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Organocatalytic Synthesis of β-Alkylaspartates via β-Lactone Ring Opening

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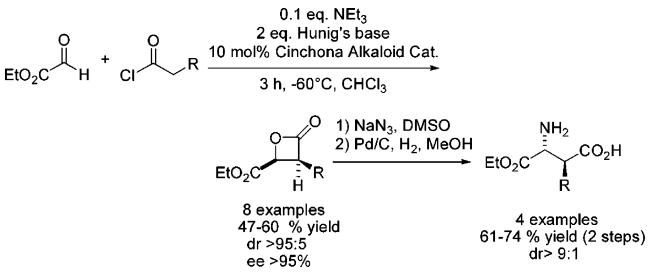
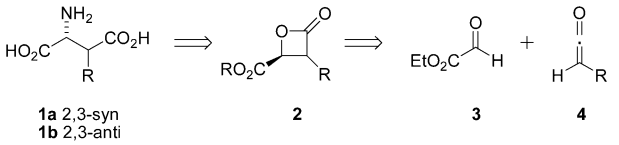
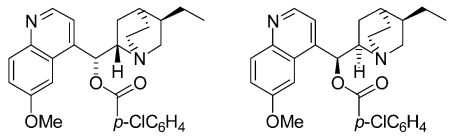


Cinchona alkaloid-catalyzed reaction of ethyl glyoxylate with substituted ketenes, formed in situ, gives disubstituted β-lactones in moderate yield and high enantiomeric excess. Subsequent azide ring opening, reduction, and ester hydrolysis allows access to chiral β-alkyl aspartates.

The β-alkyl aspartates **1** are an important class of nonproteinogenic amino acids whose diverse biological and biochemical properties[1,2] make them synthetically interesting targets. Current methods for their synthesis include the alkylation of aspartate ester-derived dianons,[3,4] but this generally requires highly reactive electrophiles (e.g., allyl or benzyl bromide, isopropyl triflate) and often provides mixtures of diastereomers. Enantioselective hydrogenation of tetrasubstituted aminoacrylates is an attractive possibility, but requires the synthesis of a geometrically pure alkene precursor.[5] Lectka's glyoxylate imine−ketene cycloaddition chemistry provides a versatile organocatalytic route,[6] but allows access only to the 2,3-*syn*-diastereomer **1a**.

As part of our program aimed at the total synthesis of the 20*S*-proteasome inhibitor belactosin A,[7,8] we needed access to a diastereomerically pure 2,3-*trans*-β-lactone carboxylate **2** (R = ^{s}Bu). Inspired by the pioneering work of Wynberg[9,10] and others[11] on β-lactone synthesis by cinchona alkaloid-catalyzed cycloaddition between electrophilic aldehydes and ketenes, including the more recent demonstration of in situ ketene generation from acid chlorides,[12,13] we explored this approach with ethyl glyoxylate **3**. This type of aldehyde has rarely been used in the amine-catalyzed ketene cycloaddition,[14] although Evans has described the use of **3** in the enantioselective Cu(pybox)-catalyzed [2+2]-reaction with silylketene as well as several synthetically useful ring-opening reactions of the desilylated β-lactone product (**2**, R = H).[15] Literature precedent indicated that the cinchona alkaloid-mediated reaction between chloral and the ketene **4** (R = Me) afforded predominantly the *trans*-β-lactone product,[16] making this approach attractive for our belactosin synthesis. However, in line with general findings for other aldehydes,[12,17] we found that the cycloaddition of **3** with substituted ketenes (**4**, R ≠ H) afforded selectively the 2,3-*cis*-β-lactone **2**, corresponding to the undesired relative configuration for belactosin A. Nevertheless, we reasoned that ring opening of *cis*-**2** might provide a general route to the valuable 2,3-*anti*-β-alkyl aspartates **1b**, thus warranting a fuller study of the scope of the glyoxylate−ketene cycloaddition. Here we report the results of this work.





After some experimentation, we were able to establish reaction conditions which minimize polymerization of the base-sensitive glyoxylate and afford the *cis*-β-lactone **2** with high levels of diastereo- and enantioselectivity (Table 1). The procedure involves addition of a mixture of ethyl glyoxylate **3**

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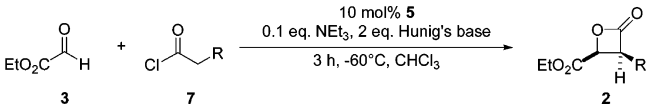
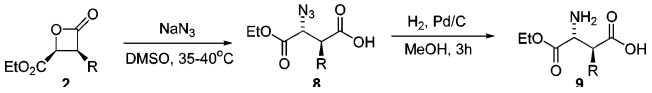
TABLE 1. Enantioselective Ketene−Glyoxylate Cycloaddition



entry	product	R	yield (%)	cis:trans[a]	ee (%)[b]
1	**a**	Me	55	>95:5	>95
2	**b**	Et	50	>95:5	>95
3[c]	**c**	Et	58	>95:5	>95
4	**d**	*i*-Pr	59	>95:5	>95
5[c]	**e**	*i*-Pr	60	>95:5	>95
6	**f**	Bn	48	>95:5	>95
7	**g**	CH_2Bn	54	>95:5	>95
8	**h**	$(CH_2)_2OSi^tBuPh_2$	47	>95:5	>95
9	**i**	*t*-Bu	*d*		

[a] Estimated by integration of the ^{1}H NMR spectrum. [b] Enantiomeric purity measured by ^{1}H NMR in the presence of a chiral shift reagent (Eu(hfc)$_3$). [c] Hydroquinine-4-chlorobenzoate **6** used as catalyst, giving *ent*-**2** as product. [d] No β-lactone product observed in the ^{1}H NMR spectrum of the crude product.

TABLE 2. β-Lactone Opening with Azide and Azide Reduction



entry	product	R	yield **8** (%)	yield **9** (%)	dr[a]
1	**a**	Me	60	99	>9:1
2	**b**	Et	74	quantitative	>9:1
3	**d**	*i*-Pr	61	quantitative	>9:1
4	**g**	CH_2Bn	66	92	>9:1

[a] Estimated by integration of the ^{1}H NMR spectrum

and acid chloride **7** to a stirred solution of Hünig's base (2 equiv), triethylamine (0.1 equiv), and hydroquinidine-4-chlorobenzoate **5** or hydroquinine-4-chlorobenzoate **6** (10 mol %). The mixture of tertiary amine bases was necessary since the rate of ketene generation from the acid chloride was too slow with Hünig's base alone, necessitating the presence of triethylamine for this purpose. However, use of stoichiometric triethylamine led to competing racemic organocatalysis (ammonium enolate generation from the ketene). The less nucleophilic Hünig's base serves to regenerate the triethylamine after it has effected ketene formation. With these conditions established, we were able to demonstrate that a range of acid chlorides **7** could be effectively converted into the *cis*-β-lactones **2** in moderate yields but with excellent diastereoselectivities (>95:5) and enantioselectivities. The cis-relative configuration was assigned to the major diastereomer based on analysis of ^{1}H NMR coupling constants (observed $^3J(H_2-H_3) = 7$ Hz; general literature values $^3J_{cis}$ = ca. 6.5 Hz, $^3J_{trans}$ = ca. 4.0−4.5 Hz).[18] As expected, use of the pseudoenantiomeric hydroquinine catalyst allowed formation of *ent*-**2** (entries 3 and 5). Protected oxygen functionality (entry 8) is tolerated. It is especially noteworthy that β-branching in the acid chloride (entries 4 and 5) was possible, since we are not aware of previous examples of in situ generation/cycloaddition of β-branched ketenes. However, the more sterically hindered *t*-Bu substrate was not successful (entry 9).

With an efficient synthesis of the β-lactones **2** in hand, we next addressed their ring opening. Azide was selected as a suitable nitrogen nucleophile in view of precedent for its attack

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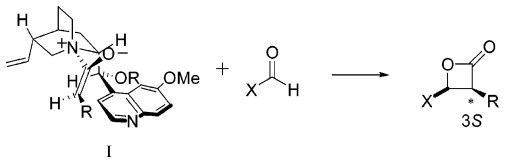

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FIGURE 1. Model for C3-stereoselectivity.

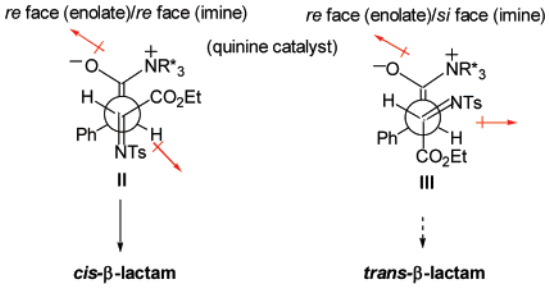
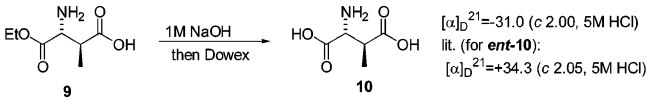


FIGURE 2. Lectka's model for stereoselective β-lactam formation.

SCHEME 1. Synthesis of β-Methylaspartic Acid 10



at C2- of β-lactones.[19] The desired opening was found to proceed cleanly (Table 2). The product was obtained with high diastereoselectivity providing the reaction was carried out at temperatures below 40 °C; at higher temperatures, some epimerization of the β-lactone appeared to precede the azide ring opening. Catalytic hydrogenation then allowed conversion to the substituted aspartate monoester **9** (Table 2).

The anti-configuration was assigned to **9** based on the expected inversion in the azide ring-opening step. To confirm this, and to demonstrate the application of the method to a biologically significant target, we converted **9** (R = Me) into β-methylaspartic acid **10** by ester hydrolysis (Scheme 1). Aspartate **10** is a constituent of the cyclic pentapeptide natural product motuporin, a phosphatase inhibitor.[20] The syn- and anti-isomers of **10** have previously been synthesized by multistep routes and ^{1}H NMR and optical rotation data have been reported for both.[2] ^{1}H NMR data for our sample of **10** showed good agreement with reported data for the anti-isomer. The optical rotation of our product was opposite, but slightly lower, than that reported for *ent*-**10**; however, chiral HPLC on the derived *N*-Fmoc-dimethyl ester indicated that our sample was essentially enantiomerically pure.

The observed 3*S*-configuration in the β-lactone products with use of dihydroquinidine-derived catalysts is in accord with the model put forward by Romo and Calter (Figure 1) involving attack on the more sterically accessible *si*-face of the *Z*-ammonium enolate in the *app-open* conformation **I**.[17,21] However, the observed C2-configuration (and hence cis-selectivity) is more difficult to rationalize, particularly since the use of chloral as aldehyde (X = CCl_3) is reported[16] to give predominantly the *trans*-β-lactone (71:29 trans/cis) in contrast to the cis-selectivity observed here with X = CO_2Et. A speculative

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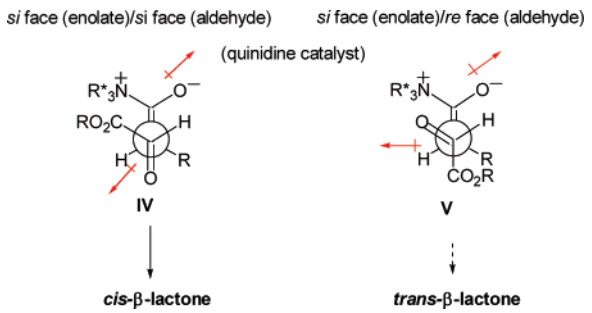

FIGURE 3. Model for C2-stereoselectivity.

explanation may be advanced by drawing an analogy with the related ketene/imine condensation. In that process, molecular modeling studies led Lectka to suggest the most favorable conformations leading to *cis*-and *trans*-β-lactams are **II** and **III**, respectively (Figure 2).[22] Possibly, these are favored since they maximize the indicated dipole−dipole repulsions, with the former being more effective in this regard, leading to the observed cis-selectivity. The assumption of analogous preferred conformations **IV** and **V** in the β-lactone synthesis (Figure 3) would again explain the observed cis-selectivity. It is then reasonable to suggest that replacement of the glyoxylate's ester group with the more bulky trichloromethyl group of chloral would disfavor TS-**IV** due to steric interactions with the ammonium substituent, thus favoring TS-**V** and hence the trans-product.[13,23] However, we cannot rule out the possibility that product epimerization is responsible for the reported trans-selectivity in the chloral case.

In conclusion, we have developed a short, diastereo- and enantioselective route to β-alkyl aspartates employing cinchona alkaloid organocatalysis. The method has been used for the synthesis of β-methyl aspartic acid **10**, a component of the phosphatase inhibitor motuporin.

Experimental Section

General Experimental Details. General experimental procedures are provided in the Supporting Information. The ethyl glyoxylate used in the lactonization reaction was obtained commercially as a quoted 50% solution in toluene. By ^{1}H NMR analysis, it was estimated to be ca. 1.4 M in glyoxaldehyde and the quantity used in the reactions was calculated on this basis. Racemic samples of β-lactones were prepared for chiral HPLC comparison, using triethylamine (1 equiv) and Hünigs base (1 equiv) (see the Supporting Information). *rac*-**2a** was also carried through to the *N*-Fmoc-dimethyl ester of *rac*-**10a** for chiral HPLC comparison.

General Procedure for Catalytic Enantioselective β-Lactone Synthesis. To a rapidly stirred solution of triethylamine (14 μL, 0.10 mmol, Hünig's base (0.35 mL, 2.0 mmol) and catalyst (47 mg, 0.10 mmol) in chloroform (1 mL), at −60 °C, was added a mixture of ethyl glyoxylate (0.71 mL of 1.4 M in toluene, 1 mmol) and acid chloride (1.5 equiv) in chloroform (1 mL) over 0.5 h. The reaction was then stirred for 2.5 h at which point most of the solvents were removed in vacuo. The crude product was purified by flash column chromatography (2:1 petrol:ether eluant) to afford β-lactone.

2a: Propionyl chloride (0.13 mL, 1.5 mmol) was used as described to afford the (2*S*,3*S*)-lactone (0.09 g, 0.52 mmol, 55%) as a colorless oil; $[\alpha]^{22}_D$ −30.3 (*c* 1.78, $CHCl_3$); >95% ee (determined by ^{1}H NMR in the presence of 40 mol % of Eu(hfc)$_3$); ν_{max}/cm^{-1}(film) 1841 (C═O lactone), 1754 (C═O); δ_H (400 MHz, $CDCl_3$) 4.93 (1H, d, J = 6.9 Hz), 4.32 (2H, dq, J = 14.2, 7.1 Hz), 4.08 (1H, app quin, J = 7.2 Hz), 1.31 (3H, t, J = 7.1 Hz), 1.27 (3H, d, J = 7.8 Hz); δ_C (100 MHz, $CDCl_3$) 169.9, 167.2, 70.4, 62.0, 50.2, 14.2, 9.4; *m*/*z* (%) (CI, NH_3) 176 (100) $[M + NH_4]^+$, found $[M + NH_4]^+$ 176.0924. $C_7H_{14}NO_4$ requires 176.0923.

General Procedure for Azide Opening. To a solution of sodium azide (2 equiv) in anhydrous DMSO (half solvent volume), at 40 °C, was added β-lactone (1 equiv) in DMSO (half solvent volume). The solution was stirred for 4 h, or until the starting material had been consumed as judged by TLC. The reaction was cooled to room temperature and saturated aqueous $NaHCO_3$ was added to give a heterogeneous solution that was then triturated with water until all precipitate dissolved. The resulting mixture was extracted with ethyl acetate (2 × 15 mL) and the aqueous layer was acidified to pH 0 with 1 M HCl. The acidic aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organics were then washed with water (2 × 10 mL) and saturated NaCl (2 × 10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford the β-azido acid.

8a: Lactone (2*S*,3*S*)-**2a** (0.14 g, 0.89 mmol) in DMSO (1.5 mL (half solvent volume)) was used as described to afford the (2*R*,3*S*)-product (0.11 g, 0.55 mmol, 60%) as a pale yellow oil in a >9:1 ratio of diastereomers; $[\alpha]^{22}_D$ +62.9 (*c* 0.35, $CHCl_3$); ν_{max}/cm^{-1} (film) 2116 (N_3), 1742 (C═O), 1741 (C═O); δ_H (400 MHz, $CDCl_3$) 9.49 (1H, s), 4.31−4.25 (2H, dq, J = 14.4, 7.2 Hz), 4.18 (1H, d, J = 6.1 Hz), 3.11−3.04 (1H, app. dq, J = 6.1, 7.1 Hz), 1.31 (3H. t, J = 7.2 Hz), 1.27 (3H, d, J = 7.1 Hz); δ_C (100 MHz, $CDCl_3$) 178.6, 168.6, 63.7, 62.4, 41.6, 14.1, 13.2; *m*/*z* (%) (CI, NH_3) 219 (100) $[M + NH_4]^+$, found $[M + NH_4]^+$ 219.1087. $C_7H_{15}N_4O_4$ requires 219.1093.

General Procedure for Azide Reduction. To a solution of azido acid (1 equiv) in methanol (10 mL) was added Pd/C (10% by mass). The reaction was stirred under a positive pressure of hydrogen, using a H_2 balloon, for 3 h, then filtered through celite and washed with methanol (25 mL). The solvent was removed in vacuo to afford the β-amino acid.

9a: Azido acid (2*R*,3*S*)-**8a** (0.12 g, 0.59 mmol) was used as described to afford the (2*R*,3*S*)-product (0.10 g, 0.57 mmol, 99%) as a white solid in a >9:1 ratio of diastereomers; $[\alpha]^{22}_D$ −8.5 (*c* 3.28, MeOH); mp 150−151 °C; ν_{max}/cm^1(neat) 3390 (O−H/N−H br), 1739 (C═O); δ_H (400 MHz, D_2O) 4.30−4.16 (2H, m), 4.09 (1H, d, J = 4.3 Hz), 3.07−3.00 (1H, dq, J = 4.3, 7.6 Hz), 1.22 (3H, d, J = 7.6 Hz); 1.21 (3H, t, J = 7.1 Hz); δ_C (100 MHz, D_2O/20 mol % MeOH) 180.4, 171.9, 64.0, 56.1, 42.3, 14.5, 13.8; *m*/*z* (%) (CI, NH_3) 176 (100) $[M + H]^+$, found $[M + H]^+$ 176.0928. $C_7H_{14}NO_4$ requires 176.0923.

Hydrolysis of 9a To Give 10. To a solution of amino acid **9a** (0.85 g, 4.9 mmol) in water (100 mL) was added 1 M NaOH (15 mL). The reaction was stirred at room temperature for 24 h after which time the solution was acidified to pH 0 with 1 M HCl. The solvent was removed in vacuo and the resulting white solid freed from the HCl salt by using a column of Dowex 50WX8-100 ion-exchange resin to afford (2*R*,3*S*)-**10**[2] (0.48 g, 3.3 mmol, 69%) as a colorless thick oil; $[\alpha]^{22}_D$ −31.0 (*c* 2.00, 5M HCl); ν_{max}/cm^{-1} (nujol) 3429−2854 (O−H/N−H br), 1588 (N−H); δ_H (400 MHz, D_2O) 3.65 (1H, d, J = 5.3 Hz), 2.87 (1H, app. qd, J = 7.5, 5.3 Hz), 1.26 (3H, d, J = 7.5 Hz); δ_C (100 MHz, D_2O/20 mol % MeOH) 181.4, 174.3, 58.0, 42.1, 15.6; *m*/*z* (ES-) found $[M - H]^-$, 146.0446. $C_5H_8NO_4$ requires 146.0453.

Enantiomeric Excess Determination for 10. To a solution of amino acid **10** (20 mg, 0.14 mmol) in water (0.5 mL) was added $NaHCO_3$ (23 mg, 0.27 mmol) with stirring. The resulting solution was cooled to 5 °C and FmocCl (50 mg, 0.20 mmol) is added slowly as a solution in dioxane (0.5 mL). The mixture was then stirred at 0 °C for 1 h and allowed to warm to room temperature overnight.

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Water (2 mL) was added to the solution and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layer was back extracted with saturated $NaHCO_3$ (2 × 10 mL) and the combined aqueous layers acidified to pH 0 with 1 M HCl. The acidic aqueous layer was extracted with ethyl acetate (3 × 15 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford the crude Fmoc protected amino acid, which was taken directly onto the next step. Thionyl chloride (16 μL, 0.22 mmol) was added to a solution of the *N*-protected amino acid (40 mg, 0.11 mmol) in methanol (4 mL) at 0 °C. The reaction was allowed to stir overnight after which time the solvent was removed in vacuo. The crude product was purified by flash column chromatography (2:1 petrol: ethyl acetate) to afford *N*-Fmoc-dimethyl ester (13 mg, 0.03 mmol, 30%) as a colorless oil; $[\alpha]^{22}_D$ −7.34 (*c* 2.73, $CHCl_3$); 99% ee (determined by HPLC analysis (column: OJ-H, flow rate 0.8, gradient 98:2 (hexane:IPA), injection vol 2 μL)); ν_{max}/cm^1 (nujol) 1734 (C═O), 1708 (C═O); δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, J = 7.5 Hz), 7.67 (2H, t, J = 7.5) Hz, 7.44 (2H, t, J = 7.5 Hz), 7.36 (2H, t, J 7.5 Hz), 5.89 (1H, d, J = 9.6 Hz), 4.68 (1H, dd, J = 9.6, 3.8 Hz), 4.53−4.42 (2H, m), 4.31 (1H, t, J = 7.2 Hz), 3.79 (3H, s), 3.75 (3H, s), 3.35 (1H, qd, J = 7.4, 3.8 Hz), 1.33 (3H, d, J = 7.4 Hz); δ_C (100 MHz, $CDCl_3$) 174.4, 171.3, 156.7, 143.9, 143.7, 141.3, 127.9, 127.8, 127.1, 120.0, 67.3, 55.9, 52.7, 52.2, 47.2, 41.3, 13.8; *m*/*z* (CI+) 415 (100%), 398 (60%) $[M + H]^+$, found $[M + H]^+$ 398.1602. $C_{22}H_{24}NO_6$ requires 398.1604.

Acknowledgment. We thank the EPSRC for their support of this work, and Bristol-Myers Squibb, Pfizer, and Merck Sharpe and Dohme for generous unrestricted funding.

Supporting Information Available: Spectroscopic data for all products, copies of ^1H and ^{13}C NMR spectra for all compounds **2**, **8**, **9**, **10**, and **11**, copies of ^1H NMR spectra in the presence of chiral shift reagents, and chiral HPLC traces for **11** and *rac*-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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