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# Stereoselective routes to substituted β-amino carbonyl compounds via heterodiene cycloadditions of an auxiliary-based $C_2$-symmetric ketene acetal

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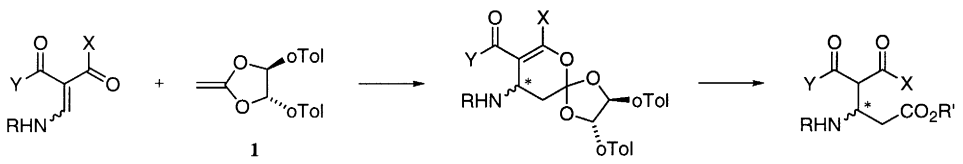
**Abstract**

Heterodiene cycloadditions of (*S*,*S*)-4,5-bis(*o*-tolyl)-2-methylene-1,3-dioxolane **1** with a series of substituted β-amido-α,β-unsaturated carbonyl compounds are diastereoselective (dr ≥4:1). The cycloadducts from *N*-(2-(1-oxoethyl)-3-oxobut-1-enyl)ethanamide **2a** can be purified by crystallisation and hydrolysed with acid to generate the corresponding β-amidoacetic esters, the sequence providing an auxiliary-based stereoselective route to such compounds. 

*Keywords:* cycloadditions; ketene acetals; diastereoselection; amino acids and derivatives.

The [4π+2π] cycloaddition of α,β-unsaturated carbonyl compounds (1-oxabutadienes) to alkenes can be an efficient route to dihydropyrans[1] and the process has been exploited in synthesis.[2] We have developed a series of auxiliary-based $C_2$-symmetric ketene acetals, e.g. **1**, for use as the 2π components of such reactions,[3,4] and herein describe the results of a recently initiated study of their potential as a source of homochiral β-amino acid derivatives (Scheme 1), which are valued synthetic intermediates.[5] Related heterodiene cycloadditions have been used en route to racemic aminosugars[6] and carbapenem precursors,[7] but a variant capable of providing useful levels of asymmetric induction remains an attractive target.




Scheme 1.

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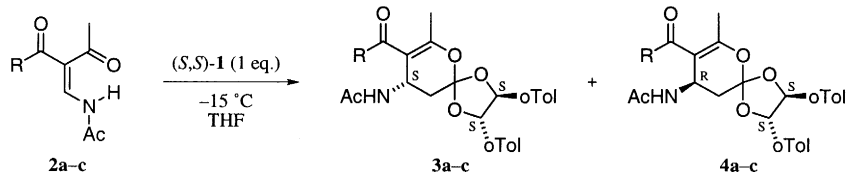
Our study was initiated with the simple amidodiene **2a**,[8] whose reaction with 1 equivalent of the ketene acetal **1**[4] in THF at −15°C over 5 days yielded a mixture of the cycloadducts **3a** and **4a** in fair yield and a diastereoisomeric ratio (dr) of ca. 4:1 as judged by 250 MHz $^1$H NMR spectroscopy (Table 1).[9] Crystallisation of the mixture from isohexane (mainly 2-methylpentane) gave the cycloadduct **3a** as colourless needles, m.p. 112–115°C. Cycloadditions of **1** with the β-acetamidoenoates **2b**[7] and **2c** proceeded in similar fashion. Crystallisation of the mixed products from **2b** yielded **3b** as a single isomer, while the purity of **3c** was significantly improved by trituration with isohexane. The heterocyclic aldehyde **5**, prepared from 1,3-dimethyluracil by Vilsmeier formylation,[10] was also found to react diastereoselectively with **1**, producing the fused spirocyclic pyrimidines **6**+**7** in moderate yield.

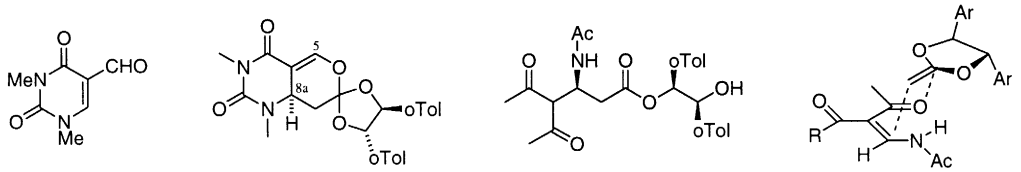



Scheme 2.

Table 1

| *ENTRY* | *STARTING DIENE* | *R* | *REACTION TIME (d)* | *PRODUCTS* | *ISOLATED MATERIAL* | |
|---|---|---|---|---|---|---|
| | | | | | *Ratio* | *Yield (%)* |
| 1 | **2a** | Me | 5 | **3a** + **4a** | ≥ 4 : 1 | 67 |
| 2 | **2b** | OMe | 3 | **3b** + **4b** | ≥ 19 : 1 | 60 |
| 3 | **2c** | OBn | 4 | **3c** + **4c** | 4.1 : 1 | 62 |
| 4 | **5** | | 3 | **6** + **7** | 4.3 : 1 | 50 |

The ortholactone function of the cycloadducts **3a**+**4a** was hydrolysed upon brief treatment with acid (0.1 M $H_2SO_4$, THF, 1 h), which generated the diastereoisomeric β-amidoesters **8** (56%) in essentially the same ratio (4.25:1 by $^1$H NMR spectroscopy) as the educt mixture. In principle, the amidoesters **8** offer a second opportunity to isolate pure stereoisomers prior to the removal and recovery of the auxiliary (*S*,*S*)-1,2-bis(*o*-tolyl)ethane-1,2-diol.[4,11]



**5** **6** 8a-*R* (shown) **7** 8a-*S* **8** **9**

The 4*S* configuration at the newly-generated stereocentre in the major products **3** is proposed on the basis of the cycloaddition model **9**, analogous to that advanced previously.[3,4] The hydrogen-bonded reacting conformations of the dienes (as depicted in Scheme 2) are supported for **2a** by the results of molecular modelling[12] and for the esters **2b** and **2c** by the $^{13}$C NMR studies described by Bayles et al.,[7] which indicated that the preparative routes to these compounds predominantly gave rise to the *E*-geometry shown. The preferential formation of **6** from the uracil-derived aldehyde **5** is tentatively suggested on the basis of the results obtained using the structurally similar heterodiene, chromone-3-carbaldehyde.[3]

The above results suggest that the sequence outlined in Scheme 1 could provide an effective stereoselective route to a variety of functionalised β-amino carbonyl systems based on a recyclable auxiliary

strategy. Further synthetic and X-ray diffraction studies,[13] which should confirm stereochemical assignments, are in progress and will be described in due course.

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9. New compounds gave satisfactory analytical data. Typical procedure: A solution of ketene acetal **1** (0.6 mmol) and the diene **2** (0.6 mmol) in THF (10 mL) was kept at −15°C until analysis by HPLC or TLC indicated that the reaction was complete. The reaction mixture was then concentrated and the residue analysed by 250 or 300 MHz NMR spectroscopy (in each case the dr at this stage was estimated to be ca. 4:1). The isolated materials described in Table 1 were obtained as follows. Entry 1: The residue was taken up in $CH_2Cl_2$ (1 mL), filtered through a plug of basic alumina using more $CH_2Cl_2$ and the filtrate concentrated to obtain the isolated product (dr by NMR). Entry 2: The residue was taken up in $CH_2Cl_2$ and filtered through a plug of basic alumina using ethyl acetate:isohexane (1:4). Concentration and crystallisation from ether:isohexane (1:1) gave the isolated product (dr by NMR). Entry 3: The residue was taken up in $CH_2Cl_2$, filtered through a plug of basic alumina using ether:isohexane (2:1) and the filtrate concentrated to obtain the isolated product (dr by HPLC). Trituration with isohexane gave material with dr 14:1 by HPLC. Entry 4: The residue was crystallised from isohexane (dr by HPLC). Selected $^1$H NMR data (signals tentatively attributed to minor products in square brackets): **3a** [**4a**] (400 MHz) 1.70 [1.67] (3H, s, ArMe), 1.79 [1.76] (3H, s, ArMe), 1.93 [1.94] (3H, s, MeCON), 2.28 (3H, s, MeCOC), 2.37 (3H, s, 6-Me), 2.42–2.56 (2H, m, 3-$H_2$), 5.27 [5.34] (1H, d, *J*=9 Hz, 4′ or 5′-H), 5.36–5.46 (1H, m, 4-H), 5.55 (1H, d, *J*=9 Hz, 4′ or 5′-H), 6.17 [6.06] (1H, d, *J*=10 Hz, NH), 7.03–7.09 (2H, m, 3,3′-ArH), 7.20–7.35 (4H, m, 4,4′,5,5′-ArH), 7.57 (2H, dd, *J*=2, 8 Hz, 6,6′-ArH); **3b** [**4b**] (250 MHz) 1.68 [1.65] (3H, s, ArMe), 1.78 [1.74] (3H, s, ArMe), 1.89 (3H, s, MeCON), 2.44 (3H, s, 2-Me), 2.40–2.50 (2H, obscured m, 5-$H_2$), 3.74 (3H, s, $CO_2$Me), 5.28 (1H, d, *J*=9 Hz, 4′-H or 5′-H), 5.30–5.40 (1H, m, 4-H), 5.54 (1H, d, *J*=9 Hz, 4′-H or 5′-H), 6.00 (1H, d, *J*=9 Hz, NH), 7.06 (2H, d, *J*=7.5 Hz, 3,3′-ArH), 7.20–7.35 (4H, m, 4,4′,5,5′-ArH), 7.57 (2H, d, *J*=8 Hz, 6,6′-ArH); **3c** [**4c**] (400 MHz) 1.69 (3H, s, ArMe), 1.77 (3H, s, MeCON), 1.79 (3H, s, ArMe), 2.20 (3H, s, Me), 2.39–2.48 (2H, m, 5-$H_2$), 2.45 (3H, s, 2-Me), 5.06 (1H, d, *J*=12 Hz, OCHPh), 5.29 (1H, d, *J*=9 Hz, 5′-H), 5.33 (1H, d, *J*=12 Hz, OCHPh), 5.37–5.45 (1H, m, 4-H), 5.54 [5.55] (1H, d, *J*=9

Hz, 4′-H), 5.97 [6.02] (1H, d, *J*=9.5 Hz, NH), 7.02–7.07 (2H, m, 3,3′-ArH), 7.18–7.40 (9H, m, ArH), 7.57 (2H, br d, *J*=8 Hz, 6,6′-ArH); **6** [**7**] (300 MHz) 1.66 (3H, s, ArMe), 1.77 (3H, s, ArMe), 2.27 (1H, t, *J*=12 Hz, 8-$H_{ax}$), 2.75 (1H, dd, *J*=5, 12 Hz, 8-$H_{eq}$), 3.07 [3.08] (3H, s, NMe), 3.23 [3.21] (3H, s, NMe), 4.40 (1H, ddd, *J*=2, 5, 12 Hz, 8-Ha), 5.31 (1H, d, *J*=9 Hz, 4′-H), 5.58 [5.43] (1H, d, *J*=9 Hz, 5′-H), 6.95–7.10 (2H, m, 3,3′-ArH), 7.15–7.30 (4H, m, 4,4′,5,5′-ArH), 7.50–7.60 (2H, m, 6,6′-ArH), 7.70 [7.62] (1H, d, *J*=2 Hz, 5-H); **8** (300 MHz) 1.80 (3H, s, ArMe), 1.87 (3H, s, ArMe), 1.92 (3H, s, MeCON), 2.15 (3H, s, 2′-Me), 2.24 (3H, s, 6-Me), 2.60 (1H, dd, *J*=7, 15 Hz, 2-H), 2.70 (1H, dd, *J*=7, 15 Hz, 2-H), 4.07 [4.24] (1H, d, *J*=6 Hz, 4-H), 5.10–5.20 (1H, m, 3-H), 5.24 (1H, d, *J*=9 Hz, 2′′-H), 6.11 (1H, d, *J*=9 Hz, 1′′-H), 6.74 (1H, d, *J*=10 Hz, NH), 6.90–7.00 (2H, m, 3,3′-ArH), 7.07–7.23 (4H, m, 4,4′,5,5′-ArH), 7.46 (1H, br d, *J*=8 Hz, 6-ArH), 7.60 (1H, br d, *J*=8 Hz, 6′-ArH).

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11. The ester **8** was readily hydrolysed with 5% NaOH in EtOH (20°C, 1 h) and the auxiliary diol recovered intact by adding water and extracting with $CH_2Cl_2$.
12. The various possible reacting (*s-cis*) conformations of the heterodiene **2a** were generated with CAChe 4.1.1 (Oxford Molecular) and their geometries optimised using an augmented MM3 force field. The results indicate that the H-bonded arrangement depicted in Scheme 2 is >4.9 kcal/mol more stable than the closest alternative.
13. A preliminary crystallographic investigation of a poorly diffracting crystal of **3a** has confirmed the gross structure and 4*S*-configuration depicted.