277, 275, 203.

Benzyl (+)-nonactyl-(−)-nonactyl-(+)-nonactyl-(−)-nonactate(30). To **29**(17.6mg, 0.018mmol) was added 40% HF/CH_3CN(5/95, 0.5mL) and the solution was stirred for 10 min. After poured into water, the mixture was extracted with CH_2Cl_2 and washed with brine. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography(hexane/EtOAc, 1.5:1) gave **30** as a colorless oil(14.8mg, 97% yield): $[\alpha]_D^{28}$ +6.5°(c 0.74, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.0-1.3(24H, m), 1.4-2.1(25H, m), 2.4-2.6(4H, m), 3.8-4.2(9H, m), 4.98(3H, m), 5.13(2H, s), 7.34(5H, m); IR(thin film) 3488, 2956, 1731, 1458, 1378, 1261, 1192, 1067 cm^{-1}; MS(FAB, DMSO) *m/z* 846(M^++1), 756, 710, 644, 571, 553, 459, 369, 315, 275, 185, 157, 119.

(+)-Nonactyl-(–)-nonactyl-(+)-nonactyl-(–)-nonactic acid(31). A mixture of **30**(20.7mg, 0.0245 mmol) and 5% palladium on charcol(10.4mg, 0.005mmol) in THF(1mL) was stirred under a hydrogen atmosphere at 1 atm for 30 min. The mixture was filtered and concentrated to give **31** as a colorless oil(8.4mg, 100% yield): $[\alpha]_D^{27}$ +7.25°(c 0.91, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.0-1.3(24H, m), 1.4-2.1(24H, m), 2.50(4H, m), 3.8-4.2(9H, m), 4.99(3H, m); IR(thin film) 2932, 1732, 1716, 1459, 1378, 1134 cm^{-1}.

Nonactin(1). Method A. To a solution of **22**(29.3mg, 0.076mmol) in THF(3mL) at 0°C was added triethylamine(11.8μL, 0.085mmol), diphenyl phosphorochloridate(17.7μL, 0.085mmol). After 40 min, the mixture was filtered under an argon atmosphere, and the filterate was diluted with benzene(5.2mL). 4-(Dimethylamino) pyridine(13.9mg, 0.114mmol) and potassium perchloridate(52.6mg, 0.38mmol) was added and the solution was heated at reflux for 2 days. The mixture was cooled, concentrated, and the residure was purified by flash chromatography(hexane/EtOAc, 3:1) to give nonactin(**1**)(4.0mg, 14% yield) as a crude product.

Method B. To a mixture of hydroxy acid **31**(9.8mg, 0.013mmol) and triethylamine(4.5μL, 0.032mmol) in THF(445μL) was added 2,4,6-trichlorobenzoyl chloride(2.6μL, 0.017mmol) in THF(26μL). The reaction mixture was stirred for 5 h 20 min at room temperature. After removal of triethylamine hydrochloride, the filterate was diluted with benzene(6mL) and added to a refluxing solution of 4-(dimethylamino)pyridine(7.9mg, 0.065mmol) in benzene(2 mL) over a period of 5 h 15 min by syringe pump. The reaction mixture was cooled, the solvent was evaporated at reduced pressure, and the residue was purified by flash chromatography(hexane/EtOAc, 2:1) to give 8.8mg of crude product. From this crude product nonactin(**1**)(5.2mg, 54% yield) was obtained by recrystallization from ether/hexane(4:1): mp 147°C(lit.[6n] 147°C); $[\alpha]_D^{21}$ 0°(c 0.4, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.08(12H, d, J=6.8Hz), 1.22(12H, d, J=6.2Hz), 1.4-2.0(24H, m), 2.49(4H, dq, J=7Hz), 3.84(4H, apparent quintet, J=6Hz), 4.00(4H, apprent quartet, J=7Hz), 4.96(4H, ddq, J=6Hz); ^{13}C NMR($CDCl_3$) δ 12.9, 20.5, 28.2, 31.4, 42.3, 45.3, 69.1, 76.4, 80.1, 174.2; IR(thin film) 2956, 1730, 1459, 1377, 1263, 1193, 1065, 755 cm^{-1}; HRMS *m/z* 736.4411(calcd for $C_{40}H_{64}O_{12}$: 736.4399).

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