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Stereoselective Synthesis of Novel *anti*-MRSA Tricyclic Carbapenems (Trinems)

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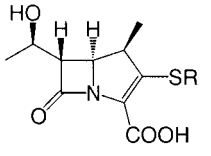
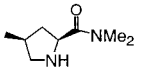
Abstract—(4*S*)-Hydroxymethyltrinem **3** was prepared via stereoselective aldol-type reaction with optically pure (*R*)-2-*t*-butyldimethylsilyloxymethylcyclohexanone ((*R*)-**16**). (4*S*)-Hydroxymethyltrinem **3** was converted into various kinds of trinem derivatives with *anti*-MRSA activity by using the Mitsunobu reaction.

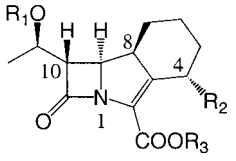
Introduction

Since the discovery of penicillin, some new classes of β-lactam antibiotics have been found from natural sources, for example, cephalosporines, cephamycins, monobactams, and carbapenems. On the other hand, different kinds of synthetic antibiotics, for example, carbacephems, oxacephems, penems, and 1β-methyl carbapenems represented by meropenem (**1**) have been developed in the last three decades.[1] Generally, β-lactam antibiotics have a wide-range of antibacterial activity for both Gram-positive and Gram-negative bacteria. However, in recent years the appearance of resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) has become a serious problem in clinical practice. The mechanism of resistance of MRSA is the production of altered Penicillin Binding Proteins PBP2a (PBP2′) which has poor affinity for any classical β-lactams.

Now, many scientists in the world are making efforts to develop effective drugs against these resistant strains.



1 R = 



2 R_1 = H R_2 = OMe R_3 = CH_2OCO_2– 

3 R_1 = TBS R_2 = CH_2OH R_3 = All

Tricyclic carbapenem (trinem)[2,3] is a novel class of synthetic antibiotic, which was recently reported by the Glaxo group. Sanfetrinem cilexetil (**2**) developed by the same group is under clinical trials as an oral trinem. We designed novel trinem derivatives to explore their possibility as anti-MRSA agents.

Initially, we focused our attention on a versatile intermediate for trinem synthesis. As an intermediate, we selected (4*S*)-hydroxymethyltrinem **3**. The best stereochemistry for combining good antimicrobial activity and dehydropeptidase-I (DHP-I) stability in the case of sanfetrinem is when the configuration of the cyclohexyl ring is (4*S*, 8*S*).[2] Therefore, we applied the same configuration to our key intermediate in our trinem synthesis. In this paper, we describe the stereoselective synthesis of our trinem derivatives.

Result and Discussion

The biological activity of trinems is influenced by the stereochemical arrangement of the cyclohexyl ring moiety. We initially studied aldol type condensations of 4-acetoxyazetidinone derivative **5** and silyl enol ether **4**.[3,4]

It is well known that the configuration at the C-4 position on the azetidinone in the carbapenem synthesis is generally down for hydrogen atom as shown by cyclohexyl

Keywords: trinems; stereoselective synthesis; Mitsunobu reaction; MRSA.
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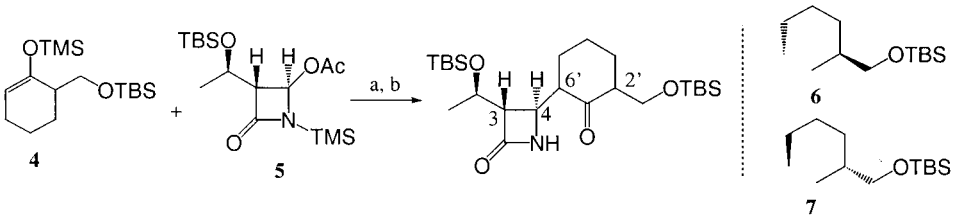


Scheme 1. Reagents: (a) $ZnCl_2$ 2 equiv. or TMSOTf 0.1 equiv./CH_2Cl_2, rt; (b) SiO_2/MeOH, 2 h rt.

Table 1. Aldol type condensation of silyl enol ether **4** and acetoxyazetidinone **5**

Entry	**4**:**5**	L.A.	Yield (%)[a]	**6**:**7**
1	1:1.2	$ZnCl_2$	86[b]	1.1:1
2	2:1	$ZnCl_2$	70[c]	2.7:1
3	2:1	TMSOTf	35[c]	1.6:1

[a] Isolated yield.
[b] Yield based on **4**.
[c] Yield based on **5**.

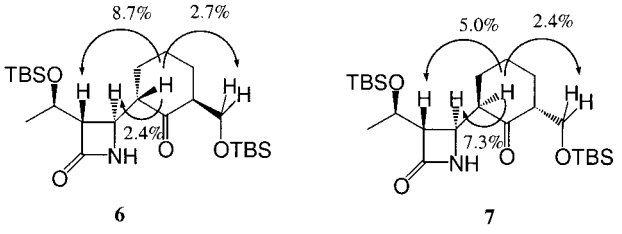


Figure 1. Determination of stereochemistry for **6** and **7** by NOE.

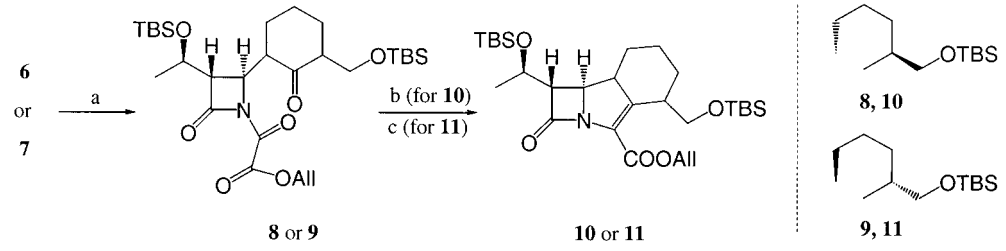
azetidinones **6** and **7** from the steric bulkiness of the protected hydroxy group at the C-3 position.[5] However, it is not as easy to construct the desired stereochemistry at the C-6′ position (corresponding to β-methyl in 1β-methylcarbapenem) on the cyclohexyl ring. Surprisingly, the reaction of 4-acetoxyazetidinone derivative **5** with **4** resulted in a controlled stereochemistry at C-2′ and C-6′ positions on the cyclohexanone ring[3,6] and provided predominantly two diastereomers **6** and **7** among the four possible diastereomers by the steric bulkiness of *t*-butyldimethylsilyloxymethyl group (Scheme 1). The ratio of **6** and **7** in this reaction depended on the ratio of **5** to **4** and kinds of Lewis acids (Table 1).

In comparison with entries 1 and 2, the rate of production of undesired isomer **6** was obviously faster than that of the desired isomer **7**. Moreover in comparison with entries 2 and 3, trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave better results for the ratio of **6** and **7** than $ZnCl_2$, but the yield was lower than $ZnCl_2$. From the results of Table 1, the reaction of 4-acetoxy azetidinone **5** with optically pure **4** is of interest in the advantageous preparation of the desired isomer **7**. The absolute configurations for these compounds were determined for **6** and **7** (at C-2′ and C-6′) by NOE experiments[7] (Fig. 1).

The compounds **6** and **7** were treated with allyl oxalyl chloride to give oxalates **8** and **9**, respectively. Cyclization[8] of **8** and **9** with diethyl ethylphosphonite[9] afforded protected trinems **10** and **11**, respectively (Scheme 2). The stereochemistry of **10** and **11** was also determined by NOE experiments (Fig. 2).

In order to obtain a large number of trinem derivatives, the efficient synthesis of the key intermediate **7** was studied. For this purpose, the synthesis of an optically pure derivative (*R*)-**16** or (*R*)-**4** was investigated (Scheme 3). The reduction of ethyl 2-cyclohexanonecarboxylate **12** with $NaBH_4$ gave *cis*- and *trans*-mixture of hexanol **13** (*cis*/*trans*=3:1). An optical resolution[10] of major isomer *cis*-**13** was accomplished with enantioselective acylation of the immobilized lipase (TOYOZYME®, LIP (TOYOBO Co. Ltd))[11] to afford acetate (1*S*, 2*R*)-**14**. Reduction of (1*S*, 2*R*)-**14** with $LiAlH_4$ followed by selective protection of the primary hydroxy group with TBSCl afforded silyl ether (1*R*, 2*R*)-**15**. On the other hand, (1*R*, 2*S*)-**13** was derived from **12** by enantioselective reduction with baker's yeast[12] under the same condition to provide (1*S*, 2*S*)-**15**. Both (1*R*, 2*R*)-**15** and (1*S*, 2*S*)-**15** were converted to (*S*)-MTPA ester **17a** and **17b** by acylation with (*R*)-MTPA chloride to determine the optical purity and confirm the absolute configurations of (1*R*, 2*R*)-**15** and (1*S*, 2*S*)-**15** by NMR In the comparison of the NMR spectra of **17a** and **17b**, the optical purity of (1*R*, 2*R*)-**15** and (1*S*, 2*S*)-**15** were more than 98 and 86% ee, respectively.

Further, the absolute configuration was confirmed by



Scheme 2. Reagent: allyl oxalylchloride, Et_3N, 0°C; (b) $EtP(OEt)_2$, xylene, reflux, 4 h, 76% in two steps; (c) $EtP(OEt)_2$, xylene, reflux, 2 h, 84% in two steps.

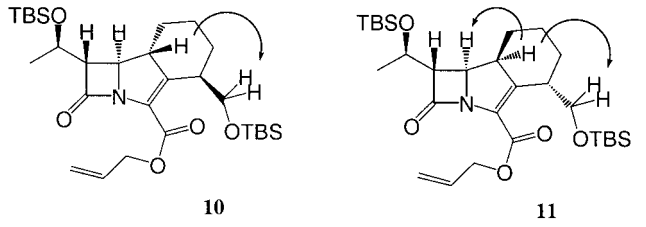
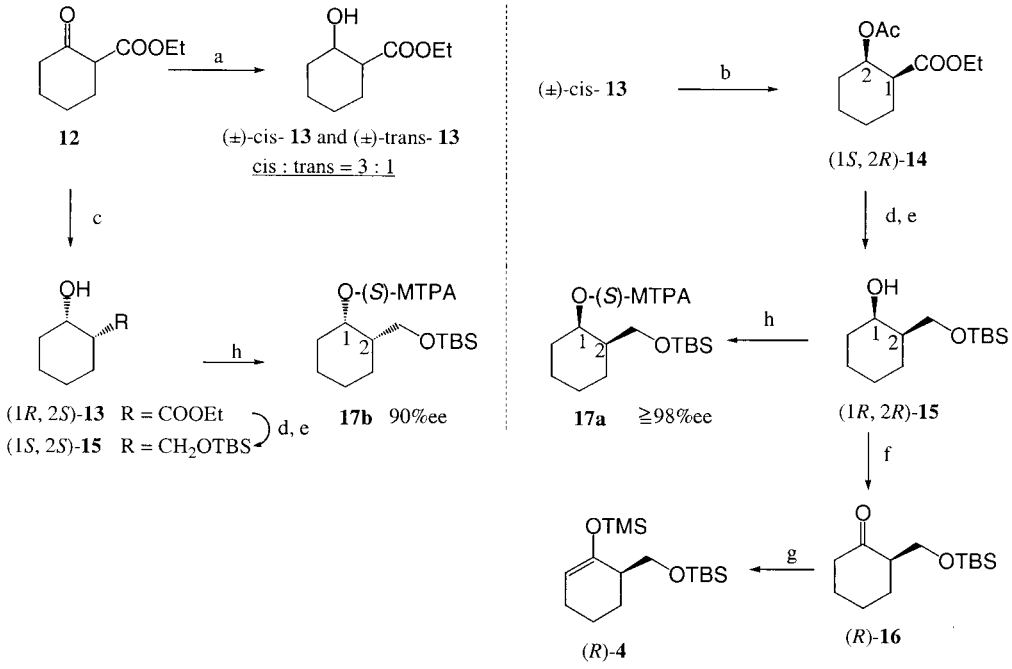
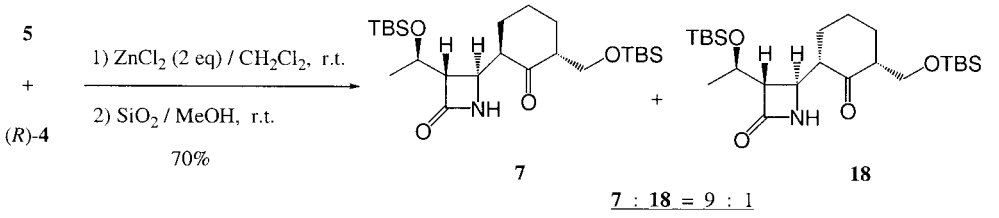


Figure 2. Determination of stereochemistry for **10** and **11** by NOE.

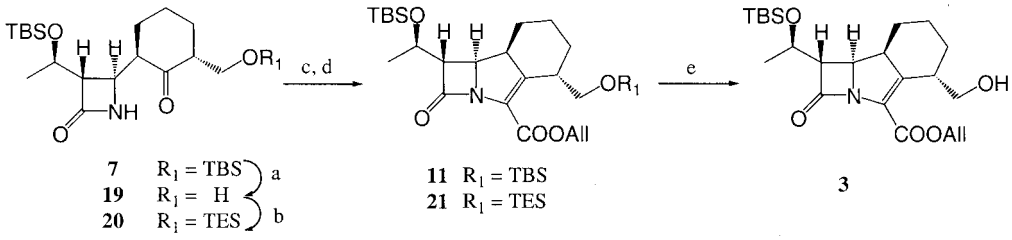
Kusumi's method.[13] The hydroxy group of (1*R*, 2*R*)-**15** was oxidized with pyridinium dichromate (PDC) to furnish (*R*)-**16**[14,15]; this was followed by an addition of lithium bis(trimethylsilyl)amide and TMSCl to lead to silyl enol ether (*R*)-**4**. As expected, the reaction of **5** with (*R*)-**4** gave predominantly the desired product **7** (Scheme 4). Though a very small amount of another isomer, which was also expected, the undesired diastereomer **18**, was observed in the TLC, the ratio of **7** and **18** was determinated by NMR analysis of the crude pruducts as the ratio of these compounds could not be determined by HPLC nor isolated by column chromatograpy.



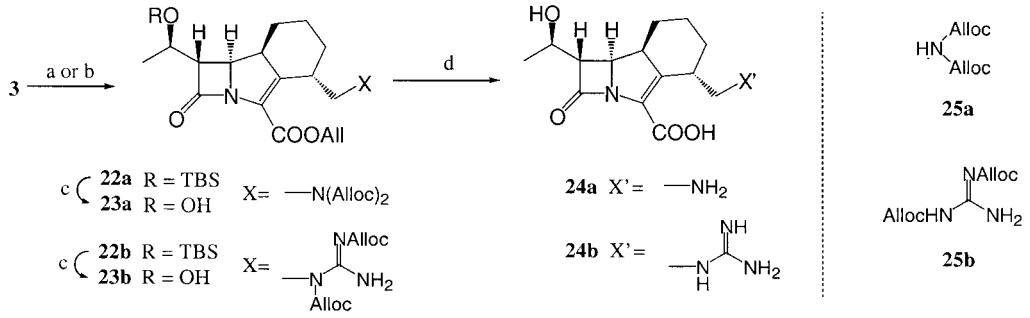
Scheme 3. Reagents: (a) $NaBH_4$, MeOH, 69%; (b) immobilized lipase, vinyl acetate; THF=4:1, 37°C, 33%; (c) baker's yeast, 78%; (d) LAH/THF; (e) TBSCl, Et_3N, DMAP/CH_2Cl_2, (1*R*, 2*R*)-**15**:81% from (1*S*, 2*R*)-**14**, (1*R*, 2)-**15**:81% from (1*R*, 2*R*)-**13**; (f) PDC/CH_2Cl_2, rt, 88%; (g) LHMDS, TNSCl/THF, −78°C; (h) (*R*)-MTPA-Cl, 4-DMAP/CH_2–Cl_2, quant.



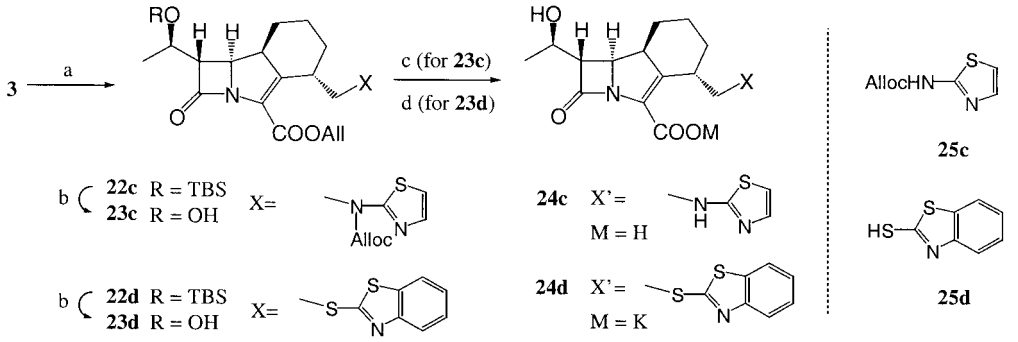
Scheme 4.



Scheme 5. Reagents: (a) HF–NH_4F, DMF, rt, 3 days, 74%; (b) TESCI, imidazole, 98%; (c) allyl oxalychloride, Et_3N, 0°C; (d) $EtP(OEt)_2$, xylene, reflux, 74% in two steps; (e) HF–NH_4F, DMF, rt, 3 days, 48% from **11** 91% from **21**.



Scheme 6. Reagents: (a) **25a**, diethyl azodicarboxylate (DEAD) 2.5 equiv., PPh_3 2.5 equiv./THF, rt, 76%; (b) **25b**, diisopropyl azodicarboxylate (DIAD) 1.5 equiv., PPh_3 1.5 equiv./toluene, rt, 70%; (c) TBAF, AcOH/THF, rt, **23a**: 66%, **23b**: 56%; (d) $PdCl_2(PPh_3)_2$ 2 mol%, *n*-Bu_3SnH 5 equiv./CH_2Cl_2–H_2O, 0°C, **24a**: 74%, **24b**: 52%.



Scheme 7. Reagents: (a) **25c** or **25d**, diethyl azodicarboxylate (DEAD) 3.0 equiv., PPh_3 3.0 equiv./toluene; (b) TBAF, AcOH/THF, rt, **23c**: 50% from **3**, **23d**: 69% from **3**; (c) $PdCl_2(PPh_3)_2$ 2 mol%, *n*-Bu_3SnH 5 equiv./CH_2–Cl_2–H_2O, 0°C, 52%; (d) $Pd(PPh_3)_4$ 2 mol%, potassium 2-ethylhexanoate/EtOAc–CH_2Cl_2, rt, 52%.

After the replacement of the TBS group of **7** to a triethylsilyl (TES) group via deprotected compound **19**, TES ether **20** was converted to trinem **21** in a similar procedure as shown in Scheme 5. Deprotection of **21** with HF–NH_4F[16] gave hydroxymethyltrinem **3**. Alternatively, the selective deprotection of TBS group of **11** with HF–NH_4F furnished **3** in 48% yield. The hydroxymethyltrinem **3** is a versatile key intermediate in the trinem synthesis because the hydroxy group of **3** can be replaced with many kinds of substituent groups.

The synthesis of trinem derivatives using **3** was carried out. Substituent groups with a nitrogen atom, such as amino and guanidino groups, and a heterocyclic moiety were introduced by the Mitsunobu reaction (Schemes 6 and 7). As shown in Schemes 6 and 7, various substituent groups **25a**,[17a] **25b**,[17b] **25c**,[17a,c] **25d**,[17d] which have protons with suitable acidity, could be introduced to **3** under mild conditions to afford the corresponding derivatives **22a–d**. Deprotection of the TBS group with tetrabutylammonium fluoride (TBAF) gave corresponding desilylated compounds **23a–d**. Finally, deprotection of the allyl (All) and allyloxycarbonyl (Alloc) groups was performed by catalytic tetrakis(triphenylphosphine)palladium and potassium 2-ethylhexanoate or catalytic bis(triphenylphosphine)palladium chloride and tributyltin hydride to furnish trinems **24a–d**.

Table 2. Antibacterial activity (MIC, μg/ml) (MIC was determined by agar diltution method with an inoculum of 10^7 cfu/ml) of trinem derivatives and vancomycin (VCM)

	24a	**24b**	**24c**	**24d**	VCM
Staphylococcus aureus 209P	0.056	<0.01	0.02	<0.012	0.2
S. aureus 56R	0.2	0.05	0.05	0.025	0.78
S. aureus 535 (MRSA)	25	6.2	3.1	1.56	1.56
Enterococcus faecalis 681	6.2	3.1	1.5	0.78	0.78
Escherichia coli NIHJ	0.1	0.1	0.8	12.5	>100
Klebsiella pneumoniae 806	0.1	0.2	0.8	25	>100
Serratia marcescens 1184	0.2	0.2	1.5	12.5	>100
Pseudomonas aeruginosa 1001	6.2	50	>100	>100	>100

The antibacterial activity of trinem derivatives **24a–d** was compared with that of vancomycin as shown in Table 2. The MIC values of **24a** and **24b** indicated that these compounds with basic amine moiety had good antibacterial activities against both Gram positive and Gram negative bacteria. Interestingly, the introduction of an aromatic moiety (**24c** and **24d**) remarkably increased the activity against Gram positive bacteria including MRSA. In particular, **24d** indicated as high activity against MRSA as vancomycin, but **24c** showed therapeutically valuable activity against Gram negative bacteria so that it could be further studied as a broad spectrum anti-MRSA agent.

In summary, the stereoselective synthesis of a versatile key intermediate for trinem derivatives was accomplished and various kinds of trinems were prepared by the Mitsunobu reaction. It was revealed that **24c** and **24d** with thiazole moiety had efficient anti-MRSA activities as potent as vancomycin.

Experimental

General

IR spectra were recorded on a Jasco FT-IR 8300 or 8900 spectrometer. NMR spectra were recorded on JEOL EX 270 (270 MHz) or GSX-400 (400 MHz) spectrometer using tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)propionate-d_4 (TSP-d_4) as an internal standard. Mass spectra were recorded on JEOL HX-100, SX-102A or AX-505H mass spectrometer. The melting point (mp) was determined using a Yanagimoto micro-melting point apparatus and was not corrected. Optical rotations were obtained with a Jasco DIP-370 polarimeter. Column chromatography was carried out on Silica gel 60 (230–400 mesh, Art. 9385, Merck) or Cosmosil 75C_{18} PREP (75 μm, Nacalai Tesque, Inc.).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(2′*S*, 6′*S*)-2′-(*t*-butyldimethylsilyloxymethyl)cyclohexanone-6′-yl]azetidin-2-one (6) and (3*S*, 4*R*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(2′*R*, 6′*R*)-2′-(*t*-butyldimethylsilyloxymethyl) cyclohexanone-6′-yl]azetidin-2-one (7). *(Typical procedure with $ZnCl_2$)* To a solution of **4** (3.89 g, 12.4 mmol) and azetidinone **5** (5.34 g, 14.8 mmol) in CH_2Cl_2 (50 mL) was added zinc chloride (3.37 g, 24.7 mmol) at room temperature. The mixture was stirred for 3 h at the same temperature. After the addition of saturated aqueous $NaHCO_3$ (50 mL) to the mixture, the insoluble material formed was removed by filtration. The filtrate was extracted with EtOAc (200 mL×3) and the organic layer was washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo and then the residue was diluted with MeOH (50 mL). An adequate amount of silica gel was added to the solution and then the mixture was stirred for 2 h at room temperature. The silica gel was removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 5:2) to afford **6** (2.59 g, 45%) and **7** (2.39 g, 41%) as crystals. **6**: $[\alpha]_D^{25}=-59.2°$ (*c* 1.23, $CHCl_3$). Mp 134–136°C. IR (KBr) cm^{-1} 3080, 2930, 1761, 1716, 1257, 836. ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 0.88 (9H, s) 1.23 (3H, d, *J*=6.1 Hz), 1.35–2.17 (6H, m), 2.44–2.53 (1H, m), 2.58–2.65 (1H, m), 2.68–2.73 (1H, m), 3.62 (1H, dd, *J*=9.7, 2.1 Hz), 3.77 (1H, dd, *J*=10.0, 6.8 Hz), 3.86 (1H, dd, *J*=10.0, 7.2 Hz), 4.16 (1H, dq, *J*=6.0, 5.9 Hz), 6.02 (1H, br s). MS (FAB) *m*/*z*: 470 $(M+H)^+$. Anal. Calcd for $C_{24}H_{47}NO_4Si_2$: C, 61.36, H, 10.08, N, 2.98. Found: C, 61.31, H, 9.96, N, 2.97. **7**: $[\alpha]_D^{25}=+65.4°$ (*c* 0.895, $CHCl_3$). Mp 128–129°C. IR (KBr) cm^{-1} 3080, 2930, 1761, 1716, 1257, 836. ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 0.89 (9H, s) 1.17 (3H, d, *J*=6.1 Hz), 1.66–2.09 (6H, m), 2.57–2.62 (1H, m), 2.63–2.75 (1H, m), 2.87 (1H, dd, *J*=4.3, 2.4 Hz), 3.74 (1H, dd, *J*=10.2, 7.0 Hz), 3.90 (1H, dd, *J*=10.2, 7.0 Hz), 4.09 (1H, dd, *J*=5.4, 2.4 Hz), 4.21 (1H, dq, *J*=6.1, 4.3 Hz), 5.79 (1H, br s). MS (FAB) *m*/*z*: 470 $(M+H)^+$. Anal. Calcd for $C_{24}H_{47}NO_4Si_2$: C, 61.36, H, 10.08, N, 2.98. Found: C, 61.20, H, 9.90, N, 2.96.

Allyl (4*R*,8*R*,9*R*,10*S*)-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-*t*-butyldimethylsilyloxymethyl-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10) via 8. To a solution of **6** (800 mg, 1.70 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (344 mg, 3.40 mmol) and allyl oxalyl chloride (379 mg, 2.55 mmol) at 0°C. The mixture was stirred for 2 h at the same temperature. After adding 2-propanol (51 mg, 0.85 mmol) to the mixture, the solution was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford crude **8** (957 mg). A solution of crude **8** and diethyl ethylphosphonite (735 mg, 4.90 mmol) in xylene was refluxed for 4 h and the mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to afford **10** (682 mg, 76%) as an oil. IR (liquid film) cm^{-1} 2932, 2859, 1772, 1715, 1100. ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.07 (6H, s), 0.87 (9H, s), 0.88 (9H, s) 1.26 (3H, d, *J*=6.2 Hz), 1.27–1.70 (5H, m), 1.98–2.19 (2H, m), 2.89–3.04 (1H, m), 3.02 (1H, dd, *J*=4.6, 2.5 Hz), 3.51–3.72 (3H, m) 4.14 (1H, dq, *J*=6.9, 6.3 Hz), 4.63–4.82 (2H, m), 5.24 (1H, d, *J*=10.3 Hz), 5.43 (1H, d, *J*=17.2 Hz), 5.87–6.05 (1H, m). MS (FAB) *m*/*z*: 550 $(M+H)^+$. Anal. Calcd for $C_{29}H_{51}NO_5Si_2$: C, 63.34, H, 9.35, N, 2.55. Found: C, 63.90, H, 9.30, N, 2.45.

Allyl (4*S*,8*S*,9*R*,10*S*)-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)-ethyl]-4-*t*-butyldimethylsilyloxymethyl-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11) via 9. To a solution of **7** (6.0 g, 12.8 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (3.24 g, 32.0 mmol) and allyl oxalylchloride (3.80 g, 25.6 mmol) at 0°C. The mixture was stirred for 2 h at the same temperature. After adding 2-propanol (768 mg, 12.8 mmol) to the mixture, the solution was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford crude **9** (7.73 g). A solution of crude **9** and diethyl ethylphosphonite (5.77 g, 38.4 mmol) in xylene (120 mL) was refluxed for 2 h and the mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford **11** (5.92 g, 84%) as an oil. $[\alpha]_D^{25}=+96.0°$ (*c* 1.32, $CHCl_3$). IR (liquid film) cm^{-1} 2932, 2859, 1771, 1715, 1259, 1102. ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.07 (6H, s), 0.87 (9H, s), 0.88 (9H, s) 1.24 (3H, d, *J*=6.1 Hz), 1.21–2.04 (6H, m), 2.94–3.08 (1H, m), 3.17 (1H, dd, *J*=6.2, 3.2 Hz), 3.67–3.85 (3H, m) 4.08 (1H, dd, *J*=10.5, 3.2 Hz), 4.19 (1H, dq, *J*=6.3, 6.0 Hz), 4.67 (1H, dd, *J*=13.7, 5.5 Hz), 4.78 (1H, dd, *J*=10.4, 5.5 Hz), 5.24 (1H, d, *J*=10.3 Hz), 5.42 (1H, d, *J*=17.2 Hz), 5.89–6.06 (1H, m). MS (FAB) *m*/*z*: 550 $(M+H)^+$. Anal. Calcd for $C_{29}H_{51}NO_5Si_2$: C, 63.34, H, 9.35, N, 2.55. Found: C, 63.18, H, 9.12, N, 2.44.

Ethyl 2-hydroxycyclohexanecarboxylate (13). To a solution of ethyl 2-cyclohexanonecarboxylate (**12**) (10.2 g, 59.9 mmol) in methanol (200 mL) was added sodium borohydride (2.72 g, 71.9 mmol) at −40°C. The mixture was stirred for 3 h at the same temperature. After the mixture was neutralized with acetic acid, the solution was evaporated in vacuo. The residue was extracted with EtOAc (200 mL×4). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 3:2) to afford *cis*-**13** (5.47 g, 53%) and *trans*-**13** (1.59 g, 15%) as an oil. *cis*-**13**: IR (liquid film)

cm^{-1} 3513, 2937, 1713, 1185, 1040, 976. ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, J=7.0 Hz), 1.24–1.98 (8H, m), 2.48 (1H, ddd, J=11.3, 3.5, 2.8 Hz), 3.20 (1H, br d, J=2.6 Hz), 4.11–4.18 (1H, m), 4.17 (2H, q, J=7.0 Hz). MS (FAB) m/z: 172 ($M^{\cdot+}$). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77, H, 9.37. Found: C, 62.54, H, 9.20. *trans*-**13**: IR (liquid film) cm^{-1} 3448, 2936, 1733, 1180. ^1H NMR (270 MHz, $CDCl_3$) δ 1.14–1.45 (4H, m), 1.28 (3H, t, J=7.2 Hz), 1.68–1.94 (2H, m), 1.95–2.09 (2H, m), 2.25 (1H, ddd, J=12.1, 9.8, 3.7 Hz), 2.83 (1H, br s), 3.79–3.84 (1H, m), 4.17 (2H, q, J=7.2 Hz). MS (FAB) m/z: 172 ($M^{\cdot+}$). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77, H, 9.37. Found: C, 62.58, H, 9.09.

Ethyl (1*R*,2*S*)-2-hydroxycyclohexanecarboxylate ((1*R*, 2*S*)-13). To a solution of sucrose (50 g) in water (260 mL) was added baker's yeast (20 g). After stirring the mixture for 1 h at 30°C, **12** (3.40 g, 20.0 mmol) was added to the mixture. The mixture was stirred for 3 days and then filtrated with Celite. The filtrate was extracted with EtOAc (400 mL×3) and the organic layer was dried over Na_2SO_4. The solution was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford (1*R*, 2*S*)-**13** (2.67 g, 78%) as an oil. The optical purity of this compound by HPLC analysis (column: Chiralcel OJ-R (Daicel), eluent: acetonitrile/phosphate buffer (pH 7)=3:7) was 90% ee. IR (liquid film) cm^{-1} 3513, 2937, 1713, 1185, 1040, 976. ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, J=7.0 Hz), 1.24–1.98 (8H, m), 2.48 (1H, ddd, J=11.3, 3.5, 2.8 Hz), 3.20 (1H, br d, J=2.6 Hz), 4.11–4.18 (1H, m), 4.17 (2H, q, J=7.0 Hz).

Ethyl (1*S*,2*R*)-2-acetoxycyclohexanecarboxylate ((1*S*, 2*R*)-14). To a solution of *cis*-**13** (1.72 g, 9.99 mmol) in THF (75 mL) and vinyl acetate (175 mL) was added immobilized lipase (TOYOZEME® LIP, 10 g). The mixture was stirred for 9 h at 37°C and then filtrated with Celite. The filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to afford (1*R*, 2*S*)-**14** (710 mg, 33%) as an oil. $[\alpha]_D^{25}=-10.7°$ (c 0.61, $CHCl_3$). IR (liquid film) cm^{-1} 1238, 1250, 1740, 2940. ^1H NMR (270 MHz, $CDCl_3$) δ 1.19–1.38 (1H, m), 1.23 (3H, t, J=7.2 Hz), 1.41–1.65 (3H, m), 1.72–1.88 (3H, m), 1.92–2.11 (1H, m), 2.03 (3H, s), 2.43–2.59 (1H, m) 4.02–4.21 (2H,m), 5.35–5.42 (1H, m). MS (FAB) m/z: 215 ($M+H^+$). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66, H, 8.47. Found: C, 61.35, H, 8.50.

(1*R*, 2*R*)-2-*t*-Butyldimethylsilyloxymethylcyclohexanol ((1*R*, 2*R*)-15). To a suspension of lithium aluminium hydride (LAH) (158 mg, 4.19 mmol) in THF (5 mL) was added a solution of (1*S*, 2*R*)-**14** (690 mg, 3.22 mmol) in THF (5 mL) at −70°C. The mixture was allowed to warm to 0°C and stirred for 1 h at the same temperature. After adding $Na_2SO_4{\cdot}10H_2O$ to the mixture, the suspension was filtrated with Celite and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 1:1) to afford (1*R*, 2*R*)-2-hydroxymethylcyclohexanol (395 mg, 94%) as an oil. $[\alpha]_D^{25}=-32.6°$ (c 0.73, $CHCl_3$). IR (liquid film) cm^{-1} 3356, 2931, 2857, 1450. ^1H NMR (270 MHz, $CDCl_3$) δ 1.18–1.85 (9H, m), 2.24 (2H, m), 3.76 (2H, d, J=4.1 Hz), 4.13–4.19 (1H, m). To a solution of (1*R*, 2*R*)-2-hydroxymethylcyclohexanol (380 mg, 2.92 mmol) in CH_2Cl_2 (5 mL) was added 4-dimethylaminopyridine (20 mg), triethylamine (369 mg, 3.65 mmol) and *t*-butyldimethylsilylchloride (506 mg, 3.36 mmol) at room temperature. The mixture was stirred for 2 h at the same temperature. The mixture was diluted with EtOAc (150 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 10:1) to afford (1*R*, 2*R*)-**15** (610 mg, 86%) as an oil. The optical purity of (1*R*, 2*R*)-**15** determined by NMR analysis of **17a** was >98% ee. $[\alpha]_D^{25}=-12.7°$ (c 0.76, $CHCl_3$). IR (liquid film) cm^{-1} 3356, 2931, 2857, 1450. ^1H NMR (270 MHz, $CDCl_3$) δ 1.18–1.85 (9H, m), 2.24 (2H, m), 3.76 (2H, d, J=4.1 Hz), 4.13–4.19 (1H, m).

(1*S*, 2*S*)-2-*t*-Butyldimethylsilyloxymethylcyclohexanol ((1*S*, 2*S*)-15). To a suspension of lithium aluminium hydride (LAH) (573 mg, 15.1 mmol) in THF (10 mL) was added a solution of (1*R*, 2*S*)-**13** (2.6 g, 15.1 mmol) in THF (10 mL) at 0°C. The mixture was stirred for 1 h at the same temperature. After adding $Na_2SO_4{\cdot}10H_2O$ to the mixture, the suspension was filtrated with Celite and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 1:1) to afford (1*S*, 2*S*)-2-hydroxymethylcyclohexanol (1.22 g, 62%) as an oil. $[\alpha]_D^{25}=+28.8°$ (c 1.11, $CHCl_3$). IR (liquid film) cm^{-1} 3356, 2931, 2857, 1450. ^1H NMR (270 MHz, $CDCl_3$) δ 1.18–1.85 (9H, m), 2.24 (2H, m), 3.76 (2H, d, J=4.1 Hz), 4.13–4.19 (1H, m). To a solution of (1*S*, 2*S*)-2-hydroxymethylcyclohexanol (1.0 g, 7.68 mmol) in CH_2Cl_2 (10 mL) was added 4-dimethylaminopyridine (50 mg), triethylamine (933 mg, 9.22 mmol) and *t*-butyldimethylsilylchloride (1.33 g, 8.83 mmol) at room temperature and the mixture was stirred for 19 h at the same temperature. The mixture was diluted with EtOAc (300 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 10:1) to afford (1*S*, 2*S*)-**15** (1.71 g, 91%) as an oil. The enantiomeric excess of (1*S*, 2*S*)-**15** determined by NMR analysis of **17b** was 86% ee. IR (liquid film) cm^{-1} 3356, 2931, 2857, 1450. ^1H NMR (270 MHz, $CDCl_3$) δ 1.18–1.85 (9H, m), 2.24 (2H, m), 3.76 (2H, d, J=4.1 Hz), 4.13–4.19 (1H, m).

(1*R*, 2*R*)-2-*t*-Butyldimethylsilyloxymethyl-1-[(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy]cyclohexane (17a). To a solution of (1*R*, 2*R*)-**15** (25 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added 4-dimethylaminopyridine (37 mg, 0.31 mmol) and (*R*)-MTPA chloride (39 mg, 0.15 mmol) at room temperature. The mixture was then stirred for 14 h at the same temperature. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 10:1) to afford **17a** (47 mg, 100%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ −0.02 (3H, s), −0.01 (3H, s), 0.87 (9H, s), 1.15–1.65 (5H, m), 1.67–1.76 (2H, m), 2.02–2.12 (1H, m), 3.26 (1H, dd, J=10.0, 6.9 Hz), 3.35 (1H, dd, J=10.0, 8.0 Hz), 3,55 (3H, s), 5.45 (1H, d, J=1.7 Hz), 7.36–7.44 (3H, m), 7.52–7.58 (2H, m).

(1*S*, 2*S*)-2-*t*-Butyldimethylsilyloxymethyl-1-[(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy]cyclohexane (17b). To a solution of (1*S*, 2*S*)-**15** (50 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was added 4-dimethylaminopyridine (75 mg, 0.61 mmol) and (*R*)-MTPA chloride (78 mg, 0.31 mmol) at room temperature. The mixture was then stirred for 7 h at the same temperature. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 10:1) to afford **17b** (94 mg, 100%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.88 (9H, s), 1.13–1.38 (3H, m), 1.40–1.52 (3H, m), 1.56–1.78 (2H, m), 2.06–2.14 (1H, m), 3.38 (1H, dd, *J*=10.1, 6.6 Hz), 3.44 (1H, dd, *J*=10.1, 8.8 Hz), 3,54 (3H, s), 5.42 (1H, d, *J*=1.7 Hz), 7.36–7.44 (3H, m), 7.49–7.57 (2H, m).

(*R*)-2-*t*-Butyldimethylsilyloxymethylcyclohexanone ((*R*)-16). To a solution of (1*R*, 2*R*)-**15** (550 mg, 2.25 mmol) in CH_2Cl_2 (5 mL) was added pyridinium dichromate (PDC) (931 mg, 2.47 mmol) and molecular sieves 4A (931 mg) at room temperature. The mixture was stirred for 4.5 h at the same temperature. After filtrating the mixture with Celite, the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 20:1) to afford (*R*)-**16** (480 mg, 88%) as an oil. $[\alpha]_D^{25}$=+39.0° (*c* 0.58, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.88 (9H, s), 1.31–1.48 (1H, m), 1.54–1.76 (2H, m), 1.84–1.97 (1H, m), 1.96–2.13 (1H, m), 2.24–2.42(3H, m), 2.42–2.56 (1H, m), 3.56 (1H, dd, *J*=10.3, 8.0 Hz), 3.98 (1H, dd, *J*=10.3, 4.7 Hz). MS (FAB) *m/z*: 243 $(M+H)^+$.

(*R*)-2-*t*-Butyldimethylsilyloxymethyl-1-trimethylsilyloxycyclohexene ((*R*)-4). To a solution of 1.0 M lithiumhexamethyldisilazide (1.82 mL, 1.82 mmol) in THF was added a solution of (*R*)-**16** (400 mg, 1.65 mmol) in THF (2 mL) at −78°C. The mixture was then stirred for 1 h at the same temperature. After adding trimethylsilyl chloride (269 mg, 2.48 mmol) to the mixture, the resulting mixture was allowed to warm to room temperature and was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 40:1) to afford (*R*)-**4** (520 mg, 100%) as an oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04–0.0.6 (6H, m), 0.11–0.20 (9H, m), 1.35–1.87 (4H, m), 1.92–2.08 (2H, m), 2.11–2.28(1H, m), 3.48 (1H, dd, *J*=9.7, 9.4 Hz), 3.82 (1H, dd, *J*=9.7, 3.6 Hz), 4.86–4.90 (1H, m).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(2′*R*, 6′*R*)-2′-(*t*-butyldimethylsilyloxymethyl)cyclohexanone −6′-yl]azetidin-2-one (7) from (*R*)-4 and 5. To a solution of (*R*)-4 (520 mg, 1.65 mmol) and azetidinone **5** (653 mg, 1.82 mmol) in CH_2Cl_2 (6 mL) was added zinc chloride (450 mg, 3.30 mmol) at room temperature. The mixture was stirred for 3 h at the same temperature. After adding saturated aqueous $NaHCO_3$ to the mixture, the insoluble material was removed by filtration. The filtrate was extracted with EtOAc (50 mL×3) and the organic layer was washed with brine. The solvent was dried over Na_2SO_4 and evaporated in vacuo. The ratio of **7** and **18** was determined by NMR analysis of the crude mixture (N–H proton of azetidinone 7:5.79 ppm, 18:6.05 ppm, 7:18=9:1). The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford **7** (485 mg, 63%) as crystals. The isomer **18** could not be isolated because **18** and unreacted **5** could not be separated from each other by silica gel column chromatography.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(2′*R*, 6′*R*)-2′-hydroxymethylcyclohexanone-6′-yl]azetidin-2-one (19). To a solution of **7** (10 g, 21.3 mmol) in dimethylformamide (100 mL) was added ammonium hydrogen fluoride (1.34 g, 23.4 mmol) at room temperature. The mixture was then stirred for 3 days at the same temperature. After adding saturated aqueous $NaHCO_3$ to the mixture, the aqueous mixture was extracted with EtOAc (250 mL×3). The organic layer was washed with brine and then dried over Na_2SO_4. The solution was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 1:2) to afford **19** (5.61 g, 74%) as crystals. $[\alpha]_D^{25}$=+48.9° (*c* 0.84, $CHCl_3$). Mp 135–136°C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.88 (9H, s), 1.11 (3H, d, *J*=6.2 Hz), 1.64–2.05 (6H, m), 2.42 (1H, br s), 2.56–2.66 (2H, m), 2.93 (1H, dd, *J*=3.5, 2.1 Hz), 3.69 (1H, dd, *J*=11.2, 4.6 Hz), 3.82 (1H, dd, *J*=11.2, 7.8 Hz), 4.08 (1H, dd, *J*=7.8, 2.1 Hz), 4.17–4.25 (1H. m), 6.28 (1H, br s). MS (FAB) *m/z*: 356 $(M+H^+)$. Anal. Calcd for $C_{18}H_{33}NO_4Si$: C, 60.81, H, 9.36, N, 3.94. Found: C, 60.58, H, 9.18, N, 4.03.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(2′*R*, 6′*R*)-2′-(triethylsilyloxymethyl)cyclohexanone-6′-yl]azetidin-2-one (20). To a solution of **19** (4.20 g, 11.8 mmol) in dimethylformamide (30 mL) was added triethylsilylchloride (2.41 g, 14.2 mmol) and imidazole (1.21 g, 17.7 mmol) at 0°C. The mixture was then stirred for 2.5 h at 0°C. After adding saturated aqueous $NaHCO_3$ was added to the mixture, the aqueous mixture was extracted with a mixed solvent of ethyl acetate and hexane. The organic layer was washed with water and brine and then dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to give **20** (5.43 g, 98%) as crystals. Mp 124–125°C. IR (KBr) cm^{-1} 3082, 2954, 1760, 1704. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.07 (3H, s), 0.57 (6H, q, *J*=7.9 Hz), 0.87 (9H, s), 0.94 (9H, t, *J*=7.9 Hz), 1.20 (3H, d, *J*=6.1 Hz), 1.66–2.09 (6H, m), 2.57–2.70 (2H, m), 2.88 (1H, dd, *J*=4.2, 2.4 Hz), 3.73 (1H, dd, *J*=10.3, 7.1 Hz), 3.90 (1H, dd, *J*=10.3, 6.9 Hz), 4.10 (1H, dd, *J*=5.3, 2.2 Hz), 4.16–4.25 (1H, m), 5.76 (1H, br s). Anal. Calcd for $C_{24}H_{47}NO_4Si_2$: C, 61.36, H, 10.08, N, 2.98. Found: C, 61.06, H, 9.82, N, 2.99.

Allyl (4*S*,8*S*,9*R*,10*S*)-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)-ethyl]-4-triethylsilyloxymethyl-11-oxo-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (21). By a similar procedure as that described for the preparation of **11** from **7**, **21** (4.25 g, 74%) was prepared from **20** (5.00 g, 10.6 mmol). $[\alpha]_D^{25}$=+95.1° (*c* 1.20, $CHCl_3$). IR (liquid film) cm^{-1} 2954, 2877, 1782, 1720, 1282, 1146, 1101. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.59 (6H, q, *J*=7.9 Hz), 0.88 (9H, s), 0.94 (3H, t, *J*=7.9 Hz), 1.24 (3H, d, *J*=6.1 Hz), 1.21–2.04 (6H, m), 2.94–3.08 (1H, m), 3.16 (1H, dd, *J*=6.7, 3.2 Hz), 3.67–3.85 (2H, m), 4.08 (1H, dd,

J=10.8, 3.5 Hz), 4.19 (1H, dq, J=6.3, 6.0 Hz), 4.61–4.83 (2H, m), 5.20–5.28 (1H, m), 5.38–5.48 (1H, m), 5.89–6.06 (1H, m). HRMS (FAB) *m/z*: calcd for $C_{29}H_{52}NO_5Si_2$ 550.3384 $(M+H)^+$, Found: 550.3373. Anal. Calcd for $C_{29}H_{51}NO_5Si_2$: C, 63.34, H, 9.35, N, 2.55. Found: C, 63.12, H, 9.06, N, 2.59.

Allyl (4*S*,8*S*,9*R*,10*S*)-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)-ethyl]-4-hydroxymethyl-11-oxo-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (3). To a solution of **21** (500 mg, 0.91 mmol) in dimethylformamide (5 mL) was added ammonium hydrogen fluoride (52 mg, 0.91 mmol) at room temperature. The mixture was then stirred for 8.5 h at the same temperature. After adding saturated aqueous $NaHCO_3$ to the mixture, the aqueous mixture was extracted with EtOAc (50 mL×3). The organic layer was washed with brine and then dried over Na_2SO_4. The solution was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 1:1) to afford **3** (359 mg, 91%) as an oil. $[\alpha]_D^{25}$=+133° (*c* 0.78, $CHCl_3$). IR (liquid film) cm^{-1} 2933, 2859, 1771, 1720. ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.16–1.92 (6H, m), 1.23 (3H, d, J=6.1 Hz), 2.97–3.10 (1H, m), 3.20 (1H, dd, J=6.3, 3.4 Hz), 3.71–3.88 (3H, m), 4.16 (1H, dd, J=10.6, 3.4 Hz), 4.21 (1H, dq, J=6.3, 6.1 Hz), 4.69 (1H, dd, J=13.6, 5.5 Hz), 4.77 (1H, dd, J=13.6, 5.2 Hz), 5.26 (1H, dd, J=10.6, 1.2 Hz), 5.42 (1H, d, J=17.2, 1.2 Hz), 5.88–6.04 (1H, m). MS (FAB) *m/z*: 436 $(M+H)^+$. Anal. Calcd for $C_{23}H_{37}NO_5Si$: C, 63.41, H, 8.56, N, 3.22. Found: C, 63.15, H, 8.85, N, 2.98. By a similar procedure as that described for the preparation of **3** from **21**, **3** (2.22 g, 49%) was prepared from **11** (5.90 g, 10.7 mmol).

Allyl (4*S*,8*S*,9*R*,10*S*)-4-(*N*,*N*-bis(allyloxycarbonyl)amino-methyl)-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (22a). To a solution of **3** (60 mg, 0.14 mmol), **25a** (38 mg, 0.21 mmol) and triphenylphosphine (60 mg, 0.35 mmol) in tetrahydrofuran (2 mL) was added diethyl azodicarboxylate (60 mg, 0.35 mmol) at room temperature. The mixture was then stirred for 1 h at the same temperature. After adding phosphate buffer (pH 7) to the mixture, the aqueous mixture was extracted with EtOAc (10 mL×2). The organic layer was washed with brine and then dried over Na_2SO_4. The solution was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to afford **22a** (63 mg, 76%) as an oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.15–1.91 (6H, m), 1.21 (3H, d, J=6.1 Hz), 3.16 (1H, dd, J=5.8, 3.4 Hz), 3.14–3.29 (1H, m), 3.80 (1H, dd, J=12.7, 3.9 Hz), 3.99–4.28 (4H, m), 4.59–4.80 (6H, m), 5.18–5.49 (6H, m), 5.85–6.05 (3H, m). HRMS (FAB) *m/z*: calcd for $C_{31}H_{46}N_2O_8SiNa$ 625.2921 $(M+Na)^+$, found: 625.2919.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-(*N*,*N*-bis(allyloxycarbonyl)amino-methyl)-10-[(*R*)-1-hydroxyethyl]-11-oxo-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (23a). To a solution of **22a** (400 mg, 0.66 mmol) in tetrahydrofuran (5 mL) was added 1 M tetrabutylammonium fluoride in tetrahydrofuran solution (3.3 mL) and acetic acid (239 mg, 3.98 mmol) at room temperature. The mixture was then stirred for about two weeks in a refrigerator. After adding phosphate buffer (pH 7) to the mixture, the aqueous mixture was extracted with EtOAc (30 mL×2). The organic layer was washed with saturated aqueous $NaHCO_3$, brine and then dried over Na_2SO_4. The solution was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 2:3) to afford **23a** (216 mg, 66%) as an oil. ^1H NMR (270 MHz, $CDCl_3$) δ 1.21–1.95 (6H, m), 1.31 (3H, d, J=6.5 Hz), 3.21 (1H, dd, J=6.4, 3.2 Hz), 3.22–3.36 (1H, m), 3.79 (1H, dd, J=12.8, 4.1 Hz), 3.99–4.28 (4H, m), 4.53–4.80 (6H, m), 5.17–5.49 (6H, m), 5.81–6.02 (3H, m). HRMS (FAB) *m/z*: calcd for $C_{25}H_{33}N_2O_8$ 489.2237 $(M+H)^+$, found: 489.2238.

(4*S*,8*S*,9*R*,10*S*)-4-Aminomethyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid (24a). To a solution of **23a** (210 mg, 0.43 mmol), bis(triphenylphosphine)palladium dichloride (6 mg, 0.009 mmol) and water (39 μL) in dichloromethane (2 mL) was added tributyltin hydride (626 mg, 2.15 mmol) at 0°C. The mixture was then stirred for 0.5 h at the same temperature. After EtOAc (20 mL) was added to the mixture, the mixture was extracted with water (20 mL×3). The aqueous layer was evaporated in vacuo and the residue was purified by reverse phase column chromatography (Cosmosil 75C_{18} PREP, CH_3CN–H_2O, 4:96). The desired fraction was concentrated and then lyophilized to afford **24a** (89 mg, 74%) as a colorless powder. IR (KBr) cm^{-1} 3391, 2931, 1759, 1580, 1392. ^1H NMR (400 MHz, D_2O) δ 1.27 (3H, d, J=6.1 Hz), 1.28–1.44 (1H, m), 1.52–1.97 (5H, m), 3.09–3.17 (1H, m), 3.20 (1H, dd, J=12.9, 5.6 Hz), 3.32 (1H, dd, J=12.9, 10.9 Hz), 3.44 (1H, dd, J=5.9, 3.0 Hz), 4.17 (1H, dd, J=10.3, 3.1 Hz), 4.24 (1H, qd, J=6.3, 6.2 Hz). HRMS (FAB) *m/z*: calcd for $C_{14}H_{21}N_2O_4$ 281.1451 $(M+H)^+$, found: 281.1499. Anal. Calcd for $C_{14}H_{20}N_2O_4{\cdot}2.5H_2O$: C, 51.68, H, 7.74, N, 8.61. Found: C, 51.94, H, 7.42, N, 8.73.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-[[1,2-bis(allyloxycarbonyl)guanidino]methyl]-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (22b). To a solution of **3** (150 mg, 0.34 mmol), **25b** (156 mg, 0.69 mmol) and triphenylphosphine (135 mg, 0.52 mmol) in toluene (3 mL) was added diisopropyl azodicarboxylate (104 mg, 0.52 mmol) at room temperature. The mixture was then stirred for 1.5 h at the same temperature. The mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford **22b** (155 mg, 70%) as an oil. IR (KBr) cm^{-1} 2951, 1770, 1722, 1613. ^1H NMR (270 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.88 (9H, s), 1.17–1.92 (6H, m), 1.21 (3H, d, J=6.1 Hz), 3.17 (1H, dd, J=5.8, 3.5 Hz), 3.36–3.52 (1H, m), 3.78–3.91 (1H, m), 3.92–4.03 (1H, m), 4.07 (1H, dd, J=10.7, 3.3 Hz), 4.19 (1H, qd, J=6.1, 6.0 Hz), 4.49–4.85 (7H, m), 5.18–5.49 (6H, m), 5.82–6.09 (3H, m), 9.10–9.41 (2H, br). HRMS (FAB) *m/z*: calcd for $C_{32}H_{49}N_4O_8Si$ 645.3320 $(M+H)^+$, found: 645.3333.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-[[1,2-bis(allyloxycarbonyl)guanidino]methyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (23b). By a similar procedure as that described for the preparation of **23a** from **22a**, **23b** (178 mg, 56%) was prepared from **22b** (390 mg, 0.61 mmol). ^1H NMR (270 MHz, $CDCl_3$) δ 1.27–1.92 (6H, m), 1.31 (3H, d, J=6.1 Hz), 3.22 (1H, dd, J=6.0, 3.5 Hz),

3.34–3.52 (1H, m), 3.77–3.91 (1H, m), 3.92–4.03 (1H, m), 4.10 (1H, dd, *J*=10.7, 3.3 Hz), 4.22 (1H, qd, *J*=6.1, 6.0 Hz), 4.49–4.85 (7H, m), 5.18–5.49 (6H, m), 5.82–6.09 (3H, m), 9.13–9.44 (2H, br). HRMS (FAB) *m/z*: calcd for $C_{26}H_{35}N_4O_8$ 531.2455 $(M+H)^+$, found: 531.2427.

(4*S*,8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-4-guanidinomethyl-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid (24b). By a similar procedure as that described for the preparation of **24a** from **23a**, **24b** (55 mg, 52%) was prepared from **23b** (170 mg, 0.32 mmol). IR (KBr) cm^{-1} 3357, 2931, 1755, 1664, 1632, 1576, 1398. ^1H NMR (270 MHz, D_2O) δ 1.17–1.42 (1H, m), 1.24 (3H, d, *J*=6.5 Hz), 1.50–1.97 (1H, m), 3.17–3.19 (1H, m), 3.34 (3H, dd, *J*=13.9, 6.3 Hz), 3.40–3.52 (3H, m), 3.69–3.82 (1H, m), 4.16 (1H, dd, *J*=10.3, 3.2 Hz), 4.24 (1H, qd, *J*=6.2, 6.1 Hz). HRMS (FAB) *m/z*: calcd for $C_{15}H_{23}N_4O_5$ 323.1719 $(M+H)^+$, found: 531.2427. Anal. Calcd for $C_{15}H_{22}N_4O_5{\cdot}H_2O$: C, 52.93, H, 6.92, N, 16.46. Found: C, 52.71, H, 6.63, N, 16.70.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-[*N*-allyloxycarbonyl-*N*-(2-thiazolyl)aminomethyl]-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)-ethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (22c). To a solution of **3** (25 mg, 0.06 mmol), **25c** (32 mg, 0.17 mmol) and triphenylphosphine (75 mg, 0.29 mmol) in toluene (2 mL) was added diethyl azodicarboxylate (50 mg, 0.29 mmol) at room temperature. The mixture was then stirred for 2.5 h at the same temperature. After adding phosphate buffer (pH 7) to the mixture, the aqueous mixture was extracted with EtOAc (10 mL×2). The organic layer was washed with brine and then dried over Na_2SO_4. The solution was evaporated in vacuo and the residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford **22c** (24 mg, 68%) as an oil. IR (liquid film) cm^{-1} 2931, 2858, 1780, 1716, 1207. ^1H NMR (270 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 1.23 (3H, d, *J*=6.0 Hz), 1.47–1.91(5H, m), 3.11 (1H, dd, *J*=7.0, 3.2 Hz), 3.32–3.34 (1H, m), 3.91 (1H, dd, *J*=10.5, 3.2 Hz), 4.08–4.26 (3H, m), 4.48–4.64 (2H, m), 4.65–4.81 (1H, m), 4.79 (1H, d, *J*=6.0 Hz), 5.14–5.47 (4H, m), 5.73–5.91 (1H,m), 5.96–6.12(1H, m), 6.93 (1H, d, *J*=3.5 Hz), 7.37 (1H, d, *J*=3.5 Hz). HRMS (FAB) *m/z*: calcd for $C_{30}H_{44}N_3O_6SSi$ 602.2761 $(M+H)^+$, found: 602.2773.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-[*N*-allyloxycarbonyl-*N*-(2-thiazolyl)aminomethyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (23c). By a similar procedure as that described for the preparation of **23a** from **22a**, **23c** (144 mg, 74%) was prepared from **22c** (264 mg, 0.40 mmol). ^1H NMR (270 MHz, $CDCl_3$) δ 1.15–1.41 (1H, m), 1.29 (3H, d, *J*=6.1 Hz), 1.41–2.08 (5H, m), 3.19 (1H, dd, *J*=6.5, 3.2 Hz), 3.38–3.52 (1H, m), 4.00 (1H, dd, *J*=10.5, 3.1 Hz), 4.05–4.25 (3H, m), 4.45–4.64 (2H, m), 4.65–4.82 (1H, m), 4.79 (2H, d, *J*=5.6 Hz), 5.12–5.45 (4H,m), 5.95–6.13 (1H, m), 6.94 (1H, d, *J*=3.9 Hz), 7.39 (1H, d, *J*=3.9 Hz). HRMS (FAB) *m/z*: calcd for $C_{24}H_{30}N_3O_6S$ 488.1855 $(M+H)^+$, found: 488.1855.

(4*S*,8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-4-[*N*-(2-thiazolyl)aminomethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid (24c). By a similar procedure as that described for the preparation of **24a** from **23a**, **24c** (56 mg, 54%) was prepared from **23c** (140 mg, 0.29 mmol). IR (KBr) cm^{-1} 3373, 3253, 2931, 1764, 1623, 1558, 1398. ^1H NMR (400 MHz, D_2O) δ 1.05–1.28 (1H, m), 1.07 (3H, d, *J*=6.2 Hz), 1.33–1.90 (5H, m), 2.98–3.05 (1H, m), 3.24 (1H, dd, *J*=5.9, 3.2 Hz), 3.37 (1H, dd, *J*=13.8, 5.9 Hz), 3.50 (1H, dd, *J*=13.8, 10.5 Hz), 3.67–3.73 (1H, m), 3.96 (1H, dd, *J*=10.5, 3.3 Hz), 4.03 (1H, qd, *J*=6.2, 6.2 Hz), 6.62 (1H, d, *J*=4.4 Hz), 6.96 (1H, d, *J*=4.4 Hz). HRMS (FAB) *m/z*: calcd for $C_{17}H_{22}N_3O_4S$ 364.1331 $(M+H)^+$, found: 364.1335. Anal. Calcd for $C_{17}H_{21}N_3O_4{\cdot}1.5H_2O$: C, 52.29, H, 6.20, N, 10.76. Found: C, 52.04, H, 5.92, N, 11.04.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-[(benzothiazol-2-yl)thiomethyl]-10-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (22d). By a similar procedure as that described for the preparation of **22c** from **3**, the crude mixture (395 mg) of **22d**, triphenylphosphine and 2-mercaptobenzothiazole was prepared from **3** (250 mg, 0.57 mmol) and **25d** (192 mg, 1.15 mmol). ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 1.18–2.07 (6H, m), 1.22 (3H, d, *J*=6.2 Hz), 3.08–3.22 (2H, m), 3.57 (1H, dd, *J*=12.9, 6.7 Hz), 3.74 (1H, dd, *J*=12.9, 9.5 Hz), 3.99 (1H, dd, *J*=10.5, 3.2 Hz), 4.02–4.21 (2H, m), 4.61–4.69 (2H, m), 5.21–5.39 (2H, m), 5.78–5.96 (4H, m), 7.24–7.45 (2H, m), 7.70–7.88(2H, m). HRMS (FAB) *m/z*: calcd for $C_{30}H_{41}N_2O_4S_2Si$ 585.2277 $(M+H)^+$, found: 585.2272.

Allyl (4*S*,8*S*,9*R*,10*S*)-4-[(benzothiazol-2-yl)thiomethyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (23d). By a similar procedure as that described for the preparation of **23a** from **22a**, **23d** (172 mg, 69% in two steps) was prepared from the crude mixture (395 mg, 0.40 mmol) of **22d**, triphenylphosphine and 2-mercaptobenzothiazole. ^1H NMR (270 MHz, $CDCl_3$) δ 1.16–2.08 (6H, m), 1.30 (3H, d, *J*=6.2 Hz), 3.12–3.39 (2H, m), 3.59 (1H, dd, *J*=12.9, 6.8 Hz), 3.72 (1H, dd, *J*=12.9, 9.4 Hz), 4.01–4.27 (3H, m), 4.54–4.74 (2H, m), 5.12–5.38 (2H, m), 5.78–5.97 (4H, m), 7.24–7.47 (2H,m), 7.71–7.89(2H, m). HRMS (FAB) *m/z*: calcd for $C_{24}H_{26}N_2O_4S_2Na$ 493.1232 $(M+Na)^+$, found: 493.1213.

Potassium (4*S*,8*S*,9*R*,10*S*)-4-[(benzothiazol-2-yl)thiomethyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (24d). To a solution of **23d** (85 mg, 0.18 mmol), triphenylphosphine (10 mg) and potassium 2-ethylhexanoate (33 mg, 0.18 mmol) in dichloromethane (3 mL) and EtOAc (3 mL) was added *tetrakis*(triphenylphosphine)palladium (7 mg, 0.004 mmol) at room temperature. The mixture was then stirred for 1 h at the same temperature. After adding EtOAc (10 mL) to the mixture, the mixture was extracted with water (10 mL×3). The aqueous layer was evaporated in vacuo and the residue was purified by reverse phase silica gel column chromatography (Cosmosil 75C_{18} PREP,CH_3CN–H_2O 2:8). The desired fraction was concentrated and then lyophilized to afford **24d** (44 mg, 52%) as a colorless powder. IR (KBr) cm^{-1} 3414, 2928, 1754, 1590, 1427, 1392, 996. ^1H NMR (400 MHz, D_2O) δ 0.98 (3H, d, *J*=6.4 Hz), 1.01–1.31(1H, m), 1.42–1.60 (3H, m), 1.62–1.78 (2H, m),2.81–2.89 (1H, m), 3.08 (1H, dd, *J*=6.0, 3.0 Hz), 3.21 (1H, dd, *J*=13.1,

4.9 Hz), 3.61 (1H, dd, J=13.1, 11.2 Hz), 3.67–3.77 (1H, m), 3.89 (1H, qd, J=6.4, 6.0 Hz), 7.21–7.28 (1H, m), 7.33–7.39 (1H, m), 7.69 (1H, d, J=8.0 Hz), 7.74 (1H, d, J=8.0 Hz). HRMS (FAB) *m/z*: calcd for $C_{21}H_{21}N_2O_4S_2KNa$ 491.0460 $(M+Na)^+$, found: 491.0469. Anal. Calcd for $C_{21}H_{21}N_2O_4S_2K\cdot H_2O$: C, 51.83, H, 4.76, N, 5.76. Found: C, 52.07, H, 4.98, N, 5.82.

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