2-Substituted 2,3-Dihydro-4*H*-1,3-benzoxazin-4-ones: Novel Auxiliaries for Stereoselective Synthesis of 1-*β*-Methylcarbapenems[1]

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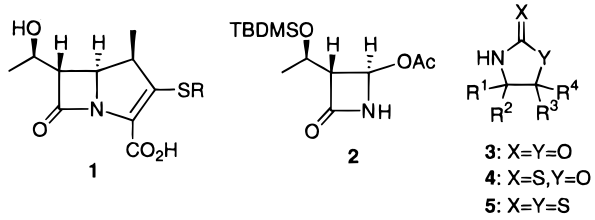
The dihydrobenzoxazone **9e**, which is easily prepared from salicylamide **11** and cyclohexanone, serves as an efficient auxiliary in the synthesis of the 1-*β*-methylcarbapenem key intermediate **10**. The stereocontrolled Reformatsky-type reactions of the acetoxyazetidinone **2** with the carboximides **6** gave the intermediates **7** with high diastereoselectivities in high chemical yields. The auxiliary **9e** also acts as a good leaving group in the TMSCl-promoted Dieckmann-type cyclization leading to a 1-*β*-methylcarbapenem skeleton. By using this auxiliary, **10** was synthesized in 58% overall yield and four steps from **2**.

Introduction

The carbapenem class of *β*-lactam antibiotics, as exemplified by thienamycin,[2] has attracted considerable attention because of their potent and broad-spectrum antibacterial activities. Recently, carbapenems **1** bearing a 1-*β*-methyl substituent at C-1 have been shown to possess superior chemical and metabolic stability, while maintaining the excellent antibacterial activities.[3] This discovery has prompted many synthetic organic chemists to develop an efficient method for constructing the 1-*β*-methylcarbapenem nucleus, and recent reviews[4] describe impressive progress in this area.

During the last decade, the diastereoselective aldol-type condensations of the acetoxyazetidinone **2** with enolates derived from carboximide auxiliaries have become a major tool for stereocontrolled approach to 1-*β*-methylcarbapenem key intermediates.[4] These reactions are thought to proceed via chelated transition states which involve the attack of (Z)-enolates on the less hindered face of an acylimine.[5] Most of the aldol-type condensations rely on auxiliaries derived from 2-oxazolidones **3**[5c] and the closely related analogs, *e. g.*, 1,3-oxazolidine-2-thiones **4**[6b] and 1,3-thiazolidine-2-thiones **5**.[5a,d,6a] Recently, the stereoselective synthesis of the key intermediate via the Reformatsky-type reaction employing 2-oxazolidones **3** has been reported.[5c,7] Although good to excellent diastereoselectivities have been obtained,



these auxiliaries possess at least one of the following drawbacks: difficult accessibility, necessity of refunctionalization before the subsequent ring construction, difficulty in recycling the auxiliaries, and requirement of expensive reagents. The use of these auxiliaries having such drawbacks is particularly problematic in the practical synthesis of the 1-*β*-methylcarbapenem antibiotics **1**.

Our research has been focussed on the development of an efficient auxiliary for the construction of the 1-*β*-methylcarbapenem nucleus. As shown in Scheme 1, our synthetic strategy involves two processes including the stereoselective Reformatsky-type reaction[7] and the Dieckmann-type cyclization.[6b,9] We were interested in the use of 2-substituted 1,3-dihydro-4*H*-1,3-benzoxazin-4-ones **9** as the auxiliaries, which can be prepared in a single step from inexpensive salicylamide **11** (Scheme 2).[8] The use of the rigid oxazinone ring fused to the benzene ring would result in an efficient asymmetric-induction in the Reformatsky-type reaction of the acetoxyazetidinone **2** with the carboximides **6**. In addition, we envisioned that the auxiliaries would serve as a good leaving group in the subsequent cyclization leading to the vinyl phosphate **10**, a key intermediate in the synthesis of the 1-*β*-methylcarbapenems **1**. We report here a practical syn-

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(8) See, for example: (a) Horrom, B. W.; Zaugg, H. E. *J. Am. Chem. Soc.* **1950**, *72*, 721−724. For the base-catalized reactions, see: (b) Gammill, R. B. *J. Org. Chem.* **1981**, *46*, 3340−3342.

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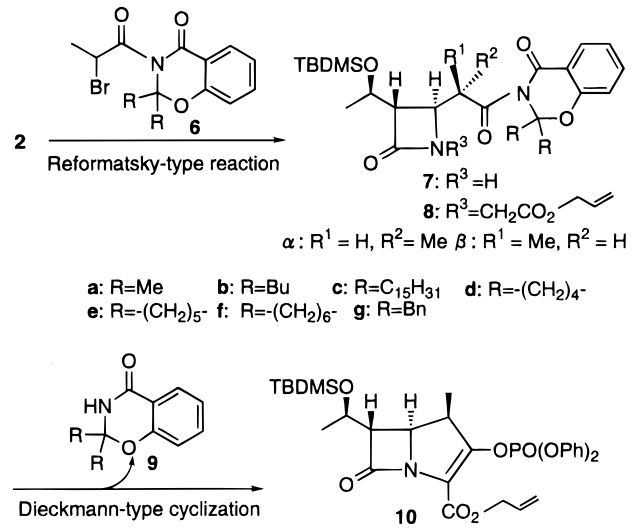
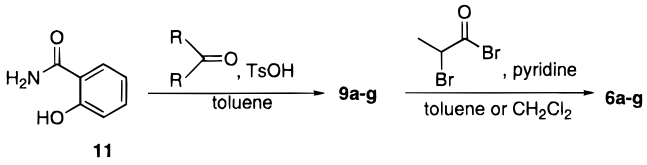
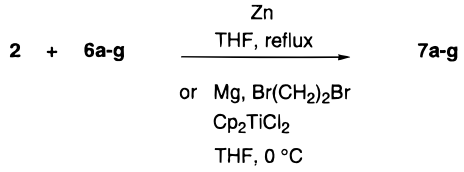
Scheme 1



Scheme 2



Scheme 3



thesis of **10** by the use of the dihydrobenzoxazones **9** as the auxiliaries.

Results and Discussion

Zinc-Induced Reformatsky-Type Reaction. We selected the achiral 2-substituted dihydrobenzoxazones **9** as the auxiliaries which were readily synthesized from **11**. The requisite **9a**−**g** were readily prepared in 69−93% yields by the acid-catalyzed condensation of salicylamide **11** with the corresponding ketones in toluene (Scheme 2).[8]

Next, we attempted the bromopropionylation of **9a**−**g**. Recent work has shown that 2-oxazolidones **3** react with 2-bromopropionyl bromide in the presence of butyllithium or sodium hydride in THF to yield the N-acylated products.[5c] However, bromopropionylation of **9** under the same conditions as those used in the case of **3** gave the carboximides **6** in low yields with concomitant formation of several byproducts. The use of triethylamine as a base also gave disappointing results. After screening a variety of bases and solvents, we found that the bromopropionylation is completed in a good yield by the use of pyridine as a base and toluene or CH_2Cl_2 as a solvent. Thus, the reaction of **9a**−**g** with 1.2 equiv of the acyl bromide in the presence of 1.2 equiv of pyridine at 5−25 °C gave **6a**−**g** in high yields (64−87%).

Having established the method for the synthesis of **6a**−**g**, we focused our attention on the Reformatsky-type reaction (Scheme 3). The best conditions involved the treatment of **2** with 1.5 equiv of **6a**−**g** and 3 equiv of zinc dust in refluxing THF. The results are summarized in Table 1. The diastereoselectivity and the yield of the azetizinones **7a**−**g** depend largely on the structure of the auxiliary. In general, the diastereoselectivity increases with increasing the steric bulkiness of the C-2 substituents on the axuiliary, while the yield decreases with the increasing the steric bulkiness. The highest diastereoselectivity was found in the use of the benzyl derivative **6g** (β:α = 99.6:0.4), and the lowest selectivity was observed in the use of the methyl derivative **6a** and the cyclopentyl derivative **6d** (β:α = 85:15). On the other hand, the highest yield was obtained in the use of **6a** and the cyclohexyl derivative **6e**. From practical point of view, the diastereoselectivity as well as the chemical yield in the Reformatsky-type reaction should be high. Furthermore, the β-isomer should be separated easily by direct crystallization. For the above reasons, we selected the cyclohexyl derivative **7e** as a key intermediate for the target compound **10**; direct crystallization of the crude **7e** gave the pure β-isomer **7e**β in 75% yield based on **2**. The structure of **7e**β was confirmed by means of X-ray crystallography.[10]

Table 1. Zinc-Induced Reformatsky-Type Reaction of 2 with 6a−g

entry	7	R	yield, %[a]	β:α[b]	mp, °C
1	**a**	Me	94	85:15	133−134[d]
2	**b**	Bu	87	98:2	oil
3	**c**	$C_{15}H_{31}$	64	98:2[c]	oil
4	**d**	$-(CH_2)_4-$	77	85:15	oil
5	**e**	$-(CH_2)_5-$	96	92:8	156−157[d]
6	**f**	$-(CH_2)_6-$	38	89:11	146−147[d]
7	**g**	Bn	76	99.6:0.4	oil

[a] Isolated yield. [b] Determined by HPLC. [c] Determined by ^{1}H-NMR. [d] Melting point of the pure β-isomer

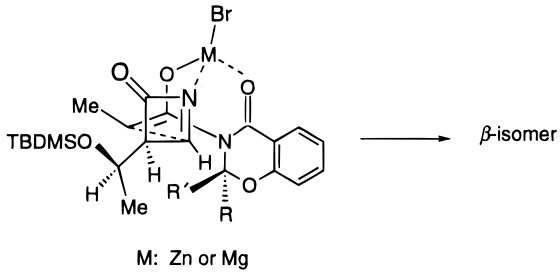
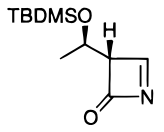


Figure 1.

The preferential formation of the β-isomers **7a**−**g**β would be explained by the chairlike transition state[5] involving the imine **12** and the (Z)-enolate **13** (Figure 1). The mechanism involving the intermediacy of the (Z)-enolate **13** is supported by the following experiment. Silylation of the crude reaction mixture obtained from the reaction of **6e** with zinc produced a 71:29 mixture of the (Z)-silyl enol ether **14e** and the reduced product **15e**; **14e** could be isolated in crystalline form. The structure of **14e** was determined by X-ray crystallography.[10] It may be deduced that the steric repulsion between β-oriented bulky substituent R′ at C-2 of the auxiliary and the imine **12** would not be critical factor in the diastereofacial selection (Figure 1). However, the decrease in chemical yields of the azetidinones **7** with increasing the size of R′ suggests that the steric repulsion would induce

(10) The author has deposited X-ray data with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.



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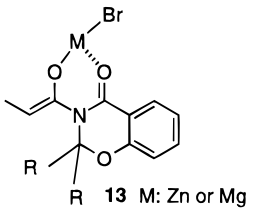
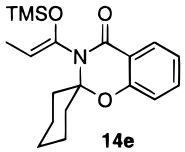
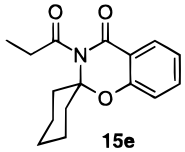


13 M: Zn or Mg



14e



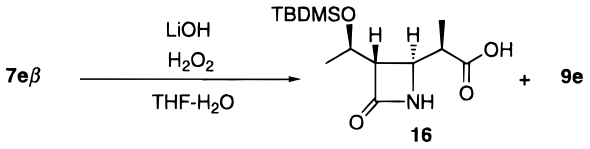
15e

the competing side-reactions by retarding the Reformatsky-type reaction leading to **7**.

In order to obtain the carboxylic acid **16**, which is an intermediate for the synthesis of carbapenem antibiotics,[4] we also examined the hydrolysis of the β-isomer **7e**β (Scheme 4). Treatment of **7e**β with LiOH[12] in aqueous THF led to a complex mixture of products. When **7e**β was treated with lithium hydroperoxide[12] in aqueous THF, the carboxylic acid **16** was obtained in 72% yield; the auxiliary **9e** was recovered in 92% yield.

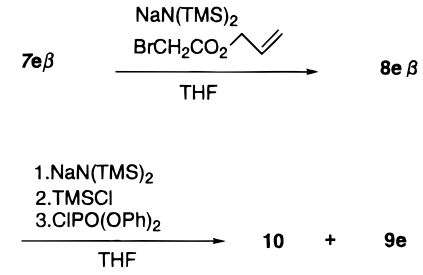
Magnesium-Induced Reformatsky-Type Reaction. Efficient modifications of the Reformatsky reaction[13a] have been reported by using magnesium as a metal component[13b] and Cp_2TiCl_2−zinc system as a catalyst.[13c] In order to improve the yield and diastereoselectivity of the β-isomer **7e**β, we investigated the Reformatsky-type reaction using magnesium instead of zinc (Scheme 3). The reaction of the acetoxyazetidinone **2** with the carboximide **6e** and magnesium in the presence of a catalytic amount of iodine in THF led to a complex mixture of products. However, pretreatment of 4.5 equiv of magnesium with 3 equiv of 1,2-dibromomethane[14] in THF followed by addition of **2** and 1.5 equiv of **6e** (10 °C, 1 h) provided **7e** in 54% yield with an excellent diastereoselectivity (β:α = 99:1). The use of a catalytic amount of Cp_2TiCl_2 in this reaction resulted in the improvement of the yield. Thus, treatment of **2** with **6e** under the reaction conditions described above in the presence of 10 mol % of Cp_2TiCl_2 at 0 °C for 30 min gave **7e** in 73% yield (β:α = 99:1). It is most likely that the magnesium bromide formed from magnesium and 1,2-dibromoethane could function as a Lewis acid and could accelerate the generation of the reactive imine **12**, which would react with the enolate **13** to give the desired product **7e**. In addition, the activated magnesium generated by using 1,2-dibromoethane as an entrainer[14] is thought to facilitate the formation of the Reformatsky reagent **13**. Although the role of the Cp_2TiCl_2 is still obscure, the increase in the yield of **7e** may be due to the formation of the titanium enolate,[15] which probably

Scheme 4



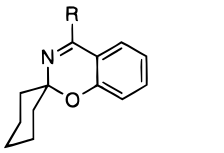
16

Scheme 5

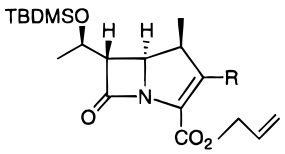


suppresses the possible self-condensation[16] of **13**. We have not attempted to refine the procedure to obtain better yields.

TMSCl-Promoted Dieckmann-Type Cyclization. We next investigated the preparation of the vinyl phosphate **10** by the Dieckmann-type cyclization of the allyl ester **8e**β (Scheme 5). The requisite **8e**β was prepared in 96% yield by the reaction of the β-isomer **7e**β with allyl bromoacetate in the presence of sodium bis(trimethylsilyl)amide [$NaN(TMS)_2$]. For the synthesis of the vinyl phosphate **10** via the Dieckman-type cyclization, the presence of good a leaving group, *e. g.*, 2-pyridylthio[9c] and phenylthio,[9d] on the C-4 side chain of the allyl ester **8e**β is required. We have previously shown that TMSCl promotes the Dieckmann-type cyclization of the thioesters, presumably due to the effective trapping of the liberated thiolate anions by TMSCl.[17] We anticipated that the dihydrobenzoxazone **9e** would serve as a good leaving group when the cyclization was carried out in the presence of TMSCl. Silylation of the liberated dihydrobenzoxazone anion **17** to form the silyl ether **18** would prevent the side reactions such as the phosphorylation of **17**, thereby leading to the recovery of the auxiliary **9e** by a simple workup.[18] As expected, treatment of **8e**β with 2.5 equiv of $NaN(TMS)_2$ and 1.3 equiv of TMSCl at −25 °C, followed by addition of 1.3 equiv of diphenyl phosphorochloridate at 0 °C in THF, gave the desired vinyl phosphate **10** in 82% yield; the auxiliary **9e** was recovered in 85% yield.[19] No 1-α-methyl isomer was detected.[9d,20] When the reaction was performed in the absence of TMSCl, **10** was obtained only in 18% yield



17: R=ONa
18: R=OTMS
19: R=OPO(OPh)$_2$



20: R=ONa
21: R=OTMS

(11) Because the Reformatsky reagent is very susceptible to hydrolysis under the silylation conditions, it was not possible to obtain the Z silyl enol ether **14e** without concomitant formation of the reduced product **15e**. For the related silylation of the Reformatsky reagents, see: (a) Slougui, N.; Rosseau, G. *Synth. Commun.* **1987**, *17*, 1−11. (b) Kitagawa, O.; Taguchi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803−1806.

(12) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.

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(16) Hussey, A. S.; Newman, M. S. *J. Am. Chem. Soc.* **1948**, *70*, 3024−3026.

(17) Seki, M.; Kondo, K.; Iwasaki, T. *Synlett* **1995**, 315−316.

(18) For the Diekmann-type cyclization with alkyl halide as a scavenger, see reference 9d.

(19) Attempts to isolate the silyl derivative **13b** prior to aqueous workup were unsuccessful.

Scheme 6

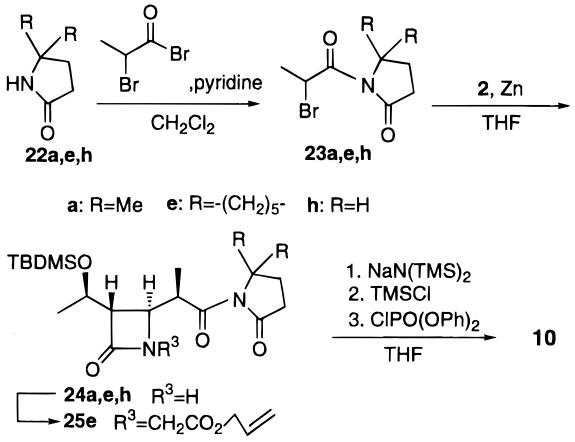

Table 2. Zinc-Induced Reformatsky-Induced Reaction of 23a,e,h with 2

entry	**24**	R	yield, %[a]	β:α[b]
1	**a**	Me	75	94:6
2	**e**	$-(CH_2)_5-$	84	95:5
3	**h**	H	28	63:37

[a] Isolated yield. [b] Determined by HPLC.

along with the phosphate **19**[21] (15%) and intractable byproducts. These results suggest that the silylation of **17** would be much faster than that of the cyclized enolate **20**, leading to the silyl enol ether **21** which is probably unreactive toward the phosphorylation. The vinyl phosphate **10** thus obtained was transformed into the thiovinyl derivatives **1** by the known method.[22] Very recently, we found a novel procedure for the deprotection of the TBDMS ether of carbapenems by using inexpensive ammonium bifluoride.[23] We have also found a new method for the deprotection of allyl ester of carbapenems employing palladium acetate−$P(OEt)_3$.[23] By utilizing these two deprotection-methods, we succeeded in the large-scale preparation of a 1-β-methylcarbapenem antibiotic **1**.

Reaction of Pyrrolidones. On the basis of the above results, we further explored an alternate synthetic method of the vinyl phosphonate **10** using the structurally related pyrrolidones **22a,e,h**[24] as the auxiliaries (Scheme 6). The zinc-mediated Reformatsky-type reaction of the acetoxyazetidinone **2** with the carboximide **23e** gave the cyclohexyl derivative **24e** in a highly diastereoselective manner (β:α = 95:5) and in 84% isolated yield (Table 2).[25] In contrast to the case of dihydrobenzoxazone series, the yield of the azetizinones **24** increases with increasing the steric bulkiness of the C-5 substituents on the auxiliary.

Unfortunately, the TMSCl-promoted Dieckmann-type cyclization of the allyl ester **25e** under the same conditions as described above led to the formation of a complex mixture of products; the desired vinyl phosphate **10** was isolated only in 9% yield. The low yield of **10** may be due to the poor leaving-group ability of the auxiliary **22e**.

Conclusion

We have demonstrated that the dihydrobenzoxazone **9e** serves not only as an effective auxiliary in the stereoselective Reformatsky-type reaction of the acetoxyazetidinone **2** but also as a good leaving group in the TMSCl-promoted Dieckmann-type cyclization leading to the key intermediate **10**. Thus, a practical and cost effective method for the preparation of 1-β-methylcarbapenems **1** has been developed by using this auxiliary. The ready availability, high reactivity, and unprecedented structural features of **9** should find wide application in a variety of asymmetric syntheses.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR were recorded on a 200 MHz spectrometer and are reported in δ values. Mass spectra were taken at an ionizing potential of 70 eV. Analytical HPLC was conducted on a 4.6 mm i.d. × 150 mm Capcell Pac C_{18}, SG-120 (Shiseido) column at a column temperature of 40 °C and UV detection at 254 nm. Flash column chromatography (FCC) was carried out on 230−400 mesh silica gel, eluting with the solvents indicated. All solvents were distilled and dried according to standard procedures prior to use. (3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**1**) was obtained from Kanegafutikagakukogyo Co., Ltd. Zinc dust was purchased from E. Merck (zinc powder GR, particle size <60 μm) and used without purification.

General Procedure for Dihydrobenzoxazone. Spiro-[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (9e). A mixture of salicylamide **11** (100 g, 0.73 mol), cyclohexanone (107 g, 1.09 mol), and *p*-toluenesulfonic acid monohydrate (13.9 g, 0.073 mol) in toluene (500 mL) was refluxed under conditions removal of water using a Dean−Stark apparatus for 8 h or until 90% of the theoretical amount of water was removed. After gradual cooling down to 10 °C, the mixture was stirred for 1 h at the same temperature. The resulting crystals were collected, washed successively with toluene (100 mL) and 2-propanol (100 mL), and dried at 50 °C to afford 145.5 g (92%) of **9e** as colorless crystals: mp 189−192 °C (lit.[8a] mp 188−190 °C); ^{1}H NMR (DMSO-d_6) δ 1.20−1.30 (m, 1H), 1.50−1.70 (m, 6H), 1.90−2.10 (m, 3H), 6.90−7.10 (m, 2H), 7.40−7.50 (m, 1H), 7.70−7.80 (m, 1H), 8.64 (brs, 1H); IR (KBr) 2939, 1670, 1608 cm^{-1}; MS *m*/*z* 217 (M^+). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.88; H, 7.02; N, 6.42.

2,3-Dihydro-2,2-dimethyl-4*H*-1,3-benzoxazin-4-one (9a) was isolated in 72% yield as colorless crystals: mp 136−138 °C (from hexane−AcOEt) (lit.[8a] mp 135−137 °C); ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 6H), 6.80−7.00 (m, 2H), 7.30−7.50 (m, 1H), 7.80−7.90 (m, 2H); IR (KBr) 3186, 1677, 1614 cm^{-1}; MS *m*/*z* 177 (M^+). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.56; H, 6.02; N, 7.80.

2,2-Dibutyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (9b) was isolated in 93% yield after FCC (hexane/AcOEt 95:5) of the crude product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.80−1.00 (m, 6H), 1.20−1.50 (m, 8H), 1.80−2.00 (m, 4H), 6.87−6.91 (m, 1H), 6.99−7.07 (m, 1H), 7.15 (s, 1H), 7.39−7.48 (m, 1H), 7.88−7.93 (m, 1H); IR (KBr) 2957, 1678, 1610 cm^{-1}; MS *m*/*z* 261 (M^+). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.50; H, 8.90; N, 5.42.

2,3-Dihydro-2,2-dipentadecanyl-4*H*-1,3-benzoxazin-4-one (9c) was isolated in 85% yield after FCC (hexane/AcOEt 95:5) of the crude product as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 6H), 1.00−1.90 (m, 56H), 6.48 (s, 1H), 6.87−6.92 (m, 1H), 7.00−7.08 (m, 1H), 7.38−7.48 (m, 1H), 7.88−7.93 (m, 1H); IR (KBr) 2955, 1676, 1612 cm^{-1}; MS *m*/*z* 569

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(21) The structure of the phosphate **19** was confirmed through X-ray analysis.[10]

(22) For example, see: reference 3.

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(25) After completion of our work, a similar transformation using pyrrolidones was reported in a patent literature: Asai, H.; Suzuki, K.; Nakada, J.; Ishikawa, M.; Nakagawa, S. Japanese Patent 06,065,195 Mar 8, 1994. *Chem. Abstr.* **1994**, *121*, 35188m. For a related method, see: Sunakawa, J.; Tamoto, K. Japanese Patent 02,178,262 Jul 11, 1990. *Chem. Abstr.* **1991**, *114*, 23689t.

(M^+). Anal. Calcd for $C_{38}H_{67}NO_2$: C, 80.08; H, 11.85; N, 2.46. Found: C, 80.15; H, 11.89; N, 2.61.

Spiro[2*H*-1,3-benzoxazine-2,1′-cyclopentan]-4(3*H*)-one (9d) was isolated in 69% yield after FCC (hexane/AcOEt 95:5) of the crude product as a colorless oil (lit.[8b] mp 135−137 °C): ^{1}H NMR (DMSO-d_6) δ 1.62−2.20 (m, 8H), 6.95−7.15 (m, 2H), 7.45−7.55 (m, 1H), 7.74−7.79 (m, 1H), 8.78 (brs, 1H); IR (KBr) 3185, 1671, 1611 cm^{-1}; MS *m*/*z* 203 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.67; H, 6.62; N, 6.89.

Spiro[2*H*-1,3-benzoxazine-2,1′-cycloheptan]-4(3*H*)-one (9f) was isolated in 86% yield as colorless crystals: mp 154−156 °C (from hexane) (lit.[8b] mp 155.1−156.8 °C); ^{1}H NMR ($CDCl_3$) δ 1.40−1.85 (m, 8H), 1.96 (dd, *J* = 9.0, 14.5 Hz, 2H), 2.26 (dd, *J* = 7.9, 14.4 Hz, 2H), 6.90−6.95 (m, 1H), 7.04−7.09 (m, 1H), 7.39−7.49 (m, 1H), 7.87−7.93 (m, 1H); IR (KBr) 1667, 1612, 1418, 1385 cm^{-1}; MS *m*/*z* 231 (M^+). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.84; H, 7.51; N, 6.43.

2,2-Dibenzyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (9g) was isolated in 74% yield as colorless crystals: mp 159−161 °C (from Et_2O); ^{1}H NMR ($CDCl_3$) δ 3.16 (s, 4H), 6.99−7.06 (m, 2H), 7.06−7.30 (m, 10H), 7.40−7.51 (m, 2H), 7.82−7.87 (m, 1H); IR (KBr) 3066, 1676, 1612 cm^{-1}; MS *m*/*z* 330 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.26; H, 6.04; N, 4.08.

Preparation of Pyrrolidones. 5,5-Dimethyl-2-pyrrolidinone (22a) was prepared according to the literature[24] in 86% yield after distillation as a colorless solid: bp 125 °C/13 mmHg (lit.[24] bp 126.5−128.5 °C/12 mmHg); mp 39−40 °C (lit.[24] mp 42−43 °C); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6H), 1.92 (t, *J* = 7.9 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 6.93 (brs, 1H); IR (KBr) 3222, 1699, 1388 cm^{-1}; MS *m*/*z* 113 (M^+). Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.85; H, 9.90; N, 12.55.

Spiro(pyrrolidine-5,1′-cyclohexan)-2-one (22e) was prepared according to the literature[24] in 65% yield from nitrocyclohexane after FCC($CHCl_3$/Et_2O 20:1) of the crude product as a colorless solid: mp 130−131 °C; ^{1}H NMR ($CDCl_3$) δ 1.30−1.70 (m, 10H), 1.90 (t, *J* = 8.1 Hz, 2H), 2.38 (t, *J* = 8.1 Hz, 2H), 7.08 (brs, 1H); IR (KBr) 3210, 1693, 1278 cm^{-1}; MS *m*/*z* 153 (M^+). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.43; H, 9.86; N, 9.28.

General Procedure for the Acylation of Auxiliaries. 3-(2-Bromopropionyl)spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (6e). To a mixture of **9e** (140 g, 0.644 mol), pyridine (61.1 g, 0.773 mol) and toluene (700 mL) was added 2-bromopropionyl bromide (168 g, 0.773 mol) at 5 to 15 °C. This mixture was stirred at the same temperature for 30 min and then at 25 °C for 17 h. The reaction mixture was poured into water (700 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (100 mL) and brine (60 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was dissolved in 2-propanol (60 mL) at 50 to 55 °C, gradually cooled to 10 °C, and stirred at the same temperature for 1 h. The resulting crystals were collected, washed with 2-propanol (140 mL), and dried at 40 °C for 17 h to afford 197.3 g (87%) of **6e** as colorless crystals: mp 74−76 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−2.50 (m, 10H), 1.92 (d, *J* = 6.6 Hz, 3H), 5.14 (q, *J* = 6.6 Hz, 1H), 7.00−7.15 (m, 2H), 7.50−7.60 (m, 1H), 7.90−7.95 (m, 1H); IR (KBr) 1723, 1682, 1613 cm^{-1}; MS *m*/*z* 353 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.47; H, 5.26; N, 4.03.

3-(2-Bromopropionyl)-2,3-dihydro-2,2-dimethyl-4*H*-1,3-benzoxazin-4-one (6a) was isolated in 72% yield as colorless crystals: mp 63−66 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 1.90 (s, 3H), 1.92 (d, *J* = 6 Hz, 3H), 5.22 (q, *J* = 6Hz, 1H), 6.94−6.98 (m, 1H), 7.07−7.16 (m, 1H), 7.50−7.59 (m, 1H), 7.92−7.96 (m, 1H); IR (KBr) 1730, 1683, 1613 cm^{-1}; MS *m*/*z* 313 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52; N, 4.49. Found: C, 50.07; H, 4.48; N, 4.63.

3-(2-Bromopropionyl)-2,2-dibutyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (6b) was isolated in 75% yield after FCC (hexane/AcOEt 95:5) of the crude product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.70−0.90 (m, 6H), 1.10−1.70 (m, 8H), 1.96 (d, *J* = 6.6 Hz, 3H), 2.00−2.50 (m, 4H), 5.25 (q, *J* = 6.6 Hz, 1H), 6.90−7.00 (m, 1H), 7.00−7.15 (m, 1H), 7.46−7.60 (m, 1H), 7.90−7.97 (m, 1H); IR (KBr) 1725, 1686, 1612 cm^{-1}; MS *m*/*z* 397 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{26}BrNO_3$: C, 57.58; H, 6.61; N, 3.53. Found: C, 57.37; H, 6.71; N, 3.81.

3-(2-Bromopropionyl)-2,3-dihydro-2,2-dipentadecanyl-4*H*-1,3-benzoxazin-4-one (6c) was isolated in 64% yield after FCC (hexane/AcOEt 95:5) of the crude product as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 6.4 Hz, 6H), 1.00−2.50 (m, 56H), 1.96 (d, *J* = 6.7 Hz, 3H), 5.26 (q, *J* = 6.6 Hz, 1H), 6.91−6.96 (m, 1H), 7.04−7.12 (m, 1H), 7.48−7.57 (m, 1H), 7.92−7.97 (m, 1H); IR (KBr) 1722, 1685, 1614 cm^{-1}; MS *m*/*z* 705 ($M^+ + 1$). Anal. Calcd for $C_{41}H_{70}BrNO_3$: C, 69.86; H, 10.01; N, 1.99. Found: C, 69.68; H, 9.95; N, 2.03.

3-(2-Bromopropionyl)spiro[2*H*-1,3-benzoxazine-2,1′-cyclopentan]-4(3*H*)-one (6d) was isolated in 67% yield as colorless crystals: mp 76−78 °C (from $CHCl_3$−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.70−2.60 (m, 8H), 1.97 (d, *J* = 8.7 Hz, 3H), 5.25 (q, *J* = 8.7 Hz, 1H), 6.90−7.20 (m, 2H), 7.50−7.60 (m, 1H), 7.91−7.95 (m, 1H); IR (KBr) 1722, 1685, 1611 cm^{-1}; MS *m*/*z* 339 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.12; H, 4.67; N, 3.98.

3-(2-Bromopropionyl)spiro[2*H*-1,3-benzoxazine-2,1′-cycloheptan]-4(3*H*)-one (6f) was isolated in 92% yield after FCC (hexane/AcOEt 10:1) of the crude product as a pale yellow solid: mp 94−96 °C; ^{1}H NMR ($CDCl_3$) δ 1.30−2.00 (m, 8H), 1.92 (d, *J* = 6.6 Hz, 3H), 2.10−2.65 (m, 4H), 5.19 (q, *J* = 6.6 Hz, 1H), 6.97−7.03 (m, 1H), 7.06−7.15 (m, 1H), 7.50−7.60 (m, 1H), 7.89−7.95 (m, 1H); IR (KBr) 1717, 1684, 1610, 1469 cm^{-1}; MS *m*/*z* 367 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{20}BrNO_3$: C, 55.75; H, 5.50; N, 3.82. Found: C, 55.55; H, 5.54; N, 4.14.

3-(2-Bromopropionyl)-2,2-dibenzyl-4-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (6g) was isolated in 77% yield as colorless crystals: mp 114−115 °C (from *i*-Pr_2O); ^{1}H NMR ($CDCl_3$) δ 1.45 (d, *J* = 6 Hz, 3H), 3.23 (d, *J* = 16 Hz, 1H), 3.40 (d, *J* = 16 Hz, 1H), 3.72 (d, *J* = 16 Hz, 2H), 5.25 (q, *J* = 6 Hz, 1H), 7.00−7.12 (m, 2H), 7.10−7.35 (m, 10H), 7.55−7.64 (m, 1H), 7.80−7.85 (m, 1H); IR (KBr) 1694, 1611 cm^{-1}; MS *m*/*z* 464 (M^+). Anal. Calcd for $C_{25}H_{22}BrNO_3$: C, 64.66; H, 4.78; N, 3.02. Found: C, 64.88; H, 4.99; N, 2.99.

1-(2-Bromopropionyl)-2-pyrrolidone (23h) was isolated in 92% yield after FCC (hexane/AcOEt 2:1) of the crude product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.82 (d, *J* = 6.8 Hz, 3H), 2.01−2.17 (m, 2H), 2.61−2.71 (m, 2H), 3.82−3.90 (m, 2H), 5.69 (q, *J* = 6.8 Hz, 1H); IR (KBr) 1740, 1694, 1367, 1255 cm^{-1}; MS *m*/*z* 221 ($M^+ + 1$). Anal. Calcd for $C_7H_{10}BrNO_2$: C, 38.21; H, 4.58; N, 6.36. Found: C, 38.12; H, 4.80; N, 6.19.

1-(2-Bromopropionyl)-5,5-dimethyl-2-pyrrolidone (23a) was isolated in 79% yield after FCC (hexane/AcOEt 4:1) of the crude product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 6H), 1.80 (d, *J* = 6.7 Hz, 3H), 1.87−1.99 (m, 2H), 2.52−2.61 (m, 2H), 5.76 (q, *J* = 6.7 Hz, 1H); IR (KBr) 1740, 1699, 1356, 1293 cm^{-1}; MS *m*/*z* 250 ($M^+ + 1$). Anal. Calcd for $C_9H_{14}BrNO_2$: C, 43.57; H, 5.69; N, 5.65. Found: C, 43.71; H, 5.56; N, 5.49.

1-(2-Bromopropionyl)spiro(pyrrolidine-5,1′-cyclohexan)-2-one (23e) was isolated in 34% yield after FCC ($CHCl_3$/Et_2O 20:1) of the crude product as a colorless solid: mp 46−48 °C; ^{1}H NMR ($CDCl_3$) δ 1.10−2.00 (m, 10H), 1.79 (d, *J* = 6.7 Hz, 3H), 2.40−2.60 (m, 4H), 5.80 (q, *J* = 6.7 Hz, 1H); IR (KBr) 1740, 1698, 1451 cm^{-1}; MS *m*/*z* 289 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{18}BrNO_2$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.47; H, 5.26; N, 4.03.

General Procedure for Zinc-Induced Reformatsky-Type Reaction. 3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}spiro-[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (7eβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-oxoazetidin-4-yl]propionyl} isomer (7eα). A mixture of **2** (5.0 g, 17.4 mmol) and zinc dust (3.4 g, 52 mg-atom) in THF (50 mL) was heated under reflux for 5 min. To the refluxing mixture was added dropwise a solution of the bromide **6e** (9.2 g, 26.1 mmol) in THF (20 mL) over 15 min. After refluxing for 5 min, the mixture was cooled, poured into phosphate buffer (pH 7.0, 200 mL), and extracted with CH_2Cl_2 (1 × 200 mL, 2 × 50 mL). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and evapo-

rated in vacuo. The residue was purified by FCC (hexane/AcOEt 4:1) to afford 8.3 g (95%) of **7e**β and **7e**α (92/8, estimated by HPLC), CH_3CN/H_2O 70:30, 1 mL/min, retention time, **7e**β: 12.3 min, **7e**α: 14.1 min). ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.87 (s, 9H), 1.22 (d, J = 6.3 Hz, 3H), 1.26 (d, J = 7.1 Hz, 3H), 1.50−2.50 (m, 10H), 2.75−2.85 (m, 1H, α), 3.18−3.22 (m, 1H, β), 3.48−3.62 (m, 1H), 3.80−3.95 (m, 1H, α), 4.01−4.05 (m, 1H, β), 4.18−4.24 (m, 1H), 5.93 (s, 1H, β), 6.10 (s, 1H, α), 6.97−7.03 (m, 1H), 7.07−7.16 (m, 1H), 7.49−7.59 (m, 1H), 7.90−7.96 (m, 1H). A pure sample of **7e**β was obtained as follows: the crude residue obtained by the evaporation of the extracts was dissolved in a mixed solvent of EtOH and water (65:35, 175 mL) at 90 to 95 °C. The mixture was gradually cooled to 25 °C and stirred at 5 to 10 °C for 1 h. The resulting crystals were collected, washed with a cooled mixture of EtOH and water (65:35, 20 mL), and dried at 40 °C for 17 h to afford 6.5 g (75% based on **2**) of pure **7e**β as colorless crystals: mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.87 (s, 9H), 1.22 (d, J = 6.3 Hz, 3H), 1.26 (d, J = 7.1 Hz, 3H), 1.50−2.50 (m, 10H), 3.18−3.22 (m, 1H), 3.48−3.62 (m, 1H), 4.01−4.05 (m, 1H), 4.18−4.24 (m, 1H), 5.93 (s, 1H), 6.97−7.03 (m, 1H), 7.07−7.16 (m, 1H), 7.49−7.59 (m, 1H), 7.90−7.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 183.2, 168.5, 163.4, 155.3 (4s), 136.0, 128.3, 122.4, 117.3 (4d), 117.3, 95.2 (2s), 65.4, 61.3, 51.6, 45.9 (4d), 33.1 (2t), 25.8 (q), 24.3 (t), 22.6 (q), 22.4, 22.3 (2t), 18.0 (s), 13.1 (q), −4.2 (q); IR (KBr) 2931, 1760, 1717, 1687, 1613 cm^{-1}; MS m/z 501 (M^+ + 1); $[\alpha]^{25}_D$ + 39.2° (*c*, 1.01, MeOH). Anal. Calcd for $C_{27}H_{40}N_2O_5Si$: C, 64.77; H, 8.05; N, 5.59. Found: C, 64.55; H, 7.88; N, 6.02.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}-2,3-dihydro-2,2-dimethyl-4*H*-1,3-benzoxazin-4-one (7aβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl} isomer (7aα) were isolated in 94% yield after FCC (hexane/AcOEt 9:1) of the crude product (**7a**β:**7a**α = 85:15 estimated by HPLC, CH_3CN/H_2O 65:35, 1 mL/min, retention time, **7a**β: 9.34 min, **7a**α: 10.33 min): ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.85 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.76 (s, 3H), 1.78 (s, 3H), 2.80−2.85 (m, 1H, α), 3.15−3.25 (m, 1H, β), 3.55−3.70 (m, 1H). 3.80−3.87 (m, 1H, α), 4.00−4.05 (m, 1H, β), 4.14−4.28 (m, 1H), 6.01 (s, 1H, β), 6.08 (s, 1H, α), 6.92−6.97 (m, 1H), 7.07−7.15 (m, 1H), 7.49−7.59 (m, 1H), 7.90−7.95 (m, 1H). A pure sample of **7a**β was obtained according to the procedure described above in 60% yield based on **2**: mp 133−134 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.85 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.76 (s, 3H), 1.78 (s, 3H), 3.15−3.25 (m, 1H), 3.55−3.70 (m, 1H), 4.00−4.05 (m, 1H), 4.14−4.28 (m, 1H), 6.08 (s, 1H), 6.92−6.97 (m, 1H), 7.07−7.15 (m, 1H), 7.49−7.59 (m, 1H), 7.90−7.95 (m, 1H); IR (KBr) 2930, 2760, 1761, 1720, 1691, 1613, 1585 cm^{-1}; MS m/z 461 (M^+ + 1); $[\alpha]^{25}_D$ + 39.0° (*c*, 1.01, MeOH). Anal. Calcd for $C_{24}H_{36}N_2O_5Si$: C, 62.58; H, 7.88; N, 6.08. Found: C, 62.34; H, 7.67; N, 6.01.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}-2,2-dibutyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (7bβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl} isomer (7bα) were isolated in 87% yield after FCC (hexane/AcOEt 95:5) of the crude product (**7b**β:**7b**α = 98:2 estimated by HPLC, CH_3CN/H_2O 70:30, 1 mL/min, retention time, **7b**β: 29.3 min, **7b**α: 33.5 min) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.86 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.40−1.65 (m, 12H), 1.95−2.50 (m, 6H), 2.75−2.85 (m, 1H, α), 3.10−3.20 (m, 1H, β), 3.70−3.83 (m, 1H), 3.90−4.05 (m, 1H, α), 4.07−4.10 (m, 1H, β), 4.15−4.28 (m, 1H), 6.00 (s, 1H, β), 6.09 (s, 1H, α), 6.88−6.95 (m, 1H), 7.05−7.13 (m, 1H), 7.49−7.58 (m, 1H), 7.90−7.95 (m, 1H); IR (Nujol) 2958, 1763, 1705, 1695, 1612 cm^{-1}; MS m/z 545 (M^+ + 1); $[\alpha]^{25}_D$ +35.3° (*c*, 1.06, MeOH). Anal. Calcd for $C_{30}H_{48}N_2O_5Si$: C, 66.14; H, 8.88; N, 5.14. Found: C, 66.35; H, 8.99; N, 4.93.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}-2,3-dihydro-2,2-dipentadecanyl-4*H*-1,3-benzoxazin-4-one (7cβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl} isomer (7cα) were isolated in 64% yield after FCC (hexane/AcOEt 95:5) of the crude product (**7c**β:**7c**α = 98:2 estimated by ^{1}H-NMR) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.85 (s, 9H), 1.00−2.40 (m, 68H), 2.78−2.82 (m, 1H, α), 3.14−3.18 (m, 1H, β), 3.65−3.85 (m, 1H), 3.90−4.00 (m, 1H, α), 4.06−4.10 (m, 1H, β), 4.15−4.27 (m, 1H), 5.97 (s, 1H, β), 6.74−6.90 (m, 1H), 7.04−7.13 (m, 1H), 7.48−7.57 (m, 1H), 7.89−7.95 (m, 1H); IR (Nujol) 2956, 1762, 1702, 1694 cm^{-1}; MS m/z 853 (M^+ + 1). Anal. Calcd for $C_{52}H_{92}N_2O_5Si$: C, 73.19; H, 10.87; N, 3.28. Found: C, 73.05; H, 11.01; N, 3.19.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}spiro[2,3-dihydro-4*H*-1,3-benzoxazine-2,1′-cyclopentan]-4-one (7dβ) and its 3-{(2*S*)-2-[(2*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl} isomer (7dα) were isolated in 77% yield after FCC (hexane/AcOEt 4:1) of the crude product (**7d**β:**7d**α = 85:15 estimated by HPLC (CH_3CN/H_2O 70:30, 0.5 mL/min, retention time: **7d**β: 24.4 min, **7d**α: 27.3 min) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.87 (s, 9H), 1.22 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.70−2.30 (m, 8H), 2.74−2.78 (m, 1H, α), 3.19−3.23 (m, 1H, β), 3.60−3.71 (m, 1H), 3.72−3.79 (m, 1H, α), 3.99−4.03 (m, 1H, β), 4.10−4.20 (m, 1H), 5.96 (s, 1H, β), 6.03 (s, 1H, α), 6.92−6.96 (m, 1H), 7.07−7.15 (m, 1H), 7.48−7.57 (m, 1H), 7.91−7.96 (m, 1H); IR (Nujol) 2934, 1760, 1715, 1686, 1613, 1588 cm^{-1}; MS m/z 487 (M^+ + 1); $[\alpha]^{25}_D$ +20.35° (*c*, 1.02, MeOH). Anal. Calcd for $C_{26}H_{38}N_2O_5Si$: C, 64.17; H, 7.87; N, 5.76. Found: C, 64.29; H, 8.01; N, 6.00.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}spiro[2,3-dihydro-4*H*-1,3-benzoxazidine-2,1′-cycloheptan]-4-one (7fβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl} isomer (7fα) were isolated in 38% yield after FCC (hexane/AcOEt 4:1) of the crude product (**7f**β:**7f**α = 89:11 estimated by HPLC (CH_3CN/H_2O 70:30, 0.5 mL/min, retention time, **7f**β: 21.5 min, **7f**α: 25.0 min). ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.85 (s, 9H), 1.22 (d, J = 6.3 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.40−1.90 (m, 8H), 1.90−2.45 (m, 4H), 2.75−2.90 (m, 1H, α), 3.15−3.25 (m, 1H, β), 3.48−3.66 (m, 1H), 3.80−3.87 (m, 1H, α), 4.01−4.06 (m, 1H, β), 4.10−4.30 (m, 1H), 5.95 (s, 1H, β), 6.06 (s, 1H, α), 6.96−7.01 (m, 1H), 7.06−7.15 (m, 1H), 7.49−7.59 (m, 1H), 7.89−7.94 (m, 1H). A pure sample of **7f**β was obtained according to the procedure described above in 23% yield based on **2**: mp 146−147 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.85 (s, 9H), 1.22 (d, J = 6.3 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.40−1.90 (m, 8H), 1.90−2.45 (m, 4H), 3.15−3.25 (m, 1H), 3.48−3.66 (m, 1H), 4.01−4.06 (m, 1H), 4.10−4.30 (m, 1H), 5.95 (s, 1H), 6.96−7.01 (m, 1H), 7.06−7.15 (m, 1H), 7.49−7.59 (m, 1H), 7.89−7.94 (m, 1H); IR (KBr) 1761, 1721, 1685, 1611, 1469 cm^{-1}; MS m/z 515 (M^+ + 1); $[\alpha]^{25}_D$ +38.8° (*c*, 0.55, MeOH). Anal. Calcd for $C_{28}H_{42}N_2O_5Si$: C, 65.34; H, 8.22; N, 4.67. Found: C, 65.45; H, 8.36; N, 4.58.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}-2,2-dibenzyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (7gβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxazetidin-4-yl]propionyl} isomer (7gα) were isolated in 76% yield after FCC (hexane/AcOEt 95:5) of the crude product (**7g**β:**7g**α = 99.6:0.4 estimated by HPLC (CH_3CN/H_2O 70:30, 1 mL/min, retention time, **7g**β: 30.26 min, **7g**α: 34.65 min) as a colorless solid: mp 75−78 °C; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.52 (d, J = 7.0 Hz, 3H), 0.82 (s, 9H), 0.80−0.94 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H), 1.20−1.35 (m, 3H), 2.93−2.96 (m, 1H), 3.15−3.35 (m, 2H), 3.40−3.80 (m, 3H), 4.05−4.17 (m, 1H), 5.50 (s, 1H), 7.09−7.25 (m, 12H), 7.60−7.69 (m, 1H), 7.88−7.93 (m, 1H); IR (Nujol) 2930, 1760, 1695, 1612, 1592 cm^{-1}; MS m/z 613 (M^+ + 1); $[\alpha]^{25}_D$ +43.8° (*c*, 1.03, MeOH). Anal. Calcd for $C_{36}H_{44}N_2O_5Si$: C, 70.56; H, 7.24; N, 4.57. Found: C, 70.33; H, 7.49; N, 4.88.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1R)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}-2-pyrrolidone (24hβ) and its 3-[(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxopyrrolidin-4-yl]propionyl} isomer (24hα) were isolated in 28% yield after FCC (hexane/AcOEt

1:2) of the crude product (**24hβ:24hα** = 63:37 estimated by HPLC (CH_3CN/H_2O 45:55, 1 mL/min, retention time, **24hβ**: 13.3 min, **24hα**: 15.4 min) as a colorless solid: mp 68−140 °C; ^{1}H NMR ($CDCl_3$) δ −0.07 (s, 6H), 0.85, 0.86 (3s, 9H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H, α), 1.25 (d, *J* = 6.2 Hz, 3H, β), 1.95−2.12 (m, 2H), 2.58−2.67 (m, 2H), 2.77−2.80 (m, 1H, α), 2.95−2.98 (m, 1H, β), 3.60−3.85 (m, 1H, α), 3.89−3.93 (m, 1H, β), 3.80 (t, *J* = 7.5 Hz, 2H), 4.03−4.30 (m, 2H), 5.91 (s, 1H, α), 5.98 (s, 1H, β); IR (KBr) 1765, 1743, 1685, 1461 cm^{-1}; MS *m*/*z* 325 (M^+ − 43). Anal. Calcd for $C_{18}H_{32}N_2O_4Si$: C, 58.66; H, 8.75; N, 7.60. Found: C, 58.81; H, 8.91; N, 7.54.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}-5,5-dimethyl-2-pyrrolidinone (24aβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxopyrrolidin-4-yl]propionyl} isomer (24aα) were isolated in 73% yield after FCC (hexane/AcOEt 2:1) of the crude product (**24aβ:24aα** = 94:6 estimated by HPLC (CH_3CN/H_2O 60:40, 1 mL/min, retention time, **24aβ**: 10.9 min, **24aα**; 12.7 min) as colorless crytals: mp 132−134 °C (from *i*-Pr_2O); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 7.5 Hz, 3H), 1.43 (s, 6H), 1.81 (t, *J* = 8.1 Hz, 2H), 2.47 (t, *J* = 8.1 Hz, 2H), 2.70−2.80 (m, 1H, α), 2.95−3.00 (m, 1H, β), 3.60−3.85 (m, 1H, α), 3.88−3.91 (m, 1H, β), 4.01−4.24 (m, 2H), 5.85 (s, 1H, β); IR (KBr) 1763, 1737, 1693 cm^{-1}; MS *m*/*z* 353 (M^+ − 43); $[\alpha]^{25}_D$ +0.74° (*c*, 1.09, MeOH, **24aβ:24aα** = 94:6). Anal. Calcd for $C_{20}H_{36}N_2O_4Si$: C, 60.57; H, 9.15; N, 7.06. Found: C, 60.37; H, 9.10; N, 6.91.

3-{(2*R*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]propionyl}spiro[pyrrolidone-5,1′-cyclohexan]-2-one (24eβ) and its 3-{(2*S*)-2-[(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxopyrrolidin-4-yl]propionyl} isomer (24eα) were isolated in 84% yield (**24eβ:24eα** = 95:5 estimated by HPLC (CH_3CN/H_2O 60:40, 1 mL/min, retention time, **24eβ**: 15.8 min, **24eα**: 19.1 min) as colorless crystals: mp 110−111 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ −0.01 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.20−1.80 (m, 8H), 1.80−2.10 (m, 2H), 2.44−2.58 (m, 2H), 2.50−2.60 (m, 2H), 2.75−2.85 (m, 1H, α), 2.95−3.05 (m, 1H, β), 3.65−3.80 (m, 1H, α), 3.90−3.92 (m, 1H, β), 4.05−4.25 (m, 2H), 5.88 (s, 1H, β); IR (KBr) 1765, 1732, 1699, 1461 cm^{-1}; MS *m*/*z* 436 (M^+); $[\alpha]^{25}_D$ −7.68° (*c*, 0.99, MeOH, **24eβ:24eα** = 95:5). Anal. Calcd for $C_{23}H_{40}N_2O_4Si$: C, 63.26; H, 9.23; N, 6.42. Found: C, 63.31; H, 9.42; N, 6.15.

3-[(Z)-1-(Trimethylsilyloxy)-1-propenyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4-(3*H*)-one (14e). To a mixture of **6e** (494 mg, 1.4 mmol) and zinc dust (189 mg, 2.9 mg-atom) in THF-d_8 (6 mL) was added TMSCl (1.78 mL, 14 mmol) at room temperature under nitrogen atmosphere. The mixture was heated under reflux for 3 min. After cooling, analysis of this mixture by ^{1}H NMR spectroscopy indicated to be a 71:29 mixture of **14e** and 3-propionylspiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (**15e**): ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 9H, **14e**), 1.50−2.40 (m, 10H), 1.21 (t, *J* = 7.4 Hz, 3H, **15e**), 1.65 (d, *J* = 6.8 Hz, 3H, **14e**), 2.84 (q, *J* = 7.4 Hz, 2H, **15e**), 4.76 (q, *J* = 6.8 Hz, 1H, **14e**), 6.93−7.14 (m, 2H), 7.39−7.57 (m, 1H), 7.91−7.98 (m, 1H). THe reaction mixture was quenched with water (5 mL) and extracted with ACOEt (10 mL). The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated in vacuo. THe residue was crystallized from hexane at −20 °C to afford 164 mg of **14e** (27%) as colorless crystals: mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 9H), 1.50−2.40 (m, 10H), 1.65 (d, *J* = 6.8 Hz, 3H), 4.76 (q, *J* = 6.8 Hz, 1H), 6.93−7.14 (m, 2H), 7.39−7.57 (m, 1H), 7.91−7.98 (m, 1H); IR (KBr) 1673, 1613, 1468 cm^{-1}; MS *m*/*z* 345 (M^+). Anal. Calcd for $C_{19}H_{27}NO_3Si$: C, 66.05; H, 7.88; N, 4.05. Found: C, 66.16; H, 7.89; N, 4.01

(3*S*,4*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetizinone (16). To a solution of **7eβ** (500 mg, 1.0 mmol) in THF 15 mL) and water (5 mL) were added 30% aqueous H_2O_2 (0.9 mL, 8.0 mmol) and LiOH (84 mg, 2.0 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. To this mixture was added 1.5 N aqueous Na_2SO_4 (5 mL) at 0 °C, and the THF was evaporated in vacuo. The resulting precipitate was collected by filteration, washed with H_2O, and dried to afford 200 mg (92%) of **9e** as a colorless solid. The filtrate was washed with $CHCl_3$, and the aqueous layer was acidified to pH 1 with 10% aqueous HCl. The mixture was extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residual solid was recrystallized from hexane/AcOEt to afford 216 mg of **16** (72%) as colorless crystals: mp 146−147 °C; $[\alpha]^{25}_D$ +33.5° (*c*, 1.0, MeOH) [lit.[7] mp 147 °C; $[\alpha]^{25}_D$ +32.4° (*c*, 0.17, MeOH)].

Magnesium-Induced Reformatsky-Type Reaction. (a) Without Added Cp_2TiCl_2. To a suspension of magnesium (0.44 g, 18 mg-atom) in THF (10 mL) was added dropwise a solution of 1,2-dibromoethane (2.26 g, 12.0 mmol) in THF (5 mL). The mixture was heated under reflux for 30 min and cooled to −5 °C. To the mixture was added dropwise a solution of **2** (1.15 g, 4.0 mmol) and **6e** (2.11 g, 6.0 mmol) in THF (5 mL) at the same temperature. The mixture was stirred at 10 °C for 1 h. The reaction mixture was quenched with phosphate buffer (pH 7.0, 30 mL) and extracted with AcOEt (2 × 30 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by FCC (hexane/AcOEt 3:1) to afford a mixture of **7eβ** and **7eα** (99:1, HPLC) as a colorless solid. Recrystallization from 65% aqueous EtOH gave pure **7eβ** (0.54 g, 54%) as colorless crystals, identical with the authentic sample prepared as above.

(b) With Cp_2TiCl_2. To a suspension of magnesium (0.22 g, 9 mg-atom) in THF (5 mL) was added dropwise a solution of 1,2-dibromoethane (1.13 g, 6.0 mmol) in THF (3 mL). The resulting mixture was heated under reflux for 30 min. After cooling to 0 °C, Cp_2TiCl_2 (0.075 g, 0.3 mmol) was added, and the mixture was stirred for 5 min. To this mixture, a solution of **2** (0.57 g, 2.0 mmol) and **6e** (1.06 g, 3.0 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with AcOEt (2 × 30 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo to afford a mixture of **7eβ** and **7eα** (99:1, HPLC) as a colorless solid. This material was recrystallized as described in a to give 0.73 g (73%) of pure **7eβ**, identical with that prepared as above.

3-{(2*R*)-2-[(3*S*,4*R*)-1-[(Allyloxycarbonyl)methyl]-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]-propionyl}spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4-(3*H*)-one (8eβ). To a solution of the azetidinone **7eβ** (7.1 g, 0.0142 mol) and allyl bromoacetate (2.94 g, 0.0164 mol) in THF (36 mL) was added $NaN(TMS)_2$ (1 M in THF) (17 mL, 0.017 mol) at −50 to −45 °C over 15 min. After stirring at −45 °C for 1 h, the mixture was poured into 10% aqueous citric acid (100 mL) and extracted with AcOEt (1 × 100 mL, 1 × 50 mL). The combined extracts were washed successively with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and water (100 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by FCC (hexane/AcOEt 8:1) to afford 8.07 g (95%) of **8eβ** as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.77 (s, 9H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.29 (d, *J* = 7.1 Hz, 3H), 1.60−1.80 (m, 6H), 1.90−2.40 (m, 4H), 3.06 (dd, *J* = 2.2, 7.3 Hz, 1H), 3.64 (dq, *J* = 2.2, 7.0 Hz, 1H), 4.05−4.20 (m, 2H), 3.99 (d, *J* = 17.9 Hz, 1H), 4.35 (d, *J* = 17.9 Hz, 1H), 4.55−4.70 (m, 2H), 5.20−5.45 (m, 2H), 5.80−6.05 (m, 1H), 6.95−7.15 (m, 2H), 7.50−7.60 (m, 1H), 7.90−8.00 (m, 1H); IR (KBr) 2936, 1768, 1740, 1710, 1680, 1612, 1588 cm^{-1}; MS *m*/*z* 599 (M^+ + 1); $[\alpha]^{25}_D$ −3.77° (*c*, 0.88, MeOH). Anal. Calcd for $C_{32}H_{46}N_2O_7Si$: C, 64.19; H, 7.74; N, 4.68. Found: C, 64.45; H, 8.02; N, 4.89.

3-{(2*R*)-2-[(3*S*,4*R*)-1-[(Allyloxycarbonyl)methyl]-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxoazetidin-4-yl]-propionyl}spiro[pyrrolidone-5,1′-cyclohexan]-2-one (25e) was isolated in 89% yield after FCC(hexane/AcOEt 4:1) of the crude product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.30−1.80 (m, 8H), 1.80−2.10 (m, 2H), 2.37−2.60 (m, 2H), 2.43−2.51 (m, 2H), 2.95−3.01 (m, 1H), 3.70−3.80 (m, 2H), 4.00−4.25 (m, 3H), 4.63 (d, *J* = 5.6 Hz,

2H), 5.20−5.39 (m, 2H), 5.82−6.20 (m, 1H); IR (KBr) 2934, 1764, 1745, 1693 cm^{-1}; MS *m/z* 534 (M^+); $[\alpha]^{25}_D$ +7.20° (*c*, 1.00, MeOH). Anal. Calcd for $C_{28}H_{46}N_2O_6Si$: C, 62.89; H, 8.67; N, 5.24. Found: C, 62.99; H, 8.75; N, 5.11.

Dieckmann-Type Cyclization. (a) With TMSCl. Allyl (4*R*,5*R*,6*S*)-6-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3-(diphenoxyphosphoryloxy)-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (10). Into a solution of $NaN(TMS)_2$ (1 M in THF, 34 mL, 34.0 mmol) was added dropwise **8e**β (8.07 g, 13.5 mmol) in THF (42 mL) at −35 to −25 °C over 10 min. TMSCl (1.91 g, 17.6 mmol) was added at −30 °C and the mixture was stirred at the same temperature for 2 min. Diphenyl phosphorochloridate (4.54 g, 16.9 mmol) was then added at −30 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into phosphate buffer (pH 7.0, 100 mL) and extracted with AcOEt (1 × 100 mL, 1 × 50 mL). The combined extracts were washed successively with the phosphate buffer (2 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was suspended in hexane (70 mL) and stirred at 5 °C for 1 h. The resulting crystals were collected by filteration and washed with hexane to recover 2.6 g (85%) of **9e**. The filtrate was evaporated in vacuo, and the residue was purified by FCC (hexane/AcOEt 4:1) to afford 6.76 g (82%) of **10** as a viscous colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.18 (d, J = 7.5 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H), 3.20−3.30 (m, 1H), 3.30−3.50 (m, 1H), 4.00−4.30 (m, 2H), 4.64 (d, J = 5.4 Hz, 2H), 5.10−5.40 (m, 2H), 5.75−5.95 (m, 1H), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 175.4, 159.0, 154.9, 150.1 (4s), 131.4, 130.0, 129.9, 126.0, 125.9, 120.0 (6d), 119.8, 119.0 (2s), 118.4 (1), 66.0 (d), 65.6 (t), 61.3, 54.2, 39.4 (3d), 25.7, 22.4 (2q), 17.9 (s), 14.6, −4.2, −5.0 (3q); IR (Nujol) 2931, 1786, 1718, 1638, 1591, 1490 cm^{-1}; MS *m/z* 614 (M^+ + 1); $[\alpha]^{25}_D$ +48.1° (*c*, 0.99, MeOH). Anal. Calcd for $C_{31}H_{40}NO_8PSi$: C, 60.67; H, 6.57; N, 2.28. Found: C, 60.78; H, 6.79; N, 2.55.

(b) Without TMSCl. To a solution of $NaN(TMS)_2$ (1 M in THF, 5.0 mL, 5.0 mmol) was added dropwise **8e**β (1.2 g, 2.0 mmol) in THF (6 mL) at −35 to −25 °C over 1 min, and the mixture was stirred at the same temperature for 10 min. Diphenyl phosphorochloride (0.67 g, 2.5 mmol) was added at −30 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was processed as described above. The crude product obtained from the evaporation was suspended in *i*-Pr_2O (10 mL) and stirred at 5 °C for 1 h. The resulting crystals were collected by filteration to recover 0.38 g (87% of **9e**. The filtrate was evaporated in vacuo, and the residue was purified by FCC (hexane:AcOEt = 4:1) to afford 0.22 g (18%) of **10**, identical with the authentic sample prepared as above. The second fraction contained **19**, which was recrystallized from AcOEt to afford 135 mg (15%) of **19** as colorless crystals: mp 100−102 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−2.20 (m, 10H), 6.60−7.60 (m, 14H); IR (KBr) 1673, 1589, 1485 cm^{-1}; MS *m/z* 449 (M^+). Anal. Calcd for $C_{25}H_{24}NO_5P$: C, 66.81; H, 5.38; N, 3.12. Found: C, 66.96; H, 5.51; N, 3.05.

(c) Cyclization of 25e. To a solution of $NaN(TMS)_2$ (1 M in THF, 1.20 mL, 1.2 mmol) in THF (1.5 mL) was added dropwise a solution of **25e** (301 mg, 0.56 mmol) in THF (1 mL) at 0 °C. The mixture was stirred at the same temperature for 30 min. TMSCl (64 mg, 0.59 mmol) was added at −50 °C, and the mixture was stirred at the same temperature for 10 min. Diphenyl phosphorochloridate (166 mg, 0.62 mmol) was then added at the same temperature, and the mixture was stirred at 0 °C for 16 h. The reaction mixture was processed as above. The crude product was purified by FCC (hexane/AcOEt 4:1) to give 31 mg (9%) of **10**, identical with that prepared as above.

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