Regio- and Stereoselective Synthesis of Key 1-Methyl Carbapenem Intermediates via Hydroformylation Using a Zwitterionic Rhodium Catalyst

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Received August 24, 1999

Abstract: The asymmetric hydroformylation of a 4-vinyl β-lactam catalyzed by a rhodium catalyst with a chiral phosphine ligand was investigated. The catalytic system consisting of a zwitterionic rhodium catalyst, (NBD)$Rh^+(C_6H_5B^-Ph_3)$ **4,** and (*S*,*S*)-2,4 bis(diphenylphosphino)pentane, (*S*,*S*)-BDPP, gave branched aldehydes in high regio- and stereoselectivity. The hydroformylated products are key intermediates in the synthesis of 1-methylcarbapenem antibiotics. Using (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethyl-silyloxy)ethyl]-4-vinyl-2-azetidinone (**5a)** as the reactant afforded aldehydes in a 97:3 branched-to-linear ratio and 91:9 to β- to α-branched isomers. The regio (branched/linear)- and stereoselectivity (β/α) was >99:1 when (3*S*,4*R*)-1-N-BOC-3-[(*R*)-1-methoxyethyl]-4-vinyl-2-azetidinone was used as the substrate **(5q)**.

Introduction

As unnatural antibiotics, 1-methylcarbapenems (**1)** are among the most extensively investigated β-lactams in the last two decades.[1] 1-Methylcarbapenem has a wide range of biological properties including strong antibacterial activity, resistance to β-lactamase, and metabolic stability.[2] Of particular note is the resistance to renal dehydropeptidase.[3] Furthermore as **1** contains 4-chiral centers, many organic chemists have been interested in the synthesis of **1**, key intermediates,[4] or related derivatives,[5] since the first discovery of its activities and structure by Merck researchers. The monocyclic β-lactam **2**, one of the most valuable intermediates of **1,** is usually derived form 4-acetoxy-2-azetidinone[7] **3** by alkylation,[8] Reformatsky reaction,[9] or by asymmetric hydrogenation.[10] Recently the diastereoselective radical cyclization of an *N*-vinyl α-bromoamide was reported as another strategy to generate **2** without involvement of the acetoxy compound **3**.[11]

In 1996, Nozaki and co-workers[12] reported the synthesis of the 1-methylcarbapenem intermediate **2** by hydroformylation of the 4-vinyl β-lactam, (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethyl-silylolxy)ethyl]-4-vinyl-2-azetidinone **5a**, using $Rh(acac)(CO)_2$ and a chiral bidentate phosphorous ligand based on BINAPHOS. While the diastereoselectiveity was good, the regioselectivity of the reaction was low with the ratio of branched/linear aldehydes being 76/24.

Previous studies by one of us have demonstrated that zwitterionic rhodium complexes such as **4** are useful catalysts for a variety of carbonylation reactions. Complex **4**,[13] either by itself or in the presence of 1,4-bis(diphenylphosphino)butane, can effect the highly regioselective hydroformylation of aryl and 1,1-disubstituted alkenes,[14] allyl acetates,[15] vinyl ethers,[16] vinyl silanes,[17] vinyl sulfones[18] and sulfoxides,[19] as well as α,β-unsaturated esters.[20] These results prompted us to apply **4** to the hydroformylation of 4-vinyl β-lactams **5** as shown in Scheme 1. Two branched (**6**β and **6**α)-chain and one linear (**7**) aldehyde are possible reaction products, with the desired aldehyde precursor to **2** being **6**β.

Herein we report the hydroformylation of a variety of 4-vinyl β-lactams (**5)** catalyzed by the zwitterionic rhodium complex **4** and chiral phosphine ligands. Steric and electronic effects of substrates at several positions of the β-lactam were investigated. This research has resulted in the determination of the substituent

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Published on Web 12/03/1999

Scheme 1

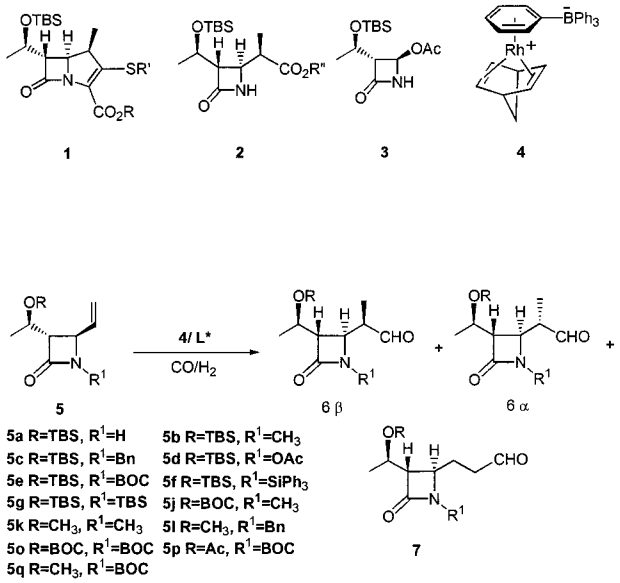

Table 1. Hydroformylation of **5a** Catalyzed by **4** in Benzene[a]

entry	ligand	cat./ lig.	*T* (°C)	time (h)	*p* (psi)	conv.[b] (%)	6/7[c]	6β/6α[c]
1	PPh_3	1/1	50	24	1400	100	58/42	53/47
2	(*S*,*S*)-DIOP	1/1	50	45	1400	60	48/52	39/61
3	(*S*,*R*)-BPPFA	1/1	80	24	700	98	38/62	48/52
4	(*S*,*S*)-Me-DUPHOS	1/2	70	24	1200	61	68/32	35/65[d]
5	NORPHOS	1/2	70	24	1200	46	77/33	55/45
6	(*S*,*S*)-BPPM	1/2	50	45	1400	95	76/24	41/59
7	(*S*,*S*)-CHIRAPHOS	1/2	95	24	700	96	81/19	41/59
8	(*S*)-BINAP	1/2	50	48	1400	100	82/18	33/87
9	(*R*)-BINAP	1/2	50	40	1400	100	90/10	36/64
10	JOCIPHOS	1/2	70	24	1200	30	86/14	49/51
11	(*R*,*S*)-BINAPHOS	1/4	50	24	1400	98	61/39	92/8
12	(*S*,*S*)-BDPP	1/2	60	24	1200	100	92/8	85/15
13	(*R*,*R*)-BDPP	1/2	60	24	1200	100	93/7	10/90

[a] Reactions were carried out using 5 mol % of **4** and 1:1 CO/H_2. [b] The % conversion was determined by GC or ^1H NMR. [c] The ratio was determined by ^1H NMR spectroscopy. [d] The reaction was carried out in THF solution.

groups needed to achieve hydroformylation with complete regio- and stereoselectivity.

Result and Discussion

We first examined the effect of different types of chiral phosphine ligands on the regio- and stereoselectivity of the hydroformylation reaction of **5a** catalyzed by **4.** Various chiral bidentate phosphorus ligands which were used for the hydroformylation of simple olefins,[21] including (*S*,*S*)-DIOP, (*S*,*S*)-BPPM, (*R*)- and (*S*)-BINAP, Joshiphos, (*S*,*S*)-Me-Duphos, Norphos, (*S*,*S*)-BDPP, (*R*,*R*)-BDPP, and BINAPHOS were applied to the reaction and the results are summarized in Table 1. When triphenylphosphine was used as a monodentate ligand, the ratio of b/l and α/β was in the range of 1:1(Table 1, entry 1). Though (*R*)- or (*S*)-BINAP gave good regioselectivity, the major branched aldehyde was **6a** α (Table 1, entries 8/9). The same observations were made (*S*,*S*)-CHIRAPHOS (Table 1, entry 7) and Joshiphos (Table 1, entry 10). In addition, Joshiphos gave low conversions due to low solubility.

High stereoselectivity (92/8) was obtained using BINAPHOS but the regioselectivity was low (61/39), consistent with the results of Nozaki and co-workers who used $Rh(CO)(acac)_2$ as the catalyst (entry 11 in Table 1).[12] Two stereoisomers of 2,4 bis(diphenylphosphino)pentane (BDPP)—(*S*,*S*)-BDPP and (*R*,*R*)-BDPP—afforded excellent regioselectivities of branched/linear aldehydes (92/8 and 93/7) using 5 mol % of **4,** 1200 psi of CO/H_2, at 60 °C for 24 h in benzene (Table 1, entries 12/13). The stereoselectivity was opposite for (*S*,*S*)- and (*R*,*R*)-BDPP, with the desired β- form as the major product in a 85/15 ratio with (*S*,*S*)-BDPP, and the undesired α-form as the dominant stereoisomer using (*R*,*R*)-BDPP (90/10). These chiral ligand effects are different from those of (*R*)- and (*S*)-BINAP which gave similar ratios of **6/7** and especially **6**β/**6**α.

Table 2. Hydroformylation of **5a** Catalyzed by **4** and (*S*,*S*)-BDPP[a]

entry	solvent	cat./ lig.	*T* (°C)	time (h)	CO/H_2 (psi)	conv.[b] (%)	6/7[c]	6β/6α[c]
1	PhH	1/2	70	24	1200	100	97/3	91/9
2	PhH	1/2	70	24	700	100	97/3	90/10
3	PhH	1/2	70	12	1200	87	92/8	89/11
4	PhH	1/1	70	24	1200	100	87/13	80/20
5	PhH	1/4	70	24	1200	80	94/6	90/10
6	THF	2/4	90	24	700	100	66/34	44/56
7	THF	2/4	70	24	1200	100	75/25	36/64
8	THF	2/8	70	24	1200	100	77/23	40/60
9	CH_2Cl_2	2/4	70	24	1200	40	60/40	77/23
10	DME	2/2	90	24	1200	100	83/17	35/65
11	DME	2/4	70	12	1200	100	76/24	32/68
12	DME	2/8	70	24	1200	50	80/20	95/5
13	DME	2/8	70	48	1200	70	93/7	92/8

[a] Reactions were carried out using 5 mol % of catalyst and 1/1 CO/H_2. [b] The % conversion was determined by GC and by ^1H NMR spectroscopy. [c] The ratio was determined by ^1H NMR spectroscopy.

To increase the regio- and stereoselectivity of the hydroformylation of the vinyl β-lactam **5a**, we examined the influence of temperature, solvent, amount of catalyst, reaction time, and pressure on the (S,S)-BDPP reaction system, and the results are summarized in Table 2. Increasing the temperature from 60 to 70 °C for the reaction in benzene enhanced the regio and stereoselectivity (97/3 **6/7**; 91/9 **6**β/**6**α**)** of the reaction (compare Table 2, entry 1 and Table 1, entry 12). The reaction proceeds essentially as well at 700 psi as it does at 1200 psi (Table 2, entries 1 and 2), but reducing the reaction time (12 h) or the chiral ligand/**4** ratio to 1/1 is deleterious for the process (entries 3 and 4). Increasing the chiral ligand/**4** ratio to 4/1 is not beneficial in terms of conversion, regio- or stereoselectivity (entry 5). Lower regio- and stereoselectivities or conversions resulted using THF, CH_2Cl_2, or DME as the solvent (entries 6−13).

The nature and effective bulk of substituents at nitrogen, and at the C-3 position of the β-lactam, play an important role in the reaction. As noted previously,[12] the bulky OTBS group of **5a** protects one side of the olefin, and the Rh complex should approach from the other side of the olefin. According to computational modeling (*CS Chem3D Pro*), the rhodium complex must approach from the side of the OTBS group in order to give the β-isomer. This suggests that the high stereoselectivity resulted from rotation of the olefin of **5a**. Consequently, the hydrogen of NH was replaced by other groups to assess the influence of such substrates in the regio- and stereoselectivity of the hydroformylation reaction. It was reasoned that since the NH group is closer to the double bond than the OTBS group, the steric effect of the substituent at nitrogen may be significant for the process. The electron density of the N of the lactam is also a factor on the hydroformylation reaction. The conversion of NH to a variety of alkylated, acylated, and silylated NR compounds was achieved by simple methods as shown in Figure 1. The N−Me (**5b**) and N−Bn

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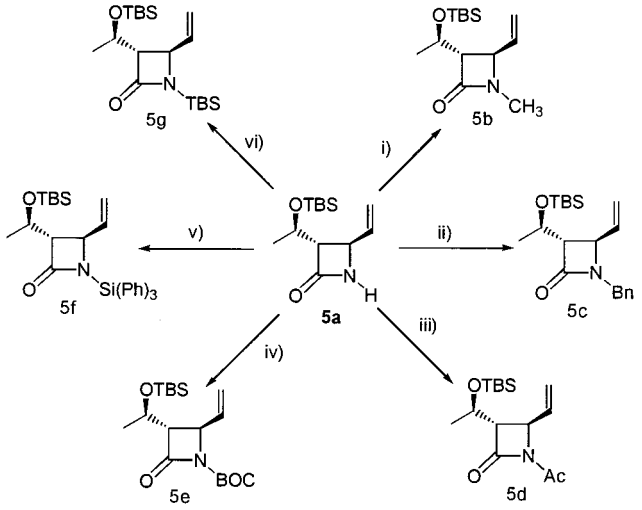


Figure 1.

Table 3. Hydroformylation of **5** Catalyzed by **4** in Benzene[a]

substrates	ligands	conv.[b] (%)	6/7[c]	6β/6α[c]
5b	(*S*,*S*)-BDPP	95	63/37	>99/1
5c	(*S*,*S*)-BDPP	98	85/15	67/33
5c	(*R*)-TolBINAP	100	75/25	85/15
5d	(*S*,*S*)-BDPP	100	50/50	80/20
5d	(*R*)-BINAP	60	60/40	84/16
5e	(*S*,*S*)-BDPP	100	13/87	>99/1
5e	(*R*)-BINAP	30	36/64	94/6
5f	(*S*,*S*)-BDPP	64	43/57	84/16
5g	(*S*,*S*)-BDPP	100	50/50	80/20
5g	(*R*)-BINAP	100	60/40	84/16

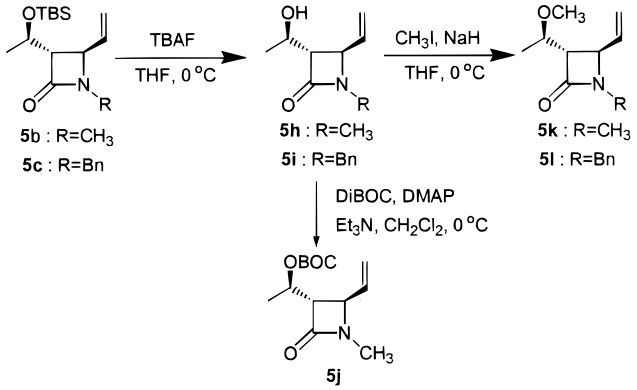
[a] Reactions were carried out by using 5 mol % of **4** under 1200 psi of CO/H_2 at 70 °C for 24 h (ligand/catalyst = 2/1). [b] The ratios were determined by GC or ^{1}H NMR. [c] The ratio was determined by ^{1}H NMR spectroscopy.

(**5c**) lactams were synthesized in good yields by simple alkylation reactions with NaH which proceeded without epimerization. The *N*-acetyl derivative (**5d**) was generated by using acetic anhydride and triethylamine, and the *t*-BOC lactam (**5e**) was obtained in excellent yield by using a weak base,[22] while triphenylsilyllactam (**5f**) and *tert*-butyldimethylsilyllactam (**5g**) were prepared with triethylamine in DMF.[23] Lactams **5b**−**5g** were hydroformylated using **4** and a chiral bidentate ligand, and results are presented in Table 3.

The regioselectivities for the hydroformylation of the *N*-alkylated *β*-lactams **5b** and **5c**, by **4** and (*S*,*S*)-BDPP, were inferior to **5a**. Stereoselectivity occurred in the N−CH_3 case (Table 3, entry 1). Note that the methyl group increases the basicity at nitrogen. This factor, together with the bulky OTBS group protecting one side of the olefin, may be responsible for the selective approach of **4** from the less hindered side.

Compared to **5b**, **5c** gave moderate stereoselectivity because the larger benzyl group also protects the other side of olefin. Substrates containing an electron deficient N atom, gave a substantial proportion of the linear aldehyde with excellent stereoselectivity in the case of **5e**. The N-silylated derivatives **5f** and **5g** gave low regio- and stereoselectivity.

Scheme 2



Appreciative of the impact of the R group at nitrogen, we next investigated replacing the OTBS function at **5a** by OAc, BOC, and OCH_3 functionalities. The preparation of the *N*-methyl and *N*-benzyl methoxy-*β*-lactams (**5k** and **5l)** required two steps: desilylation and alkylation as shown in **Scheme 2**. Transformation of the OTBS group to OH was effected with tetrabutylammonium fluoride in THF to give **5h** and **5i**. The *t*-BOC derivative **5j** was obtained from **5h** by standard methods. Alkylation of **5h** and **5i** using NaH and methyl iodide afforded **5k** and **5l**, respectively.

N-BOC derivatives were synthesized in several steps as shown in Scheme 3. The TBS group of **5a** was removed by tetrabutylammonium fluoride to give **5m** in good yield. The N-BOC lactam **5n** was generated by treatment of 1 equiv of **5m** with di-(*tert*-butyl)dicarbonate, DMAP, and triethylamine, while the N,O-DiBOC lactam **5o** was obtained using 2 equiv of di-(*tert*-butyl)dicarbonate. The acylated product (**5p**) was easily obtained by acylation of **5n**. Because simple methylation of **5m** with NaH and methyl iodide gave the *N*-methylated product, we used **5n** as a substrate to obtain the O-methyl product. Unfortunately, the *O*-methyl product was minor with epimerization as the principal pathway. Therefore, another methylation method was used involving NaOH, dimethyl sulfate, and tetrabutylammonium iodide[24] in reaction with **5n**, to form the *O*-methylated product **5q** in 75% yield. The results for the hydroformylation of **5j**, **5k**, **5l**, **5o**, **5p**, and **5q** are summarized in Table 4.

Lactam **5j** has a structure similar to that of **5b**, and gave low regio- and stereoselectivity in the hydroformylation reaction. The BOC group in **5j** does not fully protect one side of the olefin, and thus the selective approach of the rhodium complex might be difficult. Poor regio- and stereoselectivity was observed in the case of **5k** and **5l** which have electron-donating substituents at the nitrogen atom. The lower stereoselectivity may be due to the similar steric environment of both faces of the olefin. The more bulky benzyl derivative **5l** gave higher stereoselectivity than the methyl derivative (**5k**). In comparison with **5k** and **5l**, the electron deficient derivatives (**5o** and **5p**) afforded moderate regio- and appreciably higher stereoselectivities. The large difference of stereoselectivity between **5o** and **5k** resulted from the difference in steric effects. In the case of **5o**, the bulky BOC group protects both sides of olefin; therefore, it is difficult to induce high regioselectivity though the stereoselectivity is excellent. A significant result was obtained when we used **5q** as the starting material. We examined the hydroformylation of **5q** with (*S*,*S*)-BDPP and (*R*)-BINAP as the chiral ligand. In

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Scheme 3

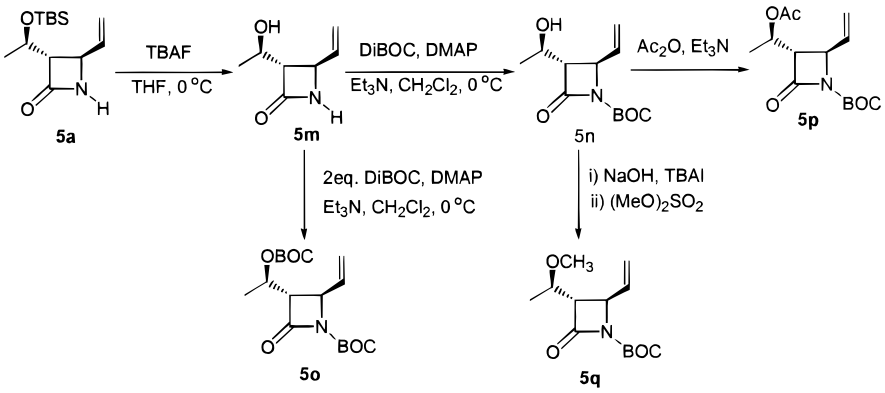

Table 4. Hydroformylation of **5j**−**l**, **5o**−**q** Catalyzed by **4** in Benzene[a]

substrates	ligands	conv.[b] (%)	6/7[c]	6β/6α[c]
5j	(*S*,*S*)-BDPP	100	55/45	60/40
5k	(*S*,*S*)-BDPP	95	57/43	50/50
5l	(*S*,*S*)-BDPP	98	47/53	76/24
5o	(*S*,*S*)-BDPP	98	76/24	>99/1
5o	(*R*)-BINAP	82	60/40	72/28
5p	(*S*,*S*)-BDPP	100	82/18	92/8
5q	(*S*,*S*)-BDPP[d]	70	>99/1	>99/1
5q	(*R*)-BINAP	30	60/40	>99/1

[a] Reactions were carried out by using 5 mol % of **4** under 1200 psi of CO/H_2 at 70 °C for 24 h (Cat/L = 1/2, CO/H_2 = 1/1). [b] The ratios were determined by GC and ^{1}H NMR. [c] The ratios were determined by ^{1}H NMR spectroscopy. [d] Note that use of $Rh(CO)_2$acac instead of **4** results in olefin hydrogenation as the major pathway, and the ratio of the byproducts **6**/**7** was 1/1.

the case of *(R)*-BINAP, we obtained moderate regioselectivity and complete stereoselectivity. We were gratified to observe that the use of (*S*,*S*)-BDPP afforded only one regio- and stereoisomer in the hydroformylation of **5q**. It is conceivable that the large difference in size of the substituent at O and N accounts for the high stereoselectivity. In the event, the bulky N-substituent, being closer to the olefin than the OCH_3 group, sterically impacts the hydroformylation process. That is, the bulky N-BOC protects one side of the olefin, and it is only possible to approach the rhodium catalyst from the less hindered OMe side.

Conclusions

In conclusion, the zwitterionic rhodium complex **4** and (S,S)-BDPP catalyzed the hydroformylation of **5a** to give the β-aldehyde in excellent regio- and diastereoselectivity. This procedure provides a more efficient method to synthesize one of the key intermediates of 1-methylcarbapenem than using the $[Rh(I)(acac)(CO)_2]$-chiral phosphite ligand.[12] While the hydroformylation of a variety of β-lactams indicates that the stereoselectivity is principally affected by the chiral ligand and steric hindrance, the regioselectivity depends on the nature of the chiral ligand, as well as steric and electronic effects of the substituents. The results for the hydroformylation of **5q** are impressive indeed. These excellent results for the synthesis of 1-methylcarbapenem intermediates, afforded a better understanding of the nature of the hydroformylation of key 4-vinyl-β-lactams.

Experimental Section

General. Unless otherwise noted materials were obtained from commercial suppliers and were used without further purification. THF, DME, and benzene were distilled from sodium benzophenone ketyl prior to use. Methylene chloride was distilled using CaH_2 as drying agent. The rhodium zwitterionic catalyst (**4**) was prepared according to the literature procedure.[13] The 4-vinyl lactam **5a** was obtained from the Takasago International Corp. Spectral measurements were determined by use of the following instruments: Bomem MB-100 (FT-IR), Varian XL 300 or 200 MHz (NMR), VG 7070E (MS).

Preparation of 5b. To a solution of NaH (55 mg, 2.2 mmol) in 10 mL of THF was added **5a** (51 mg, 2 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 30 min until no further gas evolution occurred, followed by slow addition of MeI (283.8 mg, 2.2 mmol) in THF (3 mL) at −78 °C. The reaction mixture was quenched after 6 h by saturated NH_4Cl solution and was extracted with ether (40 mL) and methylene chloride (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. Purification of the residue by flash chromatography on silica gel, with hexanes/ether (1:9) as the eluant, gave 511 mg (95%)of **5b** as a liquid. ^{1}H NMR: δ 0.032 (s, 6H), 0.82 (s, 9H), 1.13−1.16(d, 3H, J = 6 Hz), 2.69(s, 3H), 2.78−2.81 (m, 1H), 3.93−3.97(dd, 1H, J = 1.4, 7.0 Hz), 4.11−4.20-(m, 1H), 5.15−5.35(m, 2H), 5.70−5.87(m, 1H); ^{13}C NMR: δ 17.87, 22.45, 25.69, 52.01, 58.07, 67.11, 67.16, 118.59, 136.30, 167.97; IR (CH_2Cl_2): 1740 (C═O) cm^{-1}; HRMS calcd for $C_{14}H_{27}NO_2Si$ 269.1811, found 254.1592 (M^+ − 15).

Preparation of 5c. To a solution of NaH (55 mg, 2.2 mmol) in THF (10 mL) was added **5a** (510 mg, 2 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 30 min, and then benzyl bromide (342 mg, 2.2 mmol) in THF (3 mL) was added at −78 °C. The reaction mixture was stirred and, after 6 h, was treated with saturated NH_4Cl and then extracted with ether (40 mL) followed by methylene chloride (20 mL) The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuum. Purification of the residue, effected by flash chromatography on silica gel, with hexanes/ether (1:9) as the eluant, gave 655 (96%)mg of **5c** as a liquid. ^{1}H NMR: δ −0.01 (s, 3H), 0.03 (s, 3H), 0.80 (s, 9H), 1.13−1.16(d, 3H, J = 6.2 Hz), 2.84−2.87(dd, 1H, J = 2.2, 4.2 Hz), 3.9−4.1(m, 2H), 4.08−4.30(m, 1H), 4.47−4.59(d, 1H, J = 16 Hz), 5.10−5.30(m, 2H), 5.61−5.82(m, 1H), 7.10−7.41(m, 5H); ^{13}C NMR: δ 17.89, 22.39, 25.70, 44.43, 55.83, 64.64, 65.29, 118.93, 127.40, 128.41, 135.87, 136.26, 167.46; IR (CH_2Cl_2): 1757 (C═O) cm^{-1}; HRMS calcd for $C_{19}H_{31}NO_2Si$ 345. 2124, found 330.1925 (M^+ − 15).

Preparation of 5d. To a solution of **5a** (255 mg, 1 mmol) in methylene chloride (10 mL) was added triethylamine (280 μL, 2.2 mmol). After 10 min, acetic anhydride (125 mg, 1.1 mmol) in methylene chloride (2 mL) was added slowly at 0 °C. The reaction mixture was stirred for 4 h and then quenched with saturated NH_4Cl solution and extracted with ethyl acetate (40 mL) and then with methylene chloride (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with hexanes/ether (1:10) as the eluant, gave 279 mg (94%) of **5d** as a liquid. ^{1}H NMR: δ 0.015(s, 3H), 0.040(s, 3H), 0.79(s, 9H), 1.15−1.22(d, 3H, j=6), 2.31(s, 3H), 2.89−2.91(dd, 1H, J = 3.2, 3.15 Hz), 4.19−4.22(m, 1H), 4.60−4.61(dd, 1H, J = 3.2, 6.8 Hz), 5.22−5.45(m, 2H), 5.84−6.01(m, 1H); ^{13}C NMR: δ 17.75, 21.95, 23.92, 53.59, 64.53, 64.80, 118.05, 134.84, 166.31, 167.63; IR (CH_2-

Cl_2): 1710 (C═O, aldehyde), 1790 (C═O, ester) cm^{-1}; HRMS calcd for $C_{14}H_{27}NO_3Si$ 297.1760, found 282.1483 (M^+-15)

Preparation of 5e. To the mixture of di-(*tert*-butyl)dicarbonate (436 mg, 1.1 mmol), **5a** (255 mg, 1 mmol), and DMAP (123.4 mg, 1.1 mmol) in methylene chloride (10 mL) was added triethylamine (140 μL, 1.1 mmol). The reaction mixture was stirred for 6 h at room temperature and then quenched by saturated NH_4Cl and extracted with methylene chloride (40 mL) followed by extraction with ethyl acetate (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with hexanes/ether (1:10) as the eluant, gave 324 mg (91%) of **5e** as a liquid. ^{1}H NMR: δ 0.039(s, 3H), 0.049(s, 3H), 0.83(s, 9H), 1.15−1.19(d, 3H, J = 6), 1.46(s, 9H), 2.81−2.87 (dd, 1H, J = 3.2, 3.2 Hz), 4.21−4.32(m, 1H), 4.47−4.52(dd, 1H, J = 3.2, 7.4 Hz), 5.21- 5.40 (m, 2H), 5.83−6.00(m, 1H); ^{13}C NMR: δ 17.81, 22.05, 25.66, 27.99, 54.59, 63.61, 64.77, 82.90, 117.09, 135.42, 147.82, 165.64; IR (CH_2Cl_2): 1725 (C═O, lactam), 1812 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{17}H_{33}NO_4Si$ 355.2179, found 298.1083 (M^+ − 57).

Preparation of 5f. To the mixture of triphenylchlorosilane (323 mg, 1.1 mmol) and **5a** (255 mg, 1 mmol) in DMF (10 mL) was added triethylamine (280 μL, 2.2 mmol). The reaction mixture was refluxed for 12 h. The reaction mixture was treated with saturated NH_4Cl and extracted with methylene chloride (40 mL) and ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue, attained by flash chromatography on silica gel, with hexanes/ether (1:15) as the eluant, gave 410 mg (80%) of **5f** as a white solid ^{1}H NMR: δ 0.025(s, 3H), 0.089 (s, 3H), 0.8(s, 9H), 1.19−1.22(d, 3H), 3.03−3.07(dd, 1H, J = 3.0, 4.8 Hz), 4.12−4.18(dd, 1H, J = 0.8, 8.6 Hz), 4.23−4.35(p, 1H, J = 11 Hz), 4.62−4.80(m, 2H), 5.62−5.78(m, 1H), 7.3−7.5(m, 10H), 7.6−7.8(m, 5H); ^{13}C NMR: δ 17.85, 23.28, 25.70, 52.14, 54.69, 65.41, 116.37, 117.30, 127.78, 129.90, 130.22, 131.69, 134. 87, 135.42, 135.90, 137.44, 137.87, 173.01; IR (CH_2Cl_2): 1749 (C═O) cm^{-1}; HRMS calcd for $C_{30}H_{39}NO_2Si_2$ 543.2625, found: 456.1810 (M^+ − 57).

Preparation of 5 g. To a mixture of *tert*-butyl(dimethyl)chlorosilane (165 mg, 1.1 mmol) and **5a** (255 mg, 1 mmol) in DMF was added triethylamine (280 μL, 2.2 mmol). The reaction mixture was refluxed for 12 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with methylene chloride (40 mL) and then ethyl acetate (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with hexanes/ether (1:15) as the eluant, gave 306 mg (83%) of **5g** as a liquid. ^{1}H NMR: δ 0.036(s, 3H), 0.049-(s, 3H), 0.149(s, 3H), 0.162(s, 3H), 0.85(s, 9H), 0.90(s, 9H) 1.12−1.15(d, 3H, J = 6.2 Hz), 2.85−2.88 (dd, 1H, J = 3.0, 4.6 Hz), 4.01−4.07(dd, 1H, J = 2.8, 9.0 Hz), 4.11−4.22(p, 1H, J = 10.4 Hz), 5.07−5.30(m, 2H), 5.75−5.93(m, 1H); ^{13}C NMR: δ 17.97, 18.11, 22.23, 25.83, 26.27, 54.48, 65.56, 65.70, 117.16, 139.92, 173.00; IR (CH_2-Cl_2): 1724 (C═O) cm^{-1}; HRMS calcd for $C_{18}H_{39}NO_2Si_2$ 369.2519, found: 354.2290 (M^+ − 15).

Preparation of 5h. To a solution of **5b** (538.4 mg, 2 mmol) in THF (10 mL) was added 1 N $(Bu)_4NF$ in THF (3 mL, 3 mmol). The reaction mixture was stirred for 4 h and followed by the addition of a saturated solution of NH_4Cl. The crude product was extracted with ethyl acetate (40 mL) and then methylene chloride (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:1) as the eluant, gave 282 mg (91%) of **5h** as a liquid. ^{1}H NMR: δ 1.20−1.25(d, 3H, J = 6.4 Hz), 2.5−2.6(br, 1H), 2.72(s, 3H), 2.8−2.9(dd, 1H, J = 0.4, J = 2 Hz), 3.90−4.00(dd, 1H, J = 6, 8.2 Hz), 4.1−4.3(m, 2H), 5.2−5.4(m, 2H), 5.7−5.8(m, 1H); ^{13}C NMR: δ 21.18, 52.18, 57.21, 64.26, 64.40, 119.12, 135.69, 168.17; IR (CH_2-Cl_2): 1734 (C═O), 3397 (OH) cm^{-1} ; HRMS calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0919.

Preparation of 5i. To a solution of **5c** (375 mg, 1.08 mmol) in THF (10 mL) was added 1N $(Bu)_4NF$ in THF (1.5 mL). The reaction mixture was stirred for 4 h, saturated NH_4Cl was added, and the crude product was extracted with ethyl acetate (40 mL) and then methylene chloride (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:1) as the eluant, gave 230 mg (92%) of **5i** as a liquid. ^{1}H NMR: δ 0.03−0.04-(d, 6H, J = 1.4 Hz), 0.09(s, 9H), 1.21−1.24(d, 3H, J = 2.4 Hz), 2.80−2.84(m, 1H), 4.0−4.4(m, 3H), 4.6−4.8(d, 1H), 5.2−5.4(m, 2H), 5.8−5.9(m, 1H); ^{13}C NMR: δ 21.18, 44.61, 55.72, 64.10, 64.55, 119.33, 127.54, 128. 24, 128.62, 135.71, 136.78, 167.73; IR (CH_2Cl_2): 1731 (C═O), 3415 (OH) cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1278.

Preparation of 5j. To a mixture of di-(*tert*-butyl)dicarbonate (436 mg, 1 mmol), **5h** (142 mg, 0.9 mmol) , and DMAP (123 mg, 1 mmol) in methylene chloride (10 mL) was added triethylamine (140 μL, 1.1 mmol). The reaction mixture was stirred for 6 h at room temperature. Saturated NH_4Cl was added, and the product was extracted with methylene chloride (40 mL) and then with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:3) as the eluant, afforded 208 mg (86%) of **5j** as a liquid. ^{1}H NMR: 1.35−1.38(d, 3H, J = 1.2 Hz), 1.45(s, 9H), 2.73(s, 3H), 2.95−2.99(m, 1H), 3.96−4.01(dd, 1H, J = 2.0, 8.2 Hz), 4.97−5.11(p, 1H, J = 12.4 Hz), 5.2−5.4(m, 2H), 6.7−6.9(m, 1H); ^{13}C NMR: δ 18.64, 27.72, 59.08, 63.37, 68.48, 70.24, 82.29, 119.71, 135.16, 152.82, 167.06; IR (CH_2Cl_2): 1750 (C═O, lactam), 1815 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4$ 269.1811, found 269.1519.

Preparation of 5k. To a solution of NaH (28 mg, 1.1 mmol) in THF (10 mL) was added **5h** (158 mg, 1.0 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 30 min, and MeI (141.9 mg, 1.1 mmol) in THF (2 mL) was then added slowly to the reaction mixture at −78 °C. The reaction mixture was quenched after 6 h using saturated NH_4Cl solution, and extracted with ether (40 mL) and then with methylene chloride (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:4) as the eluant, gave 150.4 mg (89%) of **5k** as a liquid. ^{1}H NMR: δ 1.1−1.3-(d, 3H, J = 6.2), 2.72(s, 3H), 2.86−2.87(m, 1H), 3.31(s, 3H), 3.57−3.69(p, 1H, J = 11.6 Hz), 3.86−3.90(dd, 1H, J = 2.2, 8.2 Hz), 5.17−5.34(m, 2H), 5.69−5.83(m, 1H); ^{13}C NMR: δ 17.43, 56.46, 57.94, 63.33, 73.72, 77.57, 119.02, 135.82, 167.64; IR (CH_2Cl_2): 1731 (C═O) cm^{-1}; HRMS calcd for $C_9H_{15}NO_2$ 169.1103, found 169.1098.

Preparation of 5l. To a solution of NaH (28 mg, 1.1 mmol) in THF (10 mL) was added **5i** (229 mg, 0.99 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 30 min, and MeI (141.9 mg, 1.1 mmol) in THF (2 mL) was then added slowly to the reaction mixture at −78 °C. The reaction mixture was quenched after 6 h by aqueous NH_4Cl and extracted with ether (40 mL) and then with methylene chloride (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue effected by flash chromatography on silica gel, with ethyl acetate/hexanes (1:4) as the eluant, gave 214.02 mg (87%) of **5l** as a liquid (214.02 mg, 87% isolated yield). ^{1}H NMR: δ 1.18−1.19(d, 3H, J = 2.4 Hz), 2.90−2.94(dd, 1H, J = 1.8 Hz, J = 6 Hz), 3.32(s, 3H), 3.65−3.73(p, 1H, J = 11.4 Hz), 3.9−4.0(m, 2H), 4.65−4.73(d, 1H, J = 15.4 Hz), 5.14−5.29(m, 2H), 5.6−5.8(m, 1H), 7.2−7.4(m, 5H); ^{13}C NMR: δ 17, 44, 56.4, 56.8, 63.2, 73.9, 119.5, 127, 128.4, 128.8, 136.1, 136.2, 168; IR (CH_2Cl_2): 1755 (C═O) cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1416.

Preparation of 5m. To a solution of **5a** (1280 mg, 5 mmol) in THF (15 mL) was added 1 N $(Bu)_4NF$ in THF (6 mL). The reaction mixture was stirred for 8 h and then quenched by a solution of NH_4Cl. The crude product was extracted by ethyl acetate (90 mL) and then with methylene chloride (30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (2:1 → 4:1) as the eluant, afforded 634 mg (90%) of **5m** as a white solid. ^{1}H NMR: δ 1.26−1.29(d, 3H, J = 6.4 Hz), 1.78(s, 1H, OH), 2.94−2.95-(dd, 1H, J = 2.4 Hz), 4.1−4.3(m, 2H), 5.14−5.36(m, 2H), 5.85−6.10-(m, 1H) 6.11 (br, 1H, OH); ^{13}C NMR: δ 21.23, 52.26, 64.68, 65.35, 116.95, 137.44, 168.48; IR (CH_2Cl_2): 1731 (−NH), 1738 (C═O), 3288 (−OH) cm^{-1}; HRMS calcd for $C_7H_{11}NO_2$ 141.0790, found: 123.9054 (M^+ − 18).

Preparation of 5n. To a mixture of di-(*tert*-butyl)dicarbonate (1308 mg, 3 mmol), **5m** (423 mg, 3 mmol), and DMAP (370 mg, 3 mmol)

in methylene chloride (10 mL) was added triethylamine (420 μL, 3.3 mmol), The reaction mixture was stirred for 6 h at room temperature, quenched with saturated NH_4Cl, and extracted with methylene chloride (40 mL) and then with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:3 → 1:1) as the eluant, gave 607 mg (84%) of **5n** as a white solid. ^{1}H NMR: δ 1.12−1.19(d, 3H, J = 4 Hz), 1.39(s, 9H), 1.72(s, 1H, OH), 2.81−2.85(m, 1H), 4.08−4.20(m, 1H), 4.35−4.45-(m, 1H), 5.1−5.3(m, 1H), 5.7−5.9(m, 1H); ^{13}C NMR: δ 22.09, 28.67, 56.45, 64.12, 64.12, 64.93, 83.87, 119.02, 136.91, 148.43, 166.82; IR (CH_2Cl_2): 1725 (C═O, lactam), 1808 (C═O, carbamate), 3503 (OH) cm^{-1}; HRMS calcd for $C_{12}H_{19}NO_4$ 241.1314, found 241.1418.

Preparation of 5o. To the mixture of di-(*tert*-butyl)dicarbonate (872 mg, 2 mmol), **5m** (141 mg, 1 mmol), and DMAP (246.8 mg, 2 mmol) in methylene chloride (10 mL) was added triethylamine (280 μL, 2.2 mmol). The reaction mixture was stirred for 6 h at room temperature, quenched with saturated NH_4Cl, and extracted with methylene chloride (40 mL) and then with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue effected by flash chromatography on silica gel, with ethyl acetate/hexanes (1:7) as the eluant, afforded 272 mg (80%) of **5n** as a white solid. ^{1}H NMR: δ 1.35−1.38(d, 3H, J = 7 Hz), 1.44(s, 9H), 1.47(s, 9H), 2.98−3.04(dd, 1H, J = 1.5, 7.0 Hz), 4.43−4.47 (dd, 1H, J = 1.6, 6.8 Hz), 5.03−5.15(p, 1H, J = 11.8 Hz), 5.23−5.38(m, 2H), 5.78−5.95(m, 1H); ^{13}C NMR: δ 18.55, 27.73, 27.97, 57.14, 61.16, 70.48, 82.67, 83.52, 118.94, 134.55, 147.58, 151.62, 163.61; IR (CH_2-Cl_2): 1736 (C═O, lactam), 1818 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{17}H_{27}NO_6$ 341.1838, found 224.9302 (M^+ − 117).

Preparation of 5p. To a mixture of **5n** (241 mg, 1 mmol) and triethylamine (140 μL, 1.1 mmol) in methylene chloride (10 mL) was added acetic anhydride (125 mg, 1.1 mmol) in methylene chloride (3 mL) at 0 °C. After stirring for 6 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with methylene chloride (40 mL) and then ethyl acetate (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:3) as eluant, gave 247 mg (87%) of **5p** as liquid. ^{1}H NMR: δ 1.30−1.33(d, 3H, J = 6.6 Hz), 1.46(s, 9H), 2.00(s, 3H), 2.98−3.03(dd, 1H, J = 3.2, 7.0 Hz), 4.33−4.37(dd, 1H, J = 1.2, 7.4 Hz), 5.21−5.40(m, 3H), 5.78−5.95-(m, 1H); ^{13}C NMR: δ 13.9, 17.9, 20.5, 27.5, 56.4, 60.6, 67.0, 83.0, 118.3, 134.2, 147.1, 163.1, 169.3; IR (CH_2Cl_2): 1726 (C═O, lactam), 1809 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{14}H_{21}NO_5$ 283.1420, found 283.1433.

Preparation of 5q. To the reaction mixture of **5n** (303.5 mg, 1.19 mmol) and tetrabutylammonium iodide (13.3 mg) in petroleum ether (15 mL) was added 50% aqueous NaOH (160 mg, 4 mmol). The reaction mixture was stirred at reflux for 30 min. After cooling to below 45 °C, dimethyl sulfate (229.3 mg, 1.75 mmol) in 5 mL of H_2O was added, the reaction mixture was stirred for 3 h, and then 3 mL of NH_4-OH solution was added. After more stirring for 30 min, the reaction mixture was extracted with ether (40 mL) and washed with H_2O (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, with ethyl acetate/hexanes (1:4) as the eluant, gave 227 mg (75%) of **5q** as a white solid. ^{1}H NMR: δ 1.15−1.18(d, 3H, J = 6.0 Hz), 1.43(s, 9H), 2.5−2.6(dd, 1H, J = 3.0, 9.0 Hz), 3.62(s, 3H), 3.8−3.9(m, 1H), 4.6−4.7(m, 1H), 5.1−5.4(m, 2H), 5.6−5.8(m, 1H); ^{13}C NMR: δ 20.75, 27.10, 28.26, 50.28, 51.44, 57.32, 80.54, 115.48, 135.88, 157.16, 172.93; IR (CH_2Cl_2): 1726 (C═O, lactam), 1830 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4$ 255.1471, found 255.1512.

General Procedure for the Hydroformylation of 5. The hydroformylation reaction was carried out in a 45 mL Parr autoclave fitted with a glass liner and a stirring bar. The 4-vinyl β-lactam (0.25 or 0.5 mmol), catalyst (5 mmol % to the substrate), and phosphorus ligand (10 mmol % to the substrate) were placed in the glass liner which was then protected with a septum. Carbon monoxide was bubbled through a needle for several minutes prior to the addition of solvent. The glass liner was transferred into the autoclave, and the system was purged three times with carbon monoxide and subsequently pressurized with carbon monoxide and hydrogen. The autoclave was heated in an oil bath; at the end of the reaction time, it was cooled to room temperature, the gas was vented, and the reaction mixture was filtered through Flurosil to remove the catalyst. The conversion of the starting material was determined by gas chromatography. After evaporation of the solvent, the branched/linear ratio of the isomeric aldehydes and the stereoselectivity were determined by 1H NMR by integration of the resonances corresponding to the aldehyde protons.[25]

6aα: ^{1}H NMR: δ 0.01 (s, 3H). 0.04(s, 3H), 0.85(s, 6H), 1.18−1.23-(m, 6H), 2.4−2.6(m, 1H), 2.75−2.85(dd, 1H), 3.61−3.62(d, 1H, J = 2 Hz), 4.10−4.20(m, 1H), 6.1−6.2(br, 1H), 9.67(s, 1H); ^{13}C NMR: δ 10.74, 17.56, 22.33, 25.68, 51.02, 52.13, 63.60, 65.49, 167.86, 202.96; IR (CH_2Cl_2): 1692 (C═O, aldehyde), 1746 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{14}H_{27}NO_3Si$ 285.1760, found 228.1052 (M^+ − 57).

6aβ: ^{1}H NMR: δ 0.01 (s, 3H), 0.02 (s, 3H), 0.88(s, 6H), 1.14−1.19(m, 6H), 2.53−2.72(m, 1H), 2.94−2.98(dd, 1H, J = 2.6, J = 5.2 Hz), 3.88−3.92(dd, 1H, J = 2.4, 3.6 Hz), 4.10−4.20(m, 1H), 6.1(br, 1H), 9.727−9.731(d, 1H, J = 1.2 Hz); ^{13}C NMR: δ 9.14, 17.90, 22.64, 25.71, 49.25, 61.91, 65.64, 168.14, 202.27; IR (CH_2Cl_2): 1692 (C═O, aldehyde), 1746 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{14}H_{27}NO_3Si$ 285.1760, found 228.2171 (M^+ − 57).

6bβ: ^{1}H NMR: δ 0.003(s, 3H), 0.018(s, 3H), 0.81(s, 9H), 1.12−1.12(m, 6H), 2.8−1.9(m, 1H), 3.80−3.82(m, 1H), 4.01−4.10(m, 1H), 9.762−9.768(d, 1H, J = 1.2 Hz); ^{13}C NMR: δ 8.74, 17.76, 23.86, 25.63, 47.64, 60.70, 63.27, 65.41, 167.58, 202.25; IR cm^{-1} 1698 (C═O, aldehyde), 1731 (C═O, lactam); HRMS calcd for $C_{15}H_{24}NO_3$-Si 299.1917, found 242.1208 (M^+ − 57).

6cα: ^{1}H NMR: δ 0.003(s, 3H), 0.018(s, 3H), 0.79 (s, 9H), 0.90−1.01(d, 3H, J = 1.0 Hz), 1.19−1.28(d, 3H, J = 2 Hz), 2.40−2.50(m, 1H), 2.80−2.90(m, 1H), 3.80−3.90(m, 1H), 4.00−4.48(m, 2H), 7.19−7.50(m, 5H), 9.415(s, 1H); ^{13}C NMR: δ 10.41, 17.90, 22.87, 25.77, 45.16, 49.02, 54.11, 60.74, 65.56, 65.56, 126.78, 127.43, 128.34, 128.56, 132.72, 167.52, 202.19; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1724 (C═O, lactam) cm^{-1} ; HRMS calcd for $C_{20}H_{32}NO_3Si$ 375. 2230, found 360.1976 (M^+ − 15).

6cβ: ^{1}H NMR: δ0.01 (s, 3H), 0.02(s, 3H), 0.80 (s, 9H), 0.90−1.01-(d, 3H, J = 1.0 Hz), 1.22−1.30(d, 3H, J = 2 Hz), 2.51−2.58(m, 1H), 2.92−3.02(m, 1H), 3.81−3.98(m, 1H), 4.05−4.52(m, 2H), 7.20−7.33-(m, 5H), 9.49−9.50(d, 1H, J = 1.0); ^{13}C NMR: δ 8.88, 17.90, 22.87, 25.77, 44.55, 45.53, 54.27, 60.47, 65.86, 126.81, 127.23, 128.54, 128.56, 132.72, 167.52, 202.46; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1724 (C═O, lactam) cm^{-1} ; HRMS calcd for $C_{20}H_{32}NO_3Si$ 375.2230, found 360.1976 (M^+ − 15).

7c: ^{1}H NMR: δ 0.01 (s, 3H), 0.02(s, 3H), 0.79−0.83(d, 9H, J = 6.4 Hz), 1.13−1.16(d, 3H, J = 1.2 Hz), 1.58−1.78(m, 1H), 1.83−2.01(m, 1H), 2.32−2.40(t, 2H, J = 7.3 Hz), 2.69−2.70(d, 1H, J = 1.2 Hz), 3.47−3.55(m, 1H), 4.01−4.20(m, 1H), 4.42−4.57(2H), 7.20−7.33(m, 5H), 9.61−9.65(t, 1H, J = 2.0 Hz); ^{13}C NMR: δ 17.90, 22.87, 25.77, 39. 74, 47.37, 53.96, 53.96, 63.03, 65.74, 126.81, 127.23, 128.54, 129.36, 132.72, 167.52, 200.34; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1724 (C═O, lactam) cm^{-1} ; HRMS calcd for $C_{20}H_{32}NO_3Si$ 375. 2230, found 360.1976 (M^+ − 15).

6dα: ^{1}H NMR: δ 0.01 (s, 3H),0.03(s, 3H), 0.90(s, 9H), 1.10−1.31-(m, 6H), 2.87−2.95(m, 2H), 4.00−4.17(m, 2H), 9.69−9.70(d, 1H, J = 2.4 Hz); ^{13}C NMR: δ 10.52, 17.90, 22.87, 44.53, 49.42, 54.26, 167.53, 177.80, 201.93; IR (CH_2Cl_2): 1654 (C═O, aldehyde), 1702 (C═O, lactam), 1790 (C═O, ester) cm^{-1}; HRMS calcd for $C_{15}H_{28}$-NO_4Si 327.1866, found 270.1145 (M^+ − 57)

6dβ: ^{1}H NMR: δ 0.01 (s, 3H),0.03(s, 3H), 0.90(s, 9H), 1.10−1.31-(m, 6H), 2.88−3.00(m, 2H), 4.03−4.22(m, 2H), 9.706 (s, 1H); ^{13}C NMR: δ 8.93, 17.92, 22.22, 23.89, 25.52, 45.78, 52.51, 59.89, 64.92, 165.55, 168.29, 201.53; IR (CH_2Cl_2): 1654 (C═O, aldehyde), 1702 (C═O, lactam), 1790 (C═O, ester) cm^{-1}; HRMS calcd for $C_{15}H_{28}$-NO_4Si 327.1866, found 270.1144 (M^+ − 57).

7d: ^{1}H NMR: δ 0.01 (s, 3H),0.03(s, 3H), 0.90(s, 9H), 1.10−1.31-(m, 6H), 1.78−2.00 (m, 1H), 2.10−2.30 (m, 1H), 2.59−2.72 (t, 2H), 2.85−2.92 (m, 1H), 4.03−4.25(m, 2H), 9.75−9.76(t, 1H, J = 1.0 Hz);

(25) The ratios of β to α were determined by ^{1}H NMR, by integration of the resonances corresponding to the aldehyde protons.[12]

^{13}C NMR: δ 17.92, 22.22, 23.51, 25.18, 40.52, 52.32, 62.72, 64.88, 167.44, 168. 29, 200.55; IR (CH_2Cl_2): 1654 (C═O, aldehyde), 1702 (C═O, lactam), 1790 (C═O, ester): cm^{-1}; HRMS calcd for $C_{15}H_{28}NO_4Si$ 327.1866, found 270.1145 ($M^+ - 57$).

6e*β*: ^{1}H NMR: δ 0.01 (s, 3H),0.03(s, 3H), 0.80(s, 9H), 1.10−1.20-(d, 3H, J = 3 Hz), 1. 47 (s, 9H), 2.70−2.87(m, 1H), 3.90−4.48(m, 1H), 4.29−4.38(m, 1H), 9.689−9.702(d, 1H, J = 2.6 Hz); ^{13}C NMR: δ 8.26, 16.72, 22.26, 25.60, 27.84, 46.81, 52.97, 60.12, 64.90, 83.62, 147.92, 164.80, 201.64; IR (CH_2Cl_2): 1694 (C═O, aldehyde), 1724 (C═O, lactone), 1809 (C═O, carbamate) cm^{-1};; HRMS: calcd 371.2492, found 328.1700 ($M^+ - 57$).

7e ^{1}H NMR: δ 0.01 (s, 3H),0.03(s, 3H), 0.80(s, 9H), 1.10−1.30(d, 3H, J = 6 Hz), 1.49(s, 9H), 1.77−2.01(m, 1H), 2.20−2.30(m, 1H), 2.50−2.60(t, 2H, J = 5.8 Hz), 2.51−2.60(m, 1H), 4.00−4.10(m, 1H), 4.20−4.30(m, 1H), 9.763−9.772(t, 1H, J = 0.9 Hz); ^{13}C NMR: δ 16.72, 22.26, 25.02, 25.60, 27.93, 40.09, 52.63, 62.44, 64.76, 82.90, 148.10, 165.44, 200.38; IR (CH_2Cl_2): 1694 (C═O, aldehyde), 1724 (C═O, lactam), 1809 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{17}H_{33}NO_4Si$ 543.2625, found 586. 2437 ($M^+ - 57$).

6f*β*: ^{1}H NMR: δ -0.01(s, 3H), 0.00 (s, 3H), 0,8(s, 9H), 1.19−1.28-(d, 2H), 2.52−2.62(m, 1H), 3.01−3.6(m, 1H), 3.8−3.84(m, 1H), 4.10−4.20(m, 1H), 7.25−7.72(m, 15H), 9.504−9.508(d, 1H, J = 1.2 Hz); ^{13}C NMR: δ 8.80, 17.92, 22.63, 25.78, 46.00, 53.80, 60.88, 64.31, 127.87, 130.04, 134.97, 168.10, 201.80; IR (CH_2Cl_2): cm^{-1} 1693 (C═O, aldehyde), 1719, 1728(C═O, lactam), 1738; HRMS calcd for $C_{32}H_{41}NO_3$ 543.2625, found 466.9739 ($M^+ - 57$).

7f: ^{1}H NMR: δ -0.01 (s, 3H), 0.00 (s, 3H), 0,8(s, 9H), 1.19−1.28-(d, 2H), 2.52−2.62(m, 1H), 3.01−3.6(m, 1H), 3.8−3.84(m, 1H), 4.10−4.20(q, 1H), 7.25−7.72(m, 15H), 9.504−9.508(t, 1H, J = 1.0 Hz); ^{13}C NMR: δ 17.92, 20.71, 22.63, 41.31, 46.00, 53.80, 60.88, 64.31, 127, 130, 134, 168.10, 199.97; IR (CH_2Cl_2): 1693 (C═O, aldehyde), 1719, 1728(C═O, lactam), 1738 cm^{-1}; HRMS calcd for $C_{32}H_{41}NO_3$ 543.2625, found 466.9739 (M^+-57).

6g*β*: ^{1}H NMR: 0.01 (s, 6H), 0.03 (s, 3H), 0.034 (s, 3H), 0.045 (s, 3H 0.825(s, 9H), 0.925(s, 9H), 1.08−1.11(d, 3H), 2.70−2.81(m, 1H), 2.90−3.00(m, 1H), 3.76−3.80(m, 1H), 3.95−4.05(m, 1H), 9.385−9.843(d, 1H, J = 1.2 Hz); ^{13}C NMR: δ 8.90, 17.90, 22.95, 26.20, 25.83, 49.20, 51.28, 54.23, 61.33, 173.01, 201.72; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1748 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{19}H_{40}NO_3Si_2$ 399.2625, found 384.2411 ($M^+ - 15$).

7g: ^{1}H NMR: 0−0.05(d, 6H), 0.123(s, 6H), 0.825(s, 9H), 0.925(s, 9H), 1.21−1.23(d, 3H), 1.5−1.7(m, 1H), 2.05−2.25(m, 1H), 2.61−2.68(m, 1H), 3.40−3.50(m, 1H), 3.90−4.10(q, 1H), 9.75−9.77(t, 1H, J = 1.0); ^{13}C NMR: δ 17.90, 22.95, 25.61, 26.20, 25.83, 40.19, 52.44, 64.50, 66.55, 172.88, 200.51; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1748 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{19}H_{40}NO_3Si_2$ 399.2625, found 384.2411 ($M^+ - 15$).

6j*β*: ^{1}H NMR: 1.117−1.168 (dd, 3H, J = 2.8, 7.4 Hz), 1.370−1.407(dd, J = 1.2, 6.4 Hz), 1.439 (s, 9H), 2.6−3.2 (m, 2H), 2.74−2.8(d, 1H, J = 0.8), 3.9−4.0(m, 1H), 4.8−5.0(m, 1H), 9.83−9.85(d, 1H, J = 1.4); ^{13}C NMR: δ 8.42, 18.66, 27.72, 47.40, 57.68, 58.18, 62.46, 71.31, 82.40, 152.83, 165.55, 201.65; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1740 (C═O, lactam) cm^{-1} HRMS calcd for $C_{14}H_{22}NO_5$ 285.1576, found 285.1576.

7j: ^{1}H NMR : δ 1.117−1.168 (dd, 3H, J = 2.8, 7.4 Hz), 1.36−1.39(d, 3H, J = 6.4), 1.439 (s, 9H), 1.51−1.68 (m, 1H), 2.70−3.00(m, 1H), 3.38−3.50(m, 1H), 4.80−5.00(m, 1H), 9.74−9.76(t, 1H, J = 1.1 Hz);^{13}C NMR: δ18.80, 26.72, 27.69, 40.08, 49.20, 56.72, 60.74, 82.32, 152.95, 166.31, 200.15; IR (CH_2Cl_2): 1675 (C═O, aldehyde), 1740 (C═O, lactam) cm^{-1} HRMS calcd for $C_{14}H_{22}NO_5$ 285.1576, found 285.1576.

6kα: ^{1}H NMR: δ 1.12−1.42(m, 6H), 2.58−2.62(m, 1H), 2.73(s, 3H), 2.87−2.94(m, 1H), 3.31(s, 3H), 3.60−3.70(m, 1H), 9.725 (s, 1H); ^{13}C NMR δ 9.96, 17.46, 28.05, 47.69, 56.15, 59.11, 74.12, 74.31, 167.29, 201.06; IR (CH_2Cl_2): 1658 (C═O, aldehyde), 1738 (C═O, lactam). cm^{-1}; HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1232.

6k*β*: ^{1}H NMR: δ 1.12−1.42(m, 6H), 2.58−2.62(m, 1H), 2.73(s, 3H), 2.87−2.89(m, 1H), 3.31(s, 3H), 3.60−3.70(m, 1H), 9.74−9.75-(d, 1H, J = 1.0 Hz); ^{13}C NMR δ 8.49, 17.46, 27.68, 48.83, 56.28, 59.41, 74.39, 74.48, 167.29, 202.23; IR (CH_2Cl_2): 1658 (C═O, aldehyde), 1738 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1232.

7k: ^{1}H NMR: δ 1.20−1.24 (d, 3H, J = 6 Hz), 1.63−1.69 (m, 1H), 2.06−1.13 (m, 1H), 2.50−2.58 (t, 2H, J = 7.2), 2.75 (s, 3H), 2.87−2.90 (m, 1H), 3.28 (s, 3H), 3.6−3.7 (m, 1H), 3.5−3.6 (m, 1H), 9.757 (s, 1H); ^{13}C NMR δ 17.46, 23.86, 26.49, 39.55, 56.28, 61.89, 74.57, 73.64, 167.20, 200.59; IR (CH_2Cl_2): 1658 (C═O, aldehyde), 1738 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1232

6lα: ^{1}H NMR: δ 1.02−1.05(d, 3H, J = 7.2 Hz), 2.50−2.60(m, 1H), 3.77−3.85(m, 1H), 3.40−3.50(m, 1H), 3.70−3.80(dd, 1H), 4.01−4.19-(d, 1H), 4.50−4.59(d, 1H), 7.22−7.52(m, 5H), 9.45−9.46(d, 1H, J = 1.8 Hz); ^{13}C NMR: δ 10.34, 17.46, 45.34, 44.98, 48.82, 54.37, 59.01, 76.48, 127, 129, 167.62, 202.39; IR (CH_2Cl_2): 1702 (C═O, aldehyde), 1746 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{16}H_{20}NO_3$ 275.1521, found 275.1524.

6l*β*: ^{1}H NMR: δ 1.02−1.05(d, 3H, J = 7.2 Hz), 2.70−2.80(m, 1H), 2.90−3.00(m, 1H), 3.285(s, 3H), 3.40−3.50(m, 1H), 3.81−3.89 (dd, 1H, J = 1.4 Hz), 4.01−4.20(d, 1H), 4.61−4.70(m, 1H), 7.22−7.52(m, 5H), 9.530−9.535(d, 1H, J = 1.0 Hz); ^{13}C NMR: δ 8.83, 17.46, 44.98, 45.34, 47.52, 54.30, 58.89, 74.01, 127.13, 167.62, 202.24; IR (CH_2Cl_2): 1702 (C═O, aldehyde), 1746 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{16}H_{20}NO_3$ 275.1521, found 275.1524.

7l: ^{1}H NMR: δ 1.233−1.26(d, 3H, J = 2.8 Hz), 1.52−1.70(m, 1H), 1.90−2.10(m, 1H), 2.37−2.41(t, 2H, J = 3.5 Hz), 2.71−2.72(dd, 1H, J = 2.2 Hz), 3.272(s, 3H), 3.40−3.50(m, 1H), 3.50−3.70(m, 1H), 4.64−4.73(d, 1H), 7.21−7.35(m, 5H), 9.653−9.657(t, 1H, J = 1.4 Hz); ^{13}C NMR: δ 17.50, 24.21, 44.39, 39.62, 44.39, 54.67, 61.54, 74.35, 127, 129, 167.32, 200.58; IR (CH_2Cl_2): 1702 (C═O, aldehyde), 1746 (C═O, lactam) cm^{-1}; HRMS calcd for $C_{16}H_{20}NO_3$ 275.1521, found 275.1524.

6oα: ^{1}H NMR: δ 1.10−1.20(d, 3H, J = 6 Hz), 1.46(s, 9H), 1.47-(s, 9H), 2.80−2.90(m, 1H), 3.11−3.19(m, 1H), 4.40−4.50(m, 1H), 5.00−5.10(m, 1H), 9.635 (s, 1H); ^{13}C NMR: δ 9.88, 18.75, 27.87, 27.96, 50.54, 55.42, 59.95, 70.79, 82.80, 84.35, 147.80, 155.27, 163.25, 200.67; IR (CH_2Cl_2): 1690 (C═O, aldehyde), 1724 (C═O, lactam), 1825 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{18}H_{28}NO_7$ 387.2257, found 270.1147 ($M^+ - 101$).

6o*β*: ^{1}H NMR: δ 1.10−1.20(d, 3H, J = 6 Hz), 1.46(s, 9H), 1.47(s, 9H), 2.80−2.90(m, 1H), 3.11−3.19(m, 1H), 4.40−4.50(m, 1H), 4.90−5.00(m, 1H), 9.690−9.695(d, 1H, J = 2.4); ^{13}C NMR: δ 7.91, 18.75, 27.87, 27.96, 48.67, 55.42, 59.95, 70.79, 82.80, 84.32, 147.80, 155.27, 163.25, 202.13; IR: 1690 (C═O, aldehyde), 1724 (C═O, lactam), 1825 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{18}H_{28}NO_7$ 371.1944, found 270.1147 ($M^+ - 101$).

7o: ^{1}H NMR: δ 1.46−1.48(m, 18H), 1.8−1.9(m, 9H), 2.5−2.6(m, 1H), 2.5−2.6(t, 2H, J = 3.8 Hz), 2.7−2.8(dd, 1H), 3.8−4.0(m, 1H), 4.8−5.0(m, 1H), 9.773(s, 1H); ^{13}C NMR: δ 19.75, 24.73, 27.87, 27.67, 39.54, 57.63, 59.95, 70.91, 83.57, 82.66, 145.77, 152.45, 162.72, 200.04; IR: 1690 (C═O, aldehyde), 1724 (C═O, lactam), 1825 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{18}H_{28}NO_7$ 371.1944, found 270.1147 ($M^+ - 101$).

6p*β*: ^{1}H NMR: δ 1.21−1.32(m, 6H), 1.424(s, 9H), 2.32(s, 3H), 2.52−2.56(m, 1H), 2.98−3.01(m, 1H), 4.2−4.44(m, 2H), 4.5−4.6(m, 1H), 9.75−9.75(d, 1H, J = 1.2 Hz); ^{13}C NMR: δ 8.38, 18.36, 20.91, 27.80, 50.00, 55.35, 57.44, 67.83, 84.32, 145.71, 165.98, 169.81, 201.10; IR (CH_2Cl_2): cm^{-1}; HRMS calcd for $C_{15}H_{22}NO_6$ 313.1525, found 312.9783.

6q*β*: ^{1}H NMR: δ 1.12−1.20(m, 6H,), 1.45(s, 9H), 2.5−2.6(m, 1H), 3.5−3.6 (m, 1H), 4.0−4.2(m, 1H), 4.5−4.6(m, 1H), 9.625−9.630(d, 1H, J = 1.0); ^{13}C NMR: δ 9.32, 20.27, 28.16, 51.91, 54. 04, 65. 33, 70.43, 80.13, 148.51, 165.91, 201.10; IR (CH_2Cl_2): 1694 (C═O, aldehyde), 1737 (C═O, lactam), 1830 (C═O, carbamate) cm^{-1}; HRMS calcd for $C_{14}H_{23}NO_5$ 285.1576, found 285.1570.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and to Takasago International Corp, for support of this research.

JA993080J