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A Concise Stereoselective Approach to β-Alkylaspartates from β-Lactams via [2 + 2] Cycloaddition Reaction of Ketenes to Glyoxylic Ester-Derived Imines.

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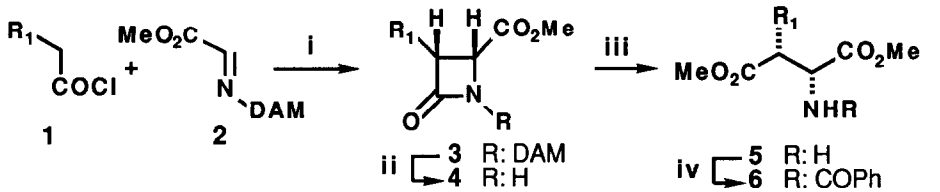
Abstract: *syn* β-Alkyl aspartates were obtained with high stereoselectivities from *cis* 4-alkoxycarbonyl-β-lactams prepared via [2 + 2] cycloaddition reaction of monoalkylketenes and glyoxalate derived imines.

Alkylation of the β-anion derived from aspartic acid or its derivatives is one of the most direct and extended procedures for the synthesis of β-alkylaspartates, but it often leads to mixtures of *syn* and *anti* diastereomers[1]. This problem can be solved by the use of β-lactams derived from aspartic acid, followed by stereospecific α-alkylation of their lithium enolates to give exclusively the corresponding *trans*-isomers[2], which at once can be directly converted into *anti*-β-alkylaspartates through an appropriate N_1-C_2 β-lactam ring cleavage[3]. However, the synthesis of *syn* diastereomers of β-alkylaspartates, still remains a challenging synthetic task[4] . In this paper we disclose our efforts towards a highly stereoselective synthesis of such a class of α-amino acids by the cycloaddition reaction of ketenes, generated from acid chlorides and triethylamine, to glyoxylic ester derived imines. We first reported the synthesis of 4-methoxycarbonyl β-lactams from alkanoyl chlorides and imines derived from p-anisidine in an approach to carbapenem compounds[5]. In parallel with our studies, a Merck group has also reported the synthesis of 4-ethoxycarbonyl β-lactams following the same approach[6]. However, in both cases, a mixture of *cis* and *trans* isomers was produced[7]. Therefore, we investigated the possibility of improving the stereochemical outcome of this reaction in order to synthesize *syn* β-alkylaspartates in a completely stereoselective fashion. We found that the treatment of alkanoyl chlorides **1** with the imine **2**, derived from methyl glyoxalate and di-p-anisylmethylamine (DAM-NH_2)[8], in refluxing hexane, benzene or methylene chloride in the presence of triethylamine, afforded *cis*-3-alkyl-4-methoxycarbonyl β-lactams **3** as single isomers.



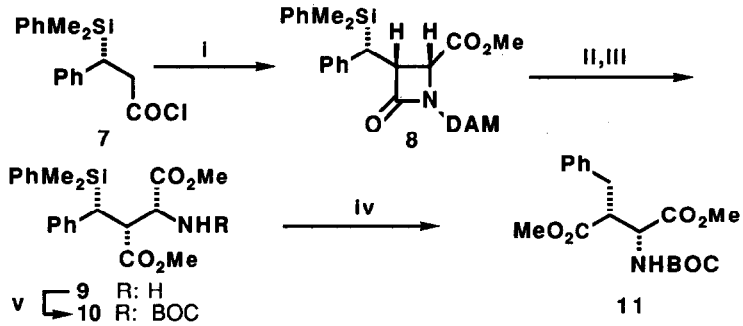
a R_1: Me **b** R_1: Et **c** R_1: iPr **d** R_1: CH_2Ph **e** R_1: Ph

Scheme 1. Reagents and conditions **i** NEt_3, CH_2Cl_2 or C_6H_6 reflux,12-14h **ii** $(NH_4)_2Ce(NO_3)_6$, MeCN-H_2O, 0-5ºC,30min, **iii** $ClSiMe_3$,MeOH, r.t. **iv** PhCOCl, NEt_3, CH_2Cl_2 r.t.

The choice of DAM-NH_2 was guided according to the general parameters that influence the *cis* stereoselectivity of the Staudinger reaction[9], by our previous observations on related [2 + 2] cycloaddition reactions[10] and by the easy transformation of the resulting β-lactams into the N-unsubstituted ones in a single step[8]. Moreover, during the course of our work, we were encouraged by the recent publication of Sasaki et al. showing the usefulness of such imines in the synthesis of 3-vinylazetidin-2-ones[11]. The deprotection of N-DAM-β-lactams was easily accomplished by treating them with cerium (IV) ammonium nitrate (CAN) in

acetonitrile-water; for instance, compound **3a** gave the expected NH-β-lactam **4a** in 83% yield (Scheme 1). Similarly, **3b-e** afforded **4b-e** in yields ranging from 80% to 88%. Finally, the β-lactam ring opening, achieved by means of trimethylchlorosilane in methanol[12], afforded the expected *syn* 3-alkylaspartates **5a-e**, which were isolated as the N-benzoyl derivatives **6**[13]. In view of the above results the next logical aspect we examined was an asymmetric version of this reaction[14].

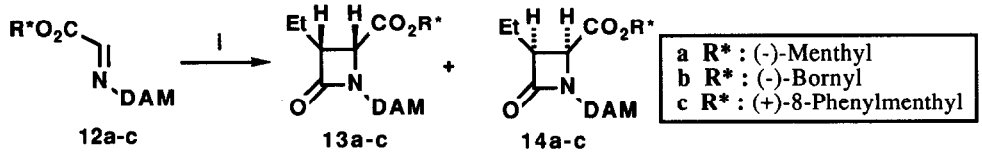
Asymmetric synthesis from the ketene partner. To test this approach β-dimethylphenylsilyl-β-phenyl propanoyl chloride[15] was selected for development. Two reasons led us to explore this proposal. First, as the silyl moiety is a masked form of the hydroxy group[16], the resulting aspartates could be transformed into β,γ-unsaturated α-amino acids[3a] and, second, these aspartates might be atractive precursors of optically active β-benzyl aspartates through a simple desilylation step.



Scheme 2. Reagents and conditions **i** **2**, NEt_3, CH_2Cl_2, reflux,12-14h **ii** $(NH_4)_2Ce(NO_3)_6$ MeCN,-H_2O, 0-5ºC, 30min **iii** $ClSiMe_3$, MeOH, r.t. **iv** BuN_4F, CH_2Cl_2, r.t. **v** $(BOC)_2O$, CH_2Cl_2, r.t.

Treatment of **7** with **2** in the presence of triethylamine in methylene chloride as solvent gave **8** in 78 % yield, [m.p. 146-147ºC (MeOH), $[\alpha]^{25}_D$= -30.6°(c: 1, CH_2Cl_2)] together with its *cis*-diastereomer in a ratio of 91:9 respectively[17]. N-Dearylation of **8** and further β-lactam opening led to the formation of the expected aspartate **9** which was isolated as its N-BOC derivative **10** in 81 % overall yield. Desilylation of **10** by means of TBAF[18] afforded **11** in nearly quantitative yield ($[\alpha]^{25}_D$= -23.4°(c: 0.8, CH_2Cl_2)]). Subsequent HPLC analysis of **11** provided the overall diastereomeric purity for the desilylation step and derivatization sequence. Additionally, to check the enantiomeric purity of the product **11**, the corresponding (+)-MTPA amide derivative was prepared by deprotection of the N-BOC group and further acylation using Mosher acid chloride and triethylamine[19]. From this result it is clear that the silicon assisted asymmetric synthesis of β-benzylaspartates should be general in scope[20].

Asymmetric synthesis from the imine partner. We first attempted to obtain asymmetric induction using the methyl glyoxalate imine derived from (R)-α-naphtylethylamine but with no success[5]. In general, the use of chiral amines as components of the imine partner produced lower levels of asymmetric induction than those obtained by changing the aldehyde component[14b]. Therefore, we studied the influence of glyoxalate imines **12**, derived from some representative chiral glyoxalates[21], on the stereochemical course of the reaction (Scheme 3). When the imine **12a**, derived from menthyl glyoxalate[21a] and DAM-NH_2, was allowed to react with butanoyl chloride and triethylamine a mixture of *cis*-diastereomers **13a** and **14a** was obtained in a 1.5: 1 ratio respectively.



Scheme 3. Reagents and conditions: **i** $EtCH_2COCl$, NEt_3, CH_2Cl_2 or hexane, reflux,12-14h

The replacement of DAM-NH_2 as the amino component of the imine partner with p-anisidine (PMP) caused formation of *cis* and *trans* isomers in a total ratio of 3:1, and virtually no diastereoselection was observed for any of the four diastereomers formed. A similar level of reaction diastereoselection was produced when imine **12b** was employed as the source of chirality and only an slight increase in diastereoselection was achieved starting from the imine **12c** derived from (+)-8-phenylmenthyl glyoxalate which produced **13c** and **14c** in a ratio of 1 : 2 respectively[22].

Taking into account the reaction mechanism of the asymmetric Staudinger reaction[23], the results disclosed in this preliminary study open up the way to prepare optically active β-alkylaspartates using either a chiral ketene partner or from glyoxalate esters derived from bulky homochiral alcohols. Further studies of this chemistry, are now in progress.

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13. Representative data for selected compounds: **6a**: Oil. I.R. (film) ν (cm^{-1}): 3309, 2943, 1736, 1645, 1525. ^{1}H-NMR ($CDCl_3$) δ : 7.82-7.41 (m, 5H, arom.), 7.14 (d, 1H, J= 8.4 Hz, NH), 5.07 (dd, 1H, J= 8.4 Hz, J= 4.8 Hz, CH), 3.78 (s, 3H, OCH_3), 3,72 (s, 3H, OCH_3), 3.11 (dq, 1H, J= 7.5Hz, J= 4.8Hz, CH), 1.32 (d, 3H, J= 7.5Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ : 173.7, 171.0, 166.9, 133.5, 131.8, 128.5, 127.0, 54.2, 52.6, 52.2, 42.0, 13.2 MS (m/z): 222 (M^+ - 57). **6b**: Oil. I.R. (film) ν (cm^{-1}): 3300, 2946, 1733, 1641, 1524. ^{1}H-NMR ($CDCl_3$) δ : 7.82-7.41 (m, 5H, arom.), 7.11 (d, 1H, J= 8.1 Hz, NH), 5.07 (dd, 1H, J= 8.1 Hz, J= 5.4 Hz, CH), 3.77 (s, 3H, OCH_3), 3,72 (s, 3H, OCH_3), 2.91 (dt, 1H, J= 5.4 Hz, J= 9.3 Hz, CH), 1.97-1.82 (m, 1H, CH), 1.74-1.60 (m, 1H, CH), 1.00 (t, 3H, J= 7.5Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ : 173.1, 171.0, 166.9, 133.5, 131.8, 128.5, 127.0, 53.2, 52.6, 52.0, 49.5, 21.5, 11.9 MS (m/z): 236 (M^+ - 57). **6c**: Oil. I.R. (film) ν (cm^{-1}): 3303, 2950, 1734, 1642.^{1}H-NMR ($CDCl_3$) δ : 7.81-7.43 (m, 5H, arom.), 6.92 (d, 1H, J= 7.8Hz, NH), 5.10 (dd, 1H, J= 5.1 Hz, J= 7.8 Hz, CH), 3.81 (s, 3H, OCH_3), 3,70 (s, 3H, OCH_3), 2.80 (dd, 1H, J= 5.1 Hz, J= 9.3 Hz, CH), 2.23 (m, 1H, CH), 1.18 (d, 3H, J=6.6Hz, CH_3), 0.97 (d, 3H, J=6.6Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ :173.1, 171.2, 166.8, 133.7, 131.9, 128.7, 127.1, 55.7, 52.7, 52.2, 51.8, 27.7, 20.8, 20.7 . **11**: Oil.^{1}H-NMR ($CDCl_3$) δ : 7.32-7.28 (m, 5H, arom.), 5.60 (s_b, 1H, NH), 4.68 (d, 1H, J=4.1Hz, CH-N), 3.75 (s, 3H, OCH_3), 3,66 (s, 3H, OCH_3), 3.41 (m, 1H, CHCOOMe), 3.02 (m, 1H, CH_2-Ph), 2.83 (m, 1H, CH_2-Ph),1.46 (s, 9H, ^{t}Bu).

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17. The stereochemistry at the C_3 and C_4 positions of the β-lactam ring was assigned on the basis of our previous studies made on racemic compounds, see ref. 10.

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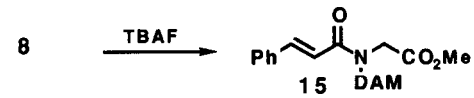
20. The desilylation step carried out directely on compound **8** caused formation of the α,β-unsaturated amide **15**.



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