Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 3133–3140
Tetrahedron
www.elsevier.com/locate/tet

An acid-catalyzed ring-switch reaction of lactams to lactones: concise synthesis of 2,4-dialkyl-3-hydroxybutanolides

Chiaki Yamauchi [a], Masami Kuriyama [b], Rumiko Shimazawa [b], Tsumoru Morimoto [a], Kiyomi Kakiuchi [a], Ryuichi Shirai [a,b,*]

[a] *Graduate School of Materials Science, Nara Institute of Science and Technology (NAIST), Takayama, Ikoma, Nara 630-0192, Japan*
[b] *Faculty of Pharmaceutical Science, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe, Kyoto 610-0395, Japan*

Received 18 December 2007; received in revised form 26 January 2008; accepted 29 January 2008
Available online 1 February 2008

Abstract

A novel approach for the synthesis of 2,4-dialkyl-3-hydroxybutanolides, having three successive stereogenic centers, by an acid-catalyzed ring-switch reaction of 2-(2-hydroxyalkyl)lactams is described. This transformation was applied to the synthesis of the key intermediates of teromerase inhibitor UCS1025A.
© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Syntheses of functionalized γ-butyrolactones are an important subject in organic and bioorganic chemistry.[1] The synthesis of 2,4-dialkyl-3-hydroxybutanolides has been of continuous interest due to their utility as chiral synthons and their biological activity.[2] Several biologically interesting 2,4-dialkyl-3-hydroxybutanolides, such as (+)-blastmycinone,[3] (−)-3-*epi*-blastmycinone,[3c] Laetianolide A,[4] NFX-2,[5] and UCS1025A,[6] are shown in Figure 1. Polyketide metabolites, blastmycinone and NFX-2, include butyl and hexyl carbon chains at the C-2 position, respectively. Laetianolide A was isolated from *Laetia procera* (Flacourtiaceae), and UCS1025A was isolated from the fermentation broth of *Acremonium* sp. KY4917 fungus.

The three contiguous chiral centers arranged precisely in these molecules provide a reasonable challenge for the development of new methodologies.

Here, we report on a novel tactic for the synthesis of 2,4-dialkyl-3-hydroxybutanolides, which have three successive stereogenic centers, by an acid-catalyzed ring-switch reaction of the 2-(2-hydroxyalkyl)lactams (outlined in Scheme 1).

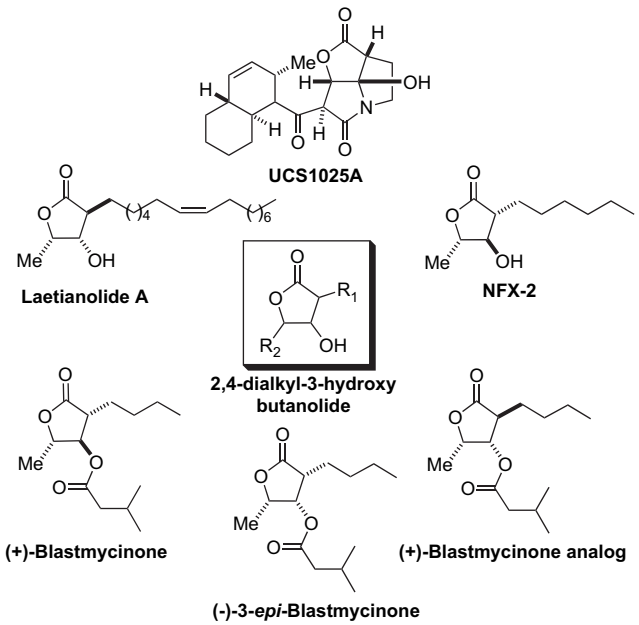
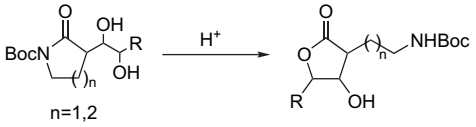


Figure 1. 2,4-Dialkyl-3-hydroxybutanolide natural products and derivatives.

* Corresponding author. Tel./fax: +81 774 65 8510.
E-mail address: rshirai@dwc.doshisha.ac.jp (R. Shirai).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.107

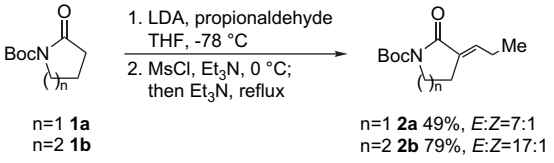


Scheme 1. Acid-catalyzed ring-switch reaction of 2-(2-hydroxyalkyl)lactams to 2,4-dialkyl-3-hydroxybutanolides.

2. Results and discussion

2.1. Acid-catalyzed ring-switch reaction

The introduction of the 2-substituent having three successive stereogenic centers was performed as follows. Deprotonation of *N*-Boc-butyrolactam **1a** and *N*-Boc-valerolactam **1b**[7] by LDA followed by an aldol reaction produced the corresponding aldol adducts, which were directly converted to the exocyclic α,β-unsaturated lactams **2a** and **2b** via methanesulfonates, respectively (Scheme 2).[8]

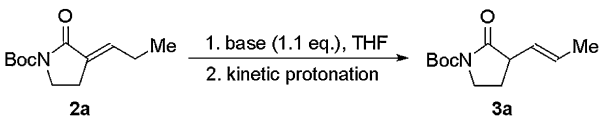


Scheme 2. Syntheses of 2-propylidenelactams by aldol condensation.

According to the reported procedures[9] on deconjugation of α,β-unsaturated esters to the corresponding unsaturated β,γ-esters, deprotonation of **2a** by different bases followed by kinetic protonation was examined. The results are summarized in Table 1.

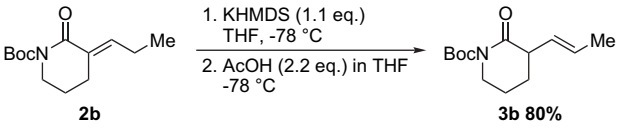
By use of potassium *tert*-butoxide as the base for deprotonation and water as the proton source for kinetic deconjugation, trace amounts of the desired product and starting materials were recovered. When LDA was employed as the base, the starting exocyclic α,β-unsaturated lactam was recovered quantitatively, and the result indicates that deprotonation did not take place under this condition. Gratifyingly, use of potassium bis(trimethylsilyl)amide (KHMDS) and subsequent kinetic protonation with acetic acid in THF gave the desired deconjugated butyrolactam **3a** as the sole product in 87% yield (Table 1, entry 3). The same reaction condition resulted in **2b** being converted into corresponding exocyclic β,γ-unsaturated valerolactam **3b** in good yields (Scheme 3).

Table 1
Kinetic isomerization of **2a** to **3a**



Entry	Base	Temperature[a] (°C)	Proton source	**2a** (%)	**3a** (%)
1	KO^{t}Bu	−20	H_2O	Trace	Trace
2	LDA	−78	AcOH in THF[b]	>99	Trace
3	KHMDS	−78	AcOH in THF[b]	Trace	87

[a] For each entry, deprotonation and subsequent protonation were conducted at the same temperature indicated.
[b] Amount: 2.2 equiv.



Scheme 3. Kinetic isomerization of **2b** to **3b**.

The hydroxyl group, which would be incorporated into the lactone ring, was introduced by dihydroxylation reaction catalyzed by osmium tetroxide (Scheme 4). Treatment of butyrolactam **3a** with a catalytic amount of osmium tetroxide in the presence of NMO as a co-oxidant in CH_2Cl_2 gave a diastereomixture of two diols: *anti*-**4a** and *syn*-**4a** (73:27). Similarly, dihydroxylation of valerolactam **3b** also took place in similar stereoselectivity to give the diols *anti*-**4b** and *syn*-**4b** (82:18).

The observed preference of *anti*-**4** over *syn*-**4** can be rationalized as shown in Figure 2. Because of the $A^{(1,3)}$ strain between the side chain and the lactam ring, conformer **3a-B** would be more stable than **3a-A**. Thus, osmium tetroxide approaches the C=C bond preferentially from the less hindered methylene side, the opposite face of the carbonyl group.

Young and co-workers reported the ring-switch reaction of optically active amino acid derivatives as shown in Scheme 5.[10] *N*-Boc protected butyrolactam **7** and valerolactam **10** with a hydroxyl group generated by reduction of the aldehyde or the carboxylic acid residue were transformed to monosubstituted butanolides **8** and **11**, respectively, under the condition of borane reduction.

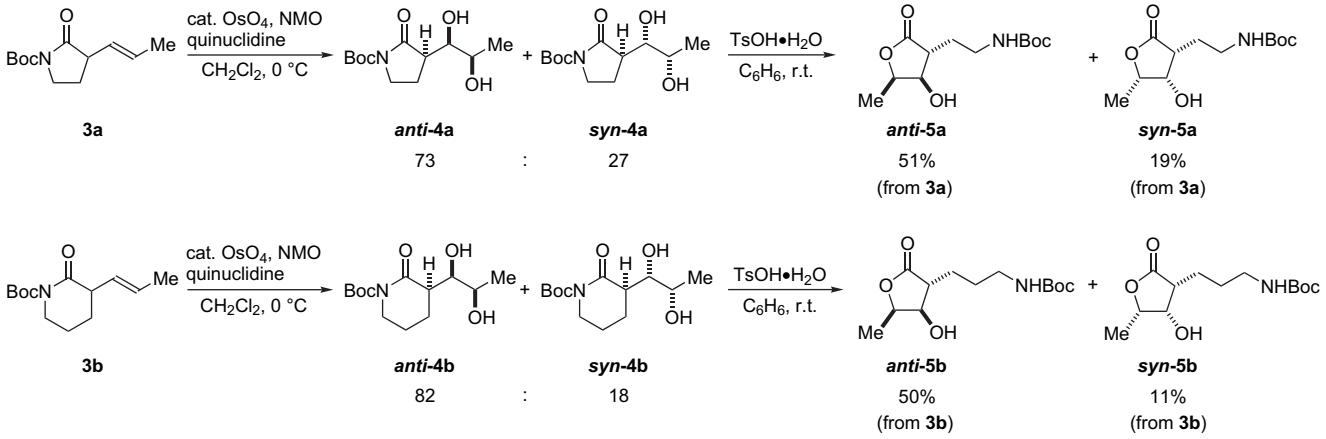
The application of this conversion from the above synthesized 2-(2-hydroxyalkyl)lactam **4** would produce 2,4-dialkyl-3-hydroxybutanolides efficiently. Because the hydroxylated lactams **4** were isolated as stable compounds that survived during the dihydroxylation in the presence of basic amines, we tried to employ mild acidic condition for a ring-switch reaction from lactams to lactones.

The mixture of diastereoisomers of **4a** and **4b** were dissolved in benzene and a catalytic amount of TsOH was added and stirred for 30 min at rt to give 2,4-dialkyl-3-hydroxybutanolide in quantitative yields from dihydroxylated lactams **4a** and **4b** (Scheme 4). The isolated yield of **5a** from deconjugated alkene (two steps) was 51 (*anti*-**5a**) and 19% (*syn*-**5a**), and **5b** from **3b** was 50 (*anti*-**5b**) and 11% (*syn*-**5b**).

The relative stereochemistry of Ha, Hb, and Hc of the ring-switched compounds *syn*-**5a**/*anti*-**5a** and *syn*-**5b**/*anti*-**5b** was determined by NOE-difference experiments as shown in Figure 3. Enhancement was observed between Ha and Hb and between Ha and Hc in *syn*-**5**. A small enhancement between Ha and Hb and no enhancement between Ha and Hc were observed in *anti*-**5**.

2.2. Synthetic approach to the 2,4-dialkyl-3-hydroxybutanolide core of UCS1025A

As an application of acid-catalyzed ring-switch reaction, we planned to synthesize the trisubstituted butanolide, a key



Scheme 4. Acid-catalyzed ring-switch reaction of **3a** and **3b**.

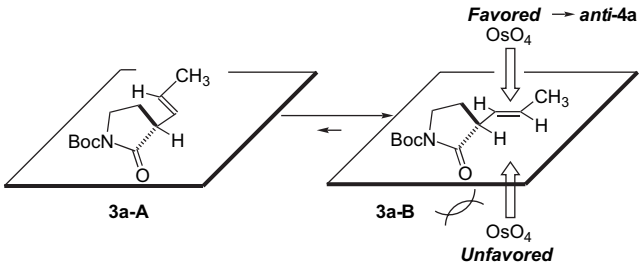


Figure 2. Stereoselective osmylation of **3a**.

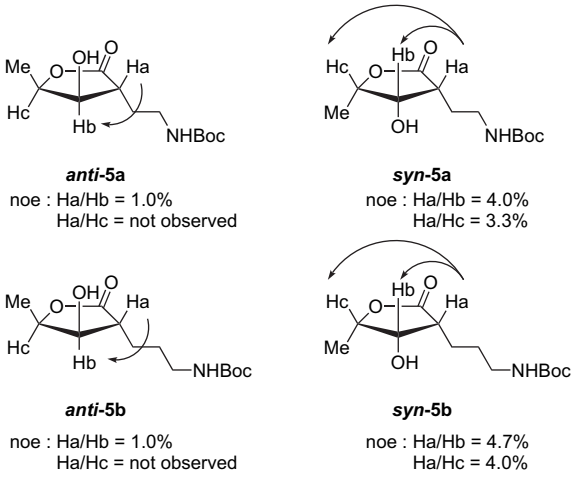


Figure 3. Determination of relative stereochemistry of **5** by NOE-difference experiment.

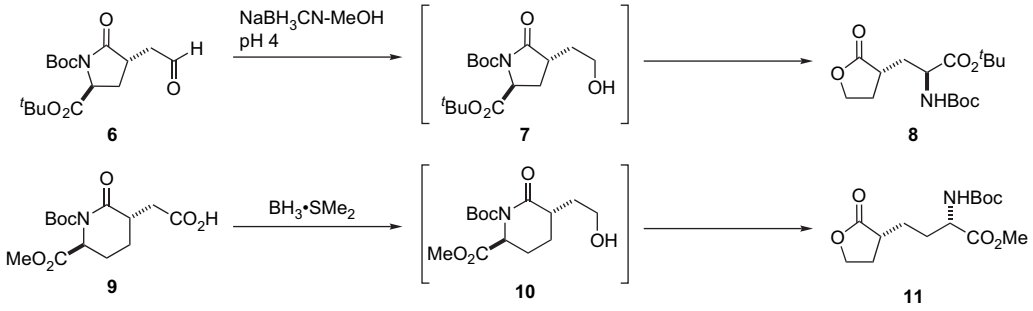
intermediate of UCS1025A having all carbon, oxygen, and nitrogen atoms in its lactone core and substituents at C-2 and C-4 centers with correct stereochemistry (Scheme 6).

Based on the kinetic deconjugation–dihydroxylation protocol described above, trisubstituted butanolide **14** was synthesized from β,γ-unsaturated butyrolactam **12**, which was prepared from **1a** and 4-*tert*-butyldimethylsiloxy-1-butyraldehyde[11] via (i) aldol reaction, (ii) methanesulfonylation followed by triethylamine-catalyzed β-elimination, and (iii) kinetic deconjugation of the dienolate (Scheme 7). Dihydroxylation of **12** with OsO_4 afforded *anti*-**13** and *syn*-**13** in 60 and 22% yields, respectively. Subsequently, a ring-switch reaction of *anti*-**13** and *syn*-**13** took place efficiently to yield *anti*-**14** and *syn*-**14**.

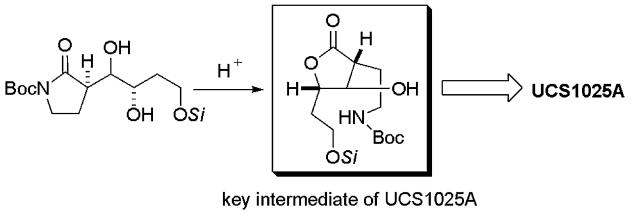
The relative stereochemistry of Ha, Hb, and Hc of the ring-switched compounds *syn*-**14**/*anti*-**14** were determined by NOE-difference experiments, as shown in Figure 4. The enhancement was observed between Ha and Hb and between Ha and Hc in *syn*-**14**. A small enhancement between Ha and Hb and no enhancement between Ha and Hc were observed in *anti*-**14**.

Kinetic resolution of Sharpless asymmetric dihydroxylation on **12** with AD-mix α and β was attempted,[12] although no dihydroxylated products were produced. Therefore, we turned our tactics to the diastereoselective aldol reaction of **1a** with chiral α-hydroxyaldehyde **15** leading to the direct production of a dihydroxylactam derivative (Scheme 8).

The aldol reaction of **1a** with (*S*)-4-(*tert*-butyldiphenylsiloxy)-2-triethylsiloxybutanal **15** prepared from (*S*)-malic



Scheme 5. Reported ring-switch reaction by Young and co-workers.[10]



Scheme 6. Synthetic approach to the key intermediate of UCS1025A.

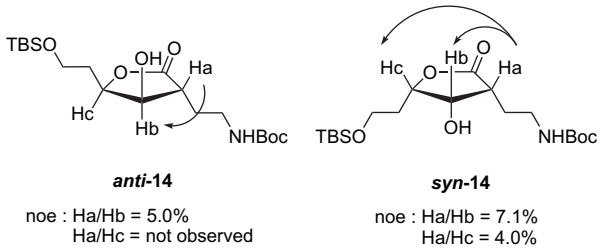


Figure 4. Determination of relative stereochemistry of **14** by NOE-difference experiment.

acid[13] afforded aldol adducts as a mixture of four diastereomers (**16a**, **17a**, **18a**, and **19a**) in the ratio of 27:60:6.5:6.5 by ^{1}H NMR analysis. We were able to separate the two major diastereomeric products **16a** and **17a** from the mixture, however, **18a** and **19a** could not be separated. Treatment of the separated aldol adducts **16a** and **17a** with TsOH at rt for 3 h resulted in a deprotection of the TES group to afford corresponding diols, which were directly subjected to in situ ring-switch lactonization to give chiral butanolides **20a** and **21a**, respectively.

The absolute configuration of **20a** and **21a** was determined by NOE-difference experiments (Fig. 5). The enhancements between Ha and Hc and between Ha and Hb in **20a** demonstrated that they are cis oriented. On the other hand, the absence of enhancement between Ha and Hc in **21a** revealed that they are trans oriented, while trans orientation between Ha and Hb was assigned by the enhancement of Hb and Hd.

3. Conclusion

We have demonstrated the synthesis of 2,4-dialkyl-3-hydroxybutanolides from the lactams via an acid-catalyzed ring-switch reaction to lactone. The relative and absolute stereochemistries of 2,4-dialkyl-3-hydroxybutanolides were assigned using NOE-difference experiments. The butanolides provided by this synthetic tactic can be utilized for the syntheses of more complicated natural products.

4. Experimental

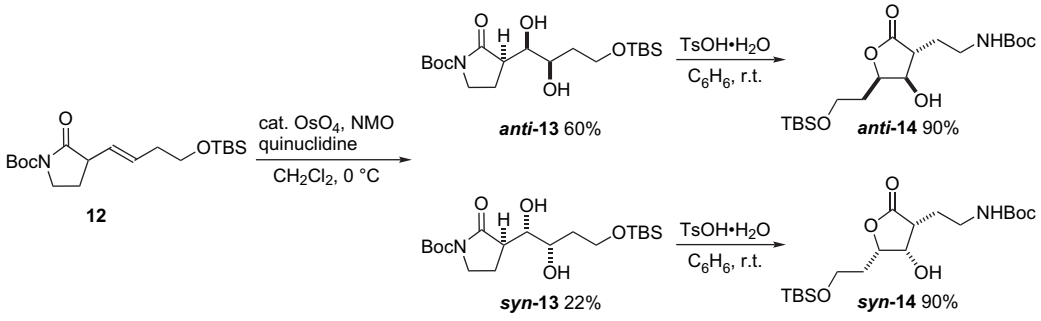
4.1. General

All nonaqueous operations were carried out in dried glassware under an N_2 atmosphere. Anhydrous dichloromethane, benzene, and tetrahydrofuran (THF) were purchased from Wako chemicals. The products were isolated by flash silica gel column chromatography (MERCK Silica Gel 60). ^{1}H NMR was recorded on a JEOL JNM-ECP500 (500 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million downfield from internal TMS. ^{13}C NMR spectra were recorded on a JEOL JNM-ECP500 (125.8 MHz) spectrometer. IR spectra were obtained from a Hitachi 270-30 Infrared Spectrophotometer and a JASCO FT/IR-420 spectrometer. High-resolution mass spectra were measured with a JEOL JMS-700. Elemental analyses were performed by a Perkin–Elmer 2400II CHNS/O.

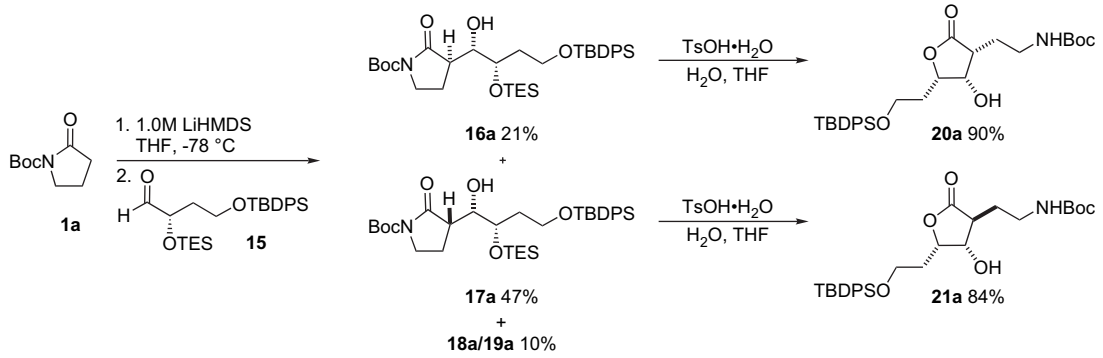
4.2. Syntheses of 2-propylidenelactams

4.2.1. tert-Butyl 2-oxo-3-propylidenepyrrolidine-1-carboxylate (*2a*)

Compound **1a**[7] (3.37 g, 18.2 mmol) was added to a solution of LDA (20.0 mmol) in THF (55 mL) at −78 °C. The reaction mixture was allowed to warm to −20 °C, stirred at this temperature for 1 h, and cooled to −78 °C. Propionaldehyde (1.30 mL, 18.2 mmol) in THF (45 mL) was added dropwise, and the mixture was stirred at this temperature for 1 h and quenched with saturated aqueous NH_4Cl solution. Extractive workup with ethyl acetate yielded the crude alcohol, which was dissolved in a mixture of dry toluene (24 mL) and triethylamine (3.8 mL, 27.3 mmol). Methanesulfonyl chloride (1.6 mL, 20.5 mmol) was added dropwise at 0 °C and the mixture was allowed to warm to rt. Additional triethylamine (6.4 mL, 45.5 mmol) was added and the mixture was refluxed for 13 h. After addition of a saturated aqueous NH_4Cl solution, the organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration. Purification by flash chromatography (ethyl acetate/hexane=1:1) gave impure **2a**



Scheme 7. Synthesis of 2,4-dialkyl-3-hydroxybutanolide **14**.



Scheme 8. Syntheses of chiral 2,4-dialkyl-3-hydroxybutanolides.

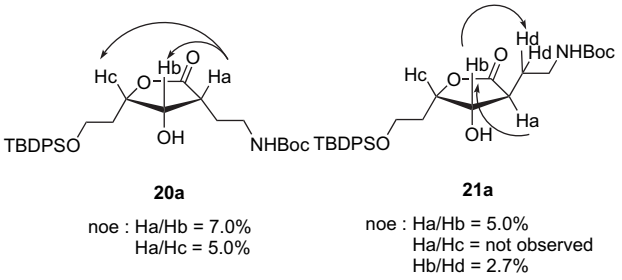


Figure 5. Determination of relative stereochemistry of **20a** and **21a** by NOE-difference experiment.

(*Z*-isomer; 0.22 g, 5%) and **2a** (*E*-isomer; 1.77 g, 44%) of 2-propylidenelactam **2a** as a yellow needle. Compound **2a** (*Z*-isomer): ^{1}H NMR ($CDCl_3$): δ 5.99 (1H, J=7.6, 2.2 Hz, tt). Compound **2a** (*E*-isomer): mp 39–41 °C. ^{1}H NMR ($CDCl_3$): δ 6.56 (1H, tt, J=7.5 Hz, 2.8 Hz), 3.65 (2H, dd, J=3.9 Hz, 10.7 Hz), 2.51–2.59 (2H, m), 2.02–2.13 (2H, m), 1.45 (9H, s), 0.97 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 12.6, 20.4, 22.4, 27.8, 27.8, 28.2, 43.0, 82.4, 103.7, 130.1, 139.2, 150.7, 166.8. IR (KBr): 3000, 1740, 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.68; H, 8.72; N, 6.11.

4.2.2. *tert*-Butyl 2-oxo-3-propylidenepiperidine-1-carboxylate (*2b*)

Operating as above with **1b**[7] (2.32 g), 2-propylidenelactam **2b** (*Z*-isomer; 0.12 g, 4%), and **2b** (*E*-isomer; 2.11 g, 75%) were isolated both as a pale yellow oil. Compound **2b** (*Z*-isomer): ^{1}H NMR ($CDCl_3$): δ 5.87 (1H, J=7.6 Hz, t), 3.64 (2H, J=6.1 Hz, t), 2.58 (2H, J=7.6, 7.9 Hz, dq), 2.45 (2H, J=6.7 Hz, t), 1.86 (2H, J=6.7, 6.1 Hz, tt), 1.54 (9H, s), 1.03 (3H, J=7.9 Hz, t). ^{13}C NMR ($CDCl_3$): δ 166.0, 152.7, 146.1, 128.8, 82.4, 45.5, 30.4, 27.9, 22.8, 22.6, 13.8. IR (neat): 2970, 1764, 1713, 1294, 1148 cm^{-1}. HRMS (FAB): calcd for $[C_{13}H_{21}NO_3+Na]^+$, 262.1414; found, 262.1425. Compound **2b** (*E*-isomer): ^{1}H NMR ($CDCl_3$): δ 6.94 (1H, J=7.3, 2.1 Hz, tt), 3.69 (2H, J=5.8 Hz, t), 2.46 (2H, J=6.9, 1.2 Hz, td), 2.15 (2H, J=7.6, 7.3, 1.2 Hz, ttt), 1.87 (2H, J=6.9, 5.8 Hz, tt), 1.54 (9H, s), 1.05 (3H, J=7.6 Hz, t). ^{13}C NMR ($CDCl_3$): δ 165.3, 152.9, 143.9, 129.1, 82.4, 45.6, 27.8, 23.9, 22.0, 21.4, 12.6. IR (neat): 2970, 1765, 1713, 1303, 1149 cm^{-1}. HRMS (EI): calcd for $[C_{13}H_{21}NO_3+Na]^+$, 239.1521; found, 239.1518.

4.3. Syntheses of β,γ-unsaturated lactams

4.3.1. (*E*)-*tert*-Butyl 2-oxo-3-(prop-1-enyl)pyrrolidine-1-carboxylate (*3a*)

To a THF (20 mL) solution of **2a** (623.6 mg, 2.77 mmol) was added a toluene solution of KHMDS (0.5 M, 6.1 mL, 3.04 mmol) at −78 °C, and the reaction mixture was stirred for 3 h. To the mixture was added a solution of acetic acid (1.6 mL, 27.7 mmol) in THF (15 mL) at −78 °C, and the reaction mixture was stirred for 30 min. After addition of a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with ethyl acetate, and the organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography (ethyl acetate/hexane=1:1) gave 539.7 mg (87%) of β,γ-unsaturated lactam **3a** as a pale yellow needle. Compound **3a**: mp 36–37 °C. ^{1}H NMR ($CDCl_3$): δ 5.61 (1H, J=15.4, 6.1 Hz, dq), 5.48 (1H, J=15.4, 6.6, 1.7 Hz, ddd), 3.78–3.73 (1H, m), 3.58 (1H, J=11.0, 9.2, 7.3 Hz, ddd), 3.13 (1H, J=8.3, 8.3, 8.0 Hz, ddd), 2.21–2.14 (1H, m), 1.84 (1H, J=18.3, 12.8, 8.6 Hz, ddd), 1.69 (3H, J=6.1 Hz, d), 1.50 (9H, s). ^{13}C NMR ($CDCl_3$): δ 174.3, 150.3, 129.0, 126.4, 82.7, 46.9, 44.3, 27.9, 24.6, 17.9. IR (KBr): 3400, 3000, 1740, 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.12; H, 8.65; N, 6.21.

4.3.2. (*E*)-*tert*-Butyl 2-oxo-3-(prop-1-enyl)piperidine-1-carboxylate (*3b*)

Operating as above with **2b** (732.3 mg), β,γ-unsaturated lactam **3b** (588.3 mg, 80%) was isolated as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 5.62 (1H, J=15.3, 6.0, 1.2 Hz, ddd), 5.55 (1H, J=15.3, 5.5 Hz, dq), 3.74 (1H, J=13.3, 6.9, 4.4 Hz, ddd), 3.60 (1H, J=13.3, 6.9, 4.4 Hz, ddd), 3.09 (1H, J=9.5, 6.0, 5.8 Hz, ddd), 2.03–1.67 (4H, m), 1.71 (3H, J=5.5 Hz, d), 1.52 (9H, s). ^{13}C NMR ($CDCl_3$): δ 172.84, 153.16, 128.49, 127.68, 82.78, 47.16, 45.71, 27.94, 27.16, 21.27, 18.02. IR (neat): 2977, 1770, 1714, 1293, 1151 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{21}NO_3$, 239.1521; found, 239.1519.

4.4. Syntheses of γ-butyrolactones

4.4.1. (*R**)-*tert*-Butyl 3-((1*R**,2*R**)-1,2-dihydroxypropyl)-2-oxopyrrolidine-1-carboxylate (anti-*4a*) and (*R**)-*tert*-butyl

3-((1S,2S*)-1,2-dihydroxypropyl)-2-oxopyrrolidine-1-carboxylate (syn-**4a**)*

To a solution of β,γ-unsaturated lactam **3a** (470.9 mg, 2.09 mmol) in CH_2Cl_2 (7 mL) were added a quinuclidine (11.8 mg, 0.10 mmol), NMO (734.4 mg, 6.27 mmol), and 2% aqueous OsO_4 (1.3 mL, 0.10 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. After addition of a saturated aqueous $Na_2S_2O_3$ solution, the organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration to give the crude diol **4a** (564.6 mg), which was used in next reaction without further purification.

4.4.2. (R)-tert-Butyl 3-((1R*,2R*)-1, 2-dihydroxypropyl)-2-oxopiperidine-1-carboxylate (anti-**4b**) and (R*)-tert-butyl 3-((1S*,2S*)-1,2-dihydroxypropyl)-2-oxopiperidine-1-carboxylate (syn-**4b**)*

Operating as above with **3b** (105.0 mg) afforded the crude diol **4b** (120.5 mg), which was used in next reaction without further purification.

4.4.3. (R)-tert-Butyl 3-((1R*,2R*)-4-(tert-butyldimethylsilyloxy)-1,2-dihydroxybutyl)-2-oxopyrrolidine-1-carboxylate (anti-**13**) and (R*)-tert-Butyl 3-((1S*,2S*)-4-(tert-butyldimethylsilyloxy)-1,2-dihydroxybutyl)-2-oxopyrrolidine-1-carboxylate (syn-**13**)*

Operating as above with **12** (236.5 mg), diol *anti*-**13** (154.4 mg, 60%) and *syn*-**13** (57.9 mg, 22%) were isolated both as a colorless needle. *anti*-**13**: mp 91–93 °C. ^{1}H NMR ($CDCl_3$): δ 3.96–3.76 (5H, m), 3.62–3.53 (1H, m), 2.74 (1H, td, *J*=9.5, 3.4 Hz), 2.24–1.99 (2H, m), 1.85–1.67 (2H, m), 1.53 (9H, s), 0.90 (9H, s), 0.09 (6H, s). ^{13}C NMR ($CDCl_3$): δ 174.7, 150.1, 82.7, 72.2, 71.9, 61.3, 46.8, 44.8, 35.2, 27.9, 25.8, 18.6, 18.0, −5.6, −5.6. IR ($CHCl_3$): 3400, 2900, 1720, 1400, 1300 cm^{-1}. Anal. Calcd for $C_{19}H_{37}NO_6Si$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.73; H, 9.48; N, 3.46. *syn*-**13**: mp 96–98 °C. ^{1}H NMR ($CDCl_3$): δ 3.89–3.76 (4H, m), 3.69–3.55 (2H, m), 2.84 (1H, dt, *J*=11.4, 8.6 Hz), 2.21–2.16 (1H, m), 1.94–1.70 (3H, m), 1.54 (9H, s), 0.89 (9H, s), 0.07 (6H, s). ^{13}C NMR ($CDCl_3$): δ 177.5, 149.8, 83.4, 74.4, 70.2, 61.1, 46.0, 44.9, 36.1, 28.0, 25.9, 21.3, 18.2, −5.4, −5.4. IR ($CHCl_3$): 3400, 2900, 1720, 1400, 1300 cm^{-1}; Anal. Calcd for $C_{19}H_{37}NO_6Si$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.78; H, 9.52; N, 3.45.

4.4.4. tert-Butyl 2-((3R,4R*,5R*)-4-hydroxy-5-methyl-2-oxotetrahydrofuran-3-yl)ethylcarbamate (anti-**5a**) and tert-butyl 2-((3R*,4S*,5S*)-4-hydroxy-5-methyl-2-oxotetrahydrofuran-3-yl)ethylcarbamate (syn-**5a**)*

To the crude **4a** (564.6 mg) were added benzene (1.0 mL) and $TsOH\cdot H_2O$ (one crystal) at rt, and the mixture was stirred for 30 min. After addition of a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography (ethyl acetate/hexane=3:1) gave 100.7 mg (19%) of γ-butyrolactone *syn*-**5a** and 275.3 mg (51%) of *anti*-**5a** both as a colorless oil. *syn*-**5a**: ^{1}H NMR ($CDCl_3$): δ 4.98 (1H, br s, −NH), 4.50 (1H, *J*=3.2, 6.7 Hz, dq), 4.45 (1H, *J*=9.8, 3.2 Hz, dd), 3.26–3.22 (2H, m), 2.62 (1H, *J*=9.8, 4.9 Hz, dt), 2.08–1.99 (1H, m), 1.94–1.87 (1H, m), 1.46 (3H, *J*=6.7 Hz, d), 1.43 (9H, s). ^{13}C NMR ($CDCl_3$): δ 177.5, 156.8, 80.0, 79.3, 70.6, 45.5, 38.4, 28.3, 24.4, 13.7. IR (neat): 3384, 2978, 2933, 1768, 1694, 1524, 1174, 1052 cm^{-1}; HRMS (FAB): calcd for $[C_{12}H_{21}NO_5+Na]^+$, 282.1312; found, 282.1312. *anti*-**5a**: ^{1}H NMR ($CDCl_3$): δ 4.69 (1H, *J*=6.7, 6.5 Hz, dq), 4.32 (1H, *J*=6.7, 6.1 Hz, dd), 3.56–3.47 (1H, m), 3.23–3.19 (1H, m), 2.58 (1H, *J*=10.4, 4.9 Hz, dt), 2.03–1.96 (1H, m), 1.71–1.65 (1H, m), 1.44 (9H, s), 1.39 (3H, *J*=6.5 Hz, d). ^{13}C NMR ($CDCl_3$): δ 177.4, 157.3, 80.4, 78.2, 73.3, 44.8, 37.7, 30.3, 28.3, 14. IR (neat): 3378, 2978, 2933, 1768, 1693, 1530, 1169, 1054 cm^{-1}. HRMS (FAB): calcd for $[C_{12}H_{21}NO_5+Na]^+$, 282.1312; found, 282.1314.

4.4.5. tert-Butyl 3-((3R,4R*,5R*)-4-hydroxy-5-methyl-2-oxotetrahydrofuran-3-yl)propylcarbamate (anti-**5b**) and tert-butyl 3-((3R*,4S*,5S*)-4-hydroxy-5-methyl-2-oxotetrahydrofuran-3-yl)propylcarbamate (syn-**5b**)*

Operating as above with crude **4b** (120.5 mg), γ-butyrolactone *anti*-**5b** (59.7 mg, 50%) and *syn*-**5b** (13.1 mg, 11%) were isolated as a colorless oil. *anti*-**5b**: mp 100–101 °C. ^{1}H NMR ($CDCl_3$): δ 4.66 (1H, *J*=6.5, 6.7 Hz, dq), 4.24 (1H, *J*=6.5, 5.5 Hz, dd), 3.23–3.08 (2H, m), 2.60 (1H, *J*=5.5, 7.5 Hz, dt), 1.83–1.58 (4H, m), 1.43 (9H, s), 1.40 (3H, *J*=6.7 Hz, d). ^{13}C NMR ($CDCl_3$): δ 177.7, 156.5, 79.6, 78.3, 73.4, 47.1, 39.6, 28.3, 27.5, 25.1, 14.1. IR (KBr): 3440, 2979, 2938, 1742, 1684, 1522, 1175, 1038 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.09; H, 8.64; N, 5.05. *syn*-**5b**: ^{1}H NMR ($CDCl_3$): δ 4.47 (1H, *J*=3.0, 6.4 Hz, dq), 4.37 (1H, *J*=4.9, 3.0 Hz, dd), 3.27–3.08 (2H, m), 2.56 (1H, *J*=9.8, 4.9 Hz, dt), 1.92–1.64 (4H, m), 1.45 (3H, *J*=6.4 Hz, d), 1.44 (9H, s). ^{13}C NMR ($CDCl_3$): δ 177.5, 156.6, 81.6, 79.0, 71.0, 48.1, 39.9, 28.7, 28.4, 19.9, 13.8. IR (neat): 3376, 2936, 1768, 1681, 1530, 1170 cm^{-1}. HRMS (FAB): calcd for $[C_{13}H_{23}NO_5+Na]^+$, 296.1468; found, 296.1480.

4.4.6. tert-Butyl 3-((3R,4R*,5R*)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-4-hydroxy-2-oxotetrahydrofuran-3-yl)propylcarbamate (anti-**14**)*

Operating as above with *anti*-**13** (1.01 g), γ-butyrolactone *anti*-**14** (908 mg, 90%) was isolated as a colorless needle. Mp 102–103 °C. ^{1}H NMR ($CDCl_3$): δ 5.07 (1H, br s), 4.61 (1H, *J*=7.5, 5.7 Hz, dt), 4.25 (1H, *J*=5.7, 3.5 Hz, dd), 3.90–3.82 (1H, m), 3.72 (1H, *J*=10.1, 2.9 Hz, td), 3.43–3.20 (2H, m), 2.60 (1H, *J*=8.7, 7.2, 3.5 Hz, ddd), 2.24–2.12 (1H, m), 2.07–1.97 (1H, m), 1.92–1.78 (2H, m), 1.44 (9H, s), 0.91 (9H, s), 0.10 (6H, s). ^{13}C NMR ($CDCl_3$): δ 177.6, 156.5, 81.0, 79.8, 73.2, 59.3, 46.4, 38.1, 31.1, 29.4, 28.4, 25.9, 18.8, −5.5, −5.6. IR (KBr): 3600, 3400, 3000, 1760, 1680 cm^{-1}. Anal. Calcd for $C_{19}H_{37}NO_6Si$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.64; H, 9.42; N 3.48.

4.4.7. tert-Butyl 3-((3R,4S*,5S*)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-4-hydroxy-2-oxotetrahydrofuran-3-yl)propylcarbamate (syn-**14**)*

Operating as above with *syn*-**13** (323.4 mg), γ-butyrolactone *syn*-**14** (290.8 mg, 90%) was isolated as a colorless

needle. Mp 107–109 °C. ^{1}H NMR ($CDCl_3$): δ 4.40–4.37 (2H, m), 3.88 (1H, J=10.5, 4.1 Hz, dt), 3.78–3.64 (1H, m), 3.33–3.21 (2H, m), 2.69–2.63 (1H, m), 2.17–2.11 (2H, m), 2.01–1.92 (2H, m), 1.44 (9H, s), 0.91 (9H, s), 0.11 (6H, s). ^{13}C NMR ($CDCl_3$): δ 177.32, 156.40, 81.86, 79.46, 69.86, 59.30, 44.77, 38.93, 31.06, 28.41, 25.85, 24.12, 18.21, −5.53, −5.62. IR (KBr): 3600, 3400, 3000, 1720 cm^{-1}. Anal. Calcd for $C_{19}H_{37}NO_6Si$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.55; H, 9.51; N, 3.44.

4.5. Syntheses of chiral trisubstituted γ-butyrolactones

4.5.1. (R)-tert-Butyl 3-((1S,2S)-4-(tert-butyldiphenylsilyloxy)-1-hydroxy-2-(triethylsilyloxy)butyl)-2-oxopyrrolidine-1-carboxylate (**16a**) and (S)-tert-butyl 3-((1S,2S)-4-(tert-butyldiphenylsilyloxy)-1-hydroxy-2-(triethylsilyloxy)butyl)-2-oxopyrrolidine-1-carboxylate (**17a**)

To a solution of **1a** (106.7 mg, 0.58 mmol) in THF (4 mL) was added a LiHMDS (0.63 mL, 1.0 M in THF) at −78 °C. To the mixture was added a solution of **15**[13] (182.7 mg, 0.40 mmol) in THF (2 mL), and the reaction mixture was stirred for 2 h at −78 °C. After addition of a saturated aqueous NH_4Cl solution, the organic layer was extracted with ethyl acetate, and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo after filtration. Purification by flash chromatography (ethyl acetate/hexane=1:4) gave 53.0 mg (21%) of **16a** as a colorless oil and 121.5 mg (47%) of **17a** as a colorless oil. Compound **16a**: $[\alpha]_D^{24}$ −12.4 (c 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.66–7.64 (4H, m), 7.43–7.35 (6H, m), 4.26 (1H, J=1.8 Hz, d), 4.02 (1H, J=6.3, 3.3 Hz, td), 3.80–3.71 (4H, m), 3.54 (1H, J=10.2, 7.1 Hz, td), 2.72 (1H, J=11.0, 9.2 Hz, td), 2.09–1.96 (2H, m), 1.78–1.72 (2H, m), 1.54 (9H, s), 1.05 (9H, s), 0.92 (9H, J=7.7 Hz, t), 0.58 (6H, J=7.7 Hz, q). ^{13}C NMR ($CDCl_3$): δ 177.2, 149.9, 135.6, 133.7, 129.6, 127.6, 83.2, 73.9, 70.2, 60.6, 44.9, 44.6, 35.4, 28.0, 26.8, 21.5, 19.1, 6.9, 5.1. IR (neat): 3472, 3071, 2955, 1779, 1718 cm^{-1}; HRMS (FAB): calcd for $[C_{35}H_{55}NO_6Si_2+Na]^+$, 664.3460; found, 664.3458. Compound **17a**: $[\alpha]_D^{24}$ −3.5 (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.67–7.65 (4H, m), 7.45–7.37 (6H, m), 4.21 (1H, J=4.3, 6.7 Hz, td), 3.89–3.70 (4H, m), 3.56 (1H, J=9.3, 7.5 Hz, td), 2.73 (1H, J=9.8, 6.7 Hz, td), 2.12–2.06 (1H, m), 1.94–1.61 (3H, m), 1.53 (5H, s), 1.05 (9H, s), 0.91 (9H, J=7.6 Hz, t), 0.60 (4H, J=7.6 Hz, q). ^{13}C NMR ($CDCl_3$): δ 176.0, 150.0, 135.5, 133.3, 129.7, 127.7, 82.9, 76.3, 70.5, 60.2, 44.9, 44.4, 35.4, 28.0, 26.8, 22.1, 19.0, 6.9, 5.0. IR (neat): 3482, 3071, 2956, 1779, 1720 cm^{-1}. HRMS (FAB): calcd for $[C_{35}H_{55}NO_6Si_2+Na]^+$, 664.3460; found, 664.3463.

4.5.2. tert-Butyl 2-((3R,4S,5S)-5-(2-(tert-butyldiphenylsilyloxy)ethyl)-4-hydroxy-2-oxotetrahydrofuran-3-yl)ethylcarbamate (**20a**)

To **16a** (453.9 mg, 0.71 mmol) were added THF (5.0 mL), H_2O (0.3 mL), and $TsOH\cdot H_2O$ (94.3 mg) at rt, and the reaction mixture was stirred for 3 h at rt. After addition of a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with ethyl acetate, and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration. Purification by flash chromatography (ethyl acetate/hexane=1:1) gave 352.4 mg (90%) of γ-butyrolactone **20a** as a oil. $[\alpha]_D^{24}$ −22.9 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.67–7.63 (4H, m), 7.47–7.40 (6H, m), 4.88 (1H, br s, −NH), 4.53–4.51 (1H, m), 4.48–4.44 (1H, m), 3.86 (1H, J=10.6, 4.4 Hz, dt), 3.75 (1H, J=10.2, 2.6 Hz, td), 3.34–3.22 (2H, m), 2.66 (1H, J=9.6, 5.0 Hz, dt), 2.22–2.08 (2H, m), 2.05–1.91 (2H, m), 1.44 (9H, s), 1.06 (9H, s). ^{13}C NMR ($CDCl_3$): δ 177.2, 156.5, 135.5, 132.5, 130.0, 127.9, 81.3, 79.6, 70.0, 60.2, 44.8, 38.7, 31.0, 28.4, 26.8, 24.3, 19.0. IR (neat): 3408, 2932, 1733, 1686, 1521, 1172, 1111 cm^{-1}. HRMS (FAB): calcd for $[C_{29}H_{41}NO_6Si+Na]^+$, 550.2601; found, 550.2604.

4.5.3. tert-Butyl 2-((3S,4S,5S)-5-(2-(tert-butyldiphenylsilyloxy)ethyl)-4-hydroxy-2-oxotetrahydrofuran-3-yl)ethylcarbamate (**21a**)

Operating as above with **17a** (1.00 g, 1.56 mmol), γ-butyrolactone **21a** (691.5 mg, 84%) was isolated as a colorless oil. $[\alpha]_D^{24}$ −17.3 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.67–7.65 (4H, m), 7.44–7.37 (6H, m), 5.03 (1H, J=5.8 Hz, t, −NH), 4.62 (1H, J=6.3, 0.8 Hz, td), 4.39–4.36 (1H, m), 3.86–3.73 (2H, m), 3.28–3.16 (2H, m), 2.58 (1H, J=10.4, 4.9 Hz, dt), 2.00–1.83 (3H, m), 1.78–1.71 (1H, m), 1.42 (9H, s), 1.05 (9H, s). ^{13}C NMR ($CDCl_3$): δ 177.3, 156.8, 135.5, 133.1, 129.8, 127.7, 83.6, 79.9, 72.4, 59.8, 42.0, 38.5, 35.3, 28.3, 26.8, 24.5, 19.1. IR (neat): 3410, 2932, 1733, 1695, 1509, 1165, 1111 cm^{-1}. HRMS (FAB): calcd for $[C_{29}H_{41}NO_6Si+Na]^+$, 550.2601; found, 550.2597.

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research (C) (No. 18590023) from the Japan Society for the Promotion of Science and Kyoto-Advanced Nanotechnology Network. We also thank Mr. Asanoma for elemental analysis and Ms. Nishikawa for measurement of HRMS.

References and notes

1. Synthesis of γ-butyrolactones, see: (a) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745; (b) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211; (c) Hannesian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276; (d) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509; (e) Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1981; (f) Mandal, A. K.; Mahajan, S. W. *Synthesis* **1991**, 311; (g) Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 5226; (h) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848; (i) Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J. *Synlett* **1996**, 343; (j) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482; (k) Fernandez, A.-M.; Plaquevent, J.-C.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007; (l) Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 7097; (m) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680; (n) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071; (o) Tobisu, M.; Chatani, N.; Asaumi,

T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663; (p) Martín, T.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 2503; (q) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604; (r) Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362; (s) Lin, Y.-L.; Cheng, M.-H.; Chen, W.-C.; Peng, S.-M.; Wang, S.-L.; Kuo, H.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 1781; (t) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675.

2. Trisubstituted γ-butyrolactone including 2,4-dialkyl-3-hydroxy butanolide, see: (a) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201; (b) Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocínio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002; (c) Chenevert, R.; Rose, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 2827; (d) Cho, K. W.; Lee, H.-S.; Rho, J.-R.; Kim, T. S.; Mo, S. J.; Shin, J. *J. Nat. Prod.* **2001**, *64*, 664; (e) Pearson, A. J.; Mesaros, E. F. *Org. Lett.* **2002**, *4*, 2001; (f) Pinto, A. C.; Freitas, C. B. L.; Dias, A. G.; Pereira, V. L. P.; Tinant, B.; Declercq, J.-P.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2002**, *13*, 1025; (g) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4097; (h) Amador, M.; Ariza, X.; Garcia, G.; Ortiz, J. *J. Org. Chem.* **2004**, *69*, 8172; (i) Dias, L. C.; de Castro, I. B. D.; Steil, L. J.; Augusto, T. *Tetrahedron Lett.* **2006**, *47*, 213; (j) Ghosh, M. *Tetrahedron* **2007**, *63*, 11710.

3. (a) Yonehara, H.; Takeuchi, S. *J. Antibiot.* **1958**, *11*, 254; (b) Kinoshita, M.; Aburaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373; (c) Krishna, P. R.; Reddy, V. V. R.; Sharma, G. V. M. *Synthesis* **2004**, *12*, 2107.

4. Jullian, V.; Bonduelle, C.; Valentin, A.; Acebey, L.; Duigou, A.-G.; Prévost, M.-F.; Sauvain, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 345.

5. Li, W.; Nihira, T.; Sakuda, S.; Nishida, T.; Yamada, Y. *J. Ferment. Bioeng.* **1992**, *74*, 214.

6. (a) Nakai, R.; Ogawa, H.; Asai, A.; Ando, K.; Agatsuma, T.; Matsumiya, S.; Akinaga, S.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 294; (b) Agatsuma, T.; Akama, T.; Nara, S.; Matsumiya, S.; Nakai, R.; Ogawa, H.; Otaki, S.; Ikeda, S.; Saitoh, Y.; Kanda, Y. *Org. Lett.* **2002**, *4*, 4387.

7. Giovannini, A.; Savoia, D.; Achille, U.-R. *J. Org. Chem.* **1989**, *54*, 228.

8. Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1995**, *60*, 5634.

9. (a) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, *13*, 4249; (b) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433; (c) Piers, E.; Gavai, A. V. *J. Org. Chem.* **1990**, *55*, 2374; (d) Alexander, P. A.; Marsden, S. P.; Munoz Subtil, D. M.; Reader, J. C. *Org. Lett.* **2005**, *7*, 5433.

10. (a) Dinsmore, A.; Doyle, P. M.; Steger, M.; Young, D. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 613; (b) Coe, D.; Dresdate, M.; Philps, O.; West, R.; Young, D. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2459.

11. Lee, A. H. F.; Chan, A. S. C.; Li, T. *Tetrahedron* **2003**, *58*, 833.

12. VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864.

13. Hayashi, Y.; Yamaguchi, J.; Shoji, M. *Tetrahedron* **2002**, *58*, 9839.