Multicomponent Reactions

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Highly Stereoselective Synthesis of Substituted γ-Lactams from Acylsilanes**

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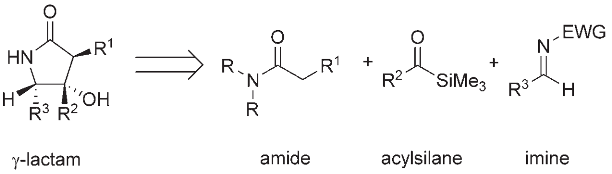
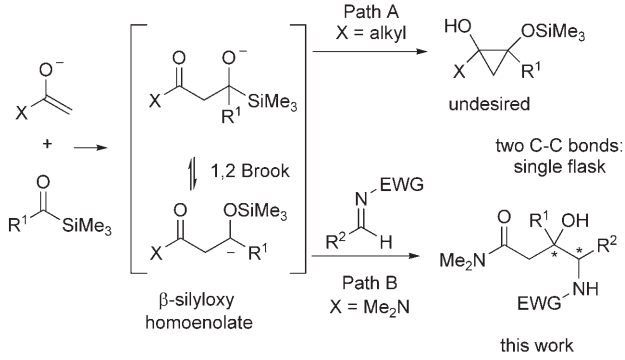
The synthesis of substituted γ-lactams is an important goal because of their use as key intermediates in the synthesis of biologically and pharmaceutically relevant molecules. Compounds containing γ-lactams have direct applications in the treatment of epilepsy,[1,2] HIV,[3,4] neurodegenerative diseases, and depression.[5,6] Because of the prevalence of this valuable heterocycle in pharmaceutical development, natural products, and materials research, methods for the efficient stereoselective synthesis of highly substituted γ-lactams are important objectives for the synthetic community.[7–11] Herein we report a highly stereoselective approach to β-hydroxy-γ-lactams from the multicomponent reaction of amides, acylsilanes, and imines [Eq. (1)]. This modular addition/cyclization process readily provides lactams in good yields with excellent levels of stereoselectivity.



(1)

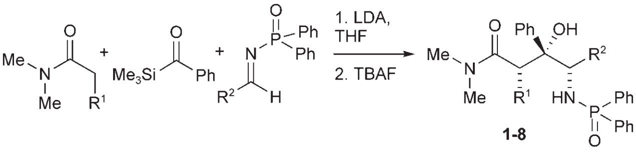


Scheme 1. Silyloxy homoenolates from acylsilanes. EWG = electron-withdrawing group.

We are currently developing new reactions that employ unconventional nucleophiles derived from acylsilanes.[12–19] From these endeavors, we have devised an efficient synthesis of β-hydroxy amides by combining amide enolates and acylsilanes to access β-silyloxy homoenolate reactivity (Scheme 1). The acylsilane acts *sequentially* as an electrophilic/nucleophilic moiety in this process by undergoing a 1,2-silyl group migration (1,2-Brook rearrangement).[20,21] We can shut down the reaction pathway leading to substituted cyclopropanols (path A; first observed by Takeda et al.)[22,23] by employing amide enolates, and instead utilize the in situ generated homoenolates for new bond forming reactions (path B). For example, the use of aldehydes as the second electrophile affords the β,γ-dihydroxy amides in good yields. By employing this distinctive characteristic of acylsilanes,[24–33] an intriguing possibility is the addition of an imine with an appropriate activating electron-withdrawing group to access highly substituted γ-amino-β-hydroxy amides. Importantly, the cyclization to the corresponding γ-lactam might be accomplished directly if the activating group on the nitrogen atom is easily removed.

Our initial reaction was conducted with dimethylacetamide and benzoyltrimethylsilane, and diphenylphosphoryl protected benzylimine as the electrophile (Table 1, entry 1).

Table 1: Synthesis of γ-amino-β-hydroxy amides.[a]



Entry	R^1	R^2	Yield [%][b]	d.r.[c]
1	H	Ph	74	> 20:1 (**1**)
2	H	4-ClPh	71	> 20:1 (**2**)
3	H	4-BrPh	70	> 20:1 (**3**)
4	H	4-OMePh	71	> 20:1 (**4**)
5	H	2-furyl	80	> 20:1 (**5**)
6	Me	Ph	84	> 20:1 (**6**)
7	Me	4-BrPh	78	> 20:1 (**7**)
8	CH$_2$Ph	Ph	75	> 20:1 (**8**)

[a] Acylsilane and imine are added sequentially to a 0.1 M enolate solution in THF at −78 °C. Silyl ether products treated with nBu$_4$NF (TBAF) in THF prior to purification. LDA = lithium diisopropylamide. [b] Yield of isolated product. [c] Determined by 500 MHz ^{1}H NMR spectroscopy.

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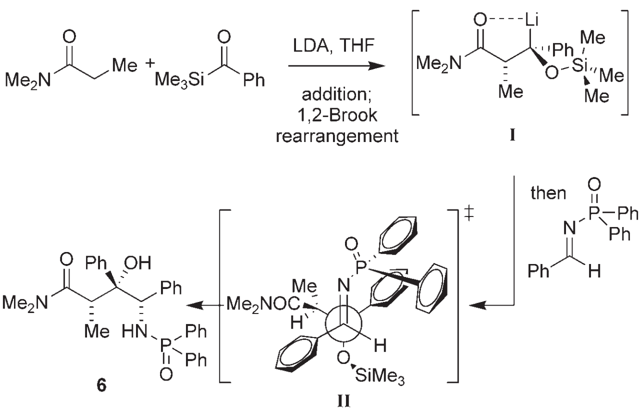
We chose the diphenylphosphoryl group because of a) its electron-withdrawing capacity, b) the steric magnitude associated with this functionality, which might provide nonbonding interactions during the addition event and influence diastereoselection, and c) the ease of removal of this group under acidic conditions, which could facilitate cyclization to the γ-lactam.[34–41] Gratifyingly, this three-component reaction provided the γ-amino-β-hydroxy amide in 74 % yield and greater than 20:1 diastereomeric ratio after desilylation (Table 1, entry 1). An examination of the imine scope of the reaction demonstrates that the reaction proceeds in good yields in the presence of both electron-deficient (Table 1, entries 2 and 3) and electron-rich (Table 1, entries 4 and 5) aromatic systems. We have also used α-substituted amides (R^1 = Me or CH_2Ph) and isolated the α-substituted γ-amino-β-hydroxy amides with excellent levels of diastereoselection (Table 1, entries 6–8).[42]

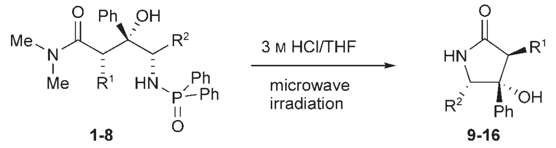
The current model for diastereoselection involves the addition of the *Z* enolate of the amide to the acylsilane (Scheme 2). A subsequent 1,2-Brook rearrangement could potentially afford internally coordinated anionic species **I**. The interaction of this anion with the imine to yield, in this example, amide **6** could occur by an open arrangement such as **II** to minimize the nonbonding interactions between the diphenylphosphoryl group of the imine and the silyloxy and amide groups of the homoenolate. This overall process generates up to three contiguous stereogenic centers with a high degree of control in a convergent, single flask operation.



Scheme 2. Model for diastereoselection.

The success of our multicomponent reaction with imines provided the impetus for us to develop a general γ-lactam synthesis. Notably, the hydrolysis of the diphenylphosphoryl amide and resulting cyclization of the amine to form the β-hydroxy-γ-lactams can be combined in a single operation. Aqueous acid and microwave irradiation leads to the concomitant deprotection and lactam formation in under 10 minutes (Table 2).[43,44] Surprisingly, the elimination of the β-hydroxy substituent to provide unsaturated products was not observed under these reaction conditions. The dimethylacetamide derived γ-amino-β-hydroxy amides (R^1 = H) undergo cyclization in 5 minutes at 150 °C (condition A) to afford the corresponding γ-substituted β-hydroxy-γ-lactams in excellent yields with retention of stereochemistry (Table 2, entries 1–4). The highest yields for the cyclization of 2-furyl amide **5** can be obtained (Table 2, entries 5 and 6) by decreasing the reaction temperature (condition B). The α-methyl substituted γ-amino-β-hydroxy amide **6** provides the desired γ-lactam in high yield with the higher temperature conditions (condition A), but with inversion of stereochemistry at the α-position (Table 2, entry 7). Fortunately, the lower temperature of condition B provides the corresponding β-hydroxy-α-methyl-γ-lactams in excellent yield with retention of stereochemistry (Table 2, entries 8–10).

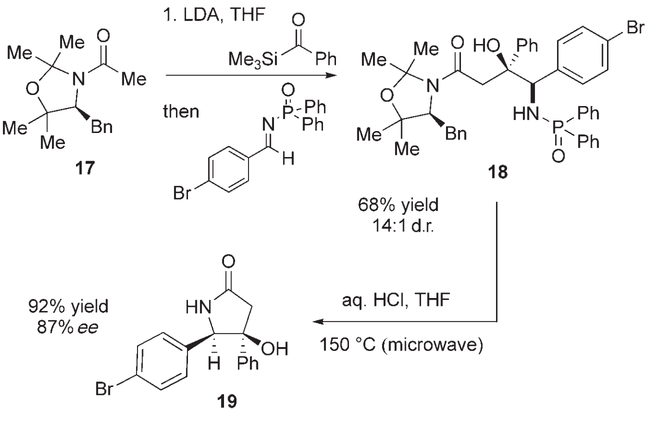
Table 2: γ-Lactam formation.[a]



Entry	R^1	R^2	Conditions[b]	Yield [%][c]	d.r.[d]
1	H	Ph	A	98	> 20:1 (**9**)
2	H	4-ClPh	A	97	> 20:1 (**10**)
3	H	4-BrPh	A	93	> 20:1 (**11**)
4	H	4-OMePh	A	94	> 20:1 (**12**)
5	H	2-furyl	A	0[e]	– (**13**)
6	H	2-furyl	B	97	> 20:1 (**13**)
7	Me	Ph	A	92	1:4 (**14**)
8	Me	Ph	B	96	> 20:1 (**14**)
9	Me	4-BrPh	B	98	> 20:1 (**15**)
10	Bn	Ph	B	90	> 20:1 (**16**)

[a] A solution of the amide (0.1 M) in THF/3 M aqueous HCl (1:1) was heated utilizing microwave irradiation. Silyl ether products treated with nBu_4NF in THF prior to purification. [b] Condition A = 150 °C for 5 min.; Condition B = 70 °C for 10 min (1:2 THF/3 M aqueous HCl). [c] Yield of product isolated after chromatography. [d] Determined by 500 MHz ^1H NMR spectroscopy. [e] Decomposition.

With an efficient route towards the diastereoselective formation of highly substituted β-hydroxy-γ-lactams, we turned our attention towards controlling the absolute stereochemistry of the process. Towards this end, the use of (*L*)-phenylalaninol derived acetamide **17**[45] in the reaction described above provides γ-amino-β-hydroxy amide **18** in good yield and excellent diastereoselectivity (Scheme 3). Our



Scheme 3. Asymmetric γ-lactam formation.

optimized amine deprotection and cyclization conditions smoothly generates optically active γ-lactam **19** in 92% yield and 87% *ee*.[46]

In summary, we have developed a modular strategy for the stereoselective synthesis of highly substituted β-hydroxy-γ-lactams by using β-silyloxy homoenolates that can be accessed from amide enolates and acylsilanes. These unconventional nucleophilic species undergo addition to imines to provide the γ-amino-β-hydroxy amides in a single flask with good yields and excellent levels of diastereoselectivity. Exposure of the linear amide products to microwave irradiation and acidic conditions promotes a cyclization to form the corresponding γ-lactams in excellent yields with retention of stereochemistry. The use of a chiral acetamide in the initial step affords γ-lactams in high enantiomeric excess. Our investigations will continue to explore the unique potential of acylsilanes when combined with enolates to generate unusual nucleophiles for use in synthesis.

Experimental Section

Procedure for the synthesis of γ-amino-β-hydroxy amides: THF (2 mL) and diisopropylamine (0.54 mmol) were added to a flame-dried, round-bottom flask equipped with a magnetic stirring bar and purged with nitrogen. The solution was cooled to −78 °C and *n*-butyllithium (1.6 M in hexanes, 0.54 mmol) was added by syringe. The reaction mixture was warmed to 0 °C and stirred for 30 min. Dimethylacetamide (0.54 mmol) was added to the LDA solution and the reaction mixture was stirred for 1 h. The reaction mixture was cooled to −78 °C, and a −78 °C solution of benzoyltrimethylsilane (0.59 mmol) in THF (0.5 mL) was added by cannula. The acylsilane delivery flask was rinsed with an additional portion of THF (0.5 mL), cooled to −78 °C, and transferred to the reaction flask. The resulting homogeneous solution was stirred for 20 min and then a solution of (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide (0.65 mmol) in THF (2.0 mL) was added by cannula, again with rinsing of the delivery flask with an additional portion of THF (0.4 mL). The resulting reaction mixture was stirred at −78 °C for 15 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (2 mL), warmed to ambient temperature, stirred for 30 min, and extracted with ethyl acetate (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated by evaporation. The unpurified silyl ether product was dissolved in THF (2 mL). Tetrabutylammonium fluoride (1.0 M in THF, 1.1 mmol) was added to this solution and the mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of water, extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated by evaporation. The residue was purified by flash chromatography (20–40% acetone/CH_2Cl_2) to afford 192 mg (74%) of **1** as a white solid. Analytical data for **1**: mp = 170 °C dec; IR (film): $\tilde{\nu}$ = 3236, 3058, 2927, 1616, 1489, 1438, 1194, 1119, 721, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (dd, 2H), 7.55–7.43 (m, 4H), 7.33 (t, 1H), 7.17–7.12 (m, 4H), 7.07–6.95 (m, 6H), 6.89 (s, 1H), 6.79 (d, 2H), 4.66 (t, 1H, *J* = 6.0 Hz), 4.24 (t, 1H, *J* = 6.5 Hz), 3.66 (d, 1H, *J* = 16.5 Hz), 3.36 (d, 1H, *J* = 16.5 Hz), 3.07 (s, 3H), 2.76 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6, 144.2, 140.3, 133.2, 133.1, 131.6, 131.5, 128.9, 128.8, 128.7, 128.3, 128.1, 127.8, 127.2, 126.6(×2), 125.6, 78.7, 63.2, 40.4, 37.8, 35.4 ppm; LRMS (ESI): Mass calculated for $C_{30}H_{31}N_2O_3P$ $[M+H]^+$, 500. Found $[M+H]^+$, 500.

Procedure for the synthesis of β-hydroxy-γ-lactams (condition A): A Biotage microwave flask (0.5–2.0 mL) was equipped with a stirbar and charged with γ-amino-β-hydroxy amide **1** (0.20 mmol), THF (1.0 mL), and 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 min, heated to 150 °C in a microwave (200 W), and stirred at this temperature for an additional 5 min. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid $NaHCO_3$ (until evolution of gas ceases), and extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated by evaporation. The residue was purified by flash chromatography (10–30% acetone/CH_2Cl_2) to afford 50 mg (98%) of **9** as a white solid. Analytical data for **9**: mp = 198–200 °C; IR (film): $\tilde{\nu}$ = 3303, 3188, 1701, 1668, 1443, 1337, 1214, 1071, 1031, 732, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 8H), 7.10 (d, 2H), 6.07 (s, 1H), 5.19 (s, 1H), 3.06 (d, 1H, *J* = 21.5 Hz), 2.83 (d, 1H, *J* = 21.5 Hz), 1.78 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5, 142.5, 133.7, 129.4, 128.8, 128.0, 127.4, 125.4, 79.6, 69.4, 47.6 ppm; LRMS (ESI): Mass calculated for $C_{16}H_{15}NO_2$ $[M+H]^+$, 254. Found $[M+H]^+$, 254.

Procedure for the synthesis of β-hydroxy-γ-lactams (condition B): A Biotage microwave flask (0.5–2.0 mL) was equipped with a stirbar and charged with γ-amino-β-hydroxy amide **6** (0.20 mmol), THF (1.0 mL), and 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 min, heated to 70 °C in the microwave, and stirred at this temperature for an additional 10 min. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid $NaHCO_3$ (until evolution of gas ceases) and extracted with CH_2Cl_2 (3 times). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated by evaporation. The residue was purified by flash chromatography (10–30% acetone/CH_2Cl_2) to afford 51 mg (96%) of **14** as white solid. Analytical data for **14**: mp = 144–146 °C; IR (film): $\tilde{\nu}$ = 3263, 3060, 2926, 1699, 1491, 1446, 1337, 1119, 1019, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.57 (d, 2H), 7.42–7.31 (m, 8H), 6.46 (s, 1H), 5.37 (s, 1H), 2.70 (q, 1H, *J* = 7.5 Hz), 1.85 (s, 1H), 0.91 ppm (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.8, 141.1, 135.2, 129.3, 129.2, 128.7, 128.2, 128.0, 126.3, 100.0, 82.2, 64.6, 49.6, 12.9 ppm; LRMS (ESI): Mass calculated for $C_{17}H_{17}NO_2$ $[M+H]^+$, 268. Found $[M+H]^+$, 268.

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Keywords: γ-lactams · acylsilanes · chiral auxiliaries · homoenolates · synthetic methods

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