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The synthesis of α-amino-γ-substituted adipic acids: stereoelectronic effects during the 1,4-addition of organocuprates to methyl *N-tert*-butoxy-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate

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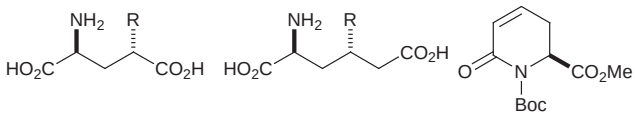
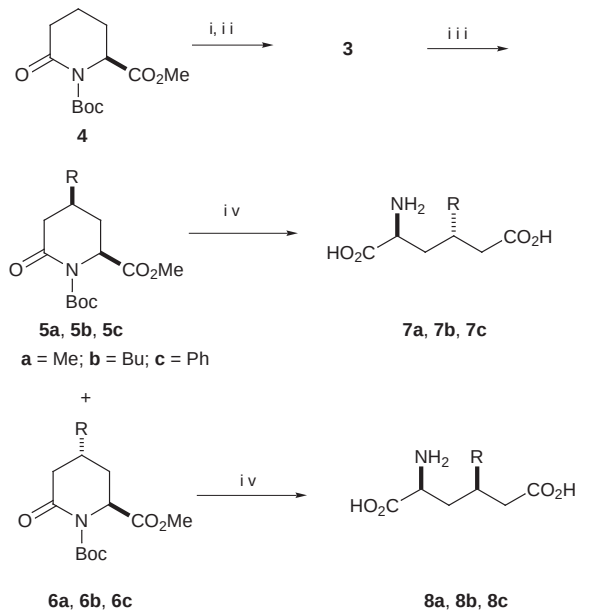
The α,β-unsaturated lactam 3 was submitted to 1,4-addition of organocuprate reagents R_2CuLiI_2 (R = Me, Bu or Ph) to provide the 4-substituted compounds 5a–c, 6a–c as a mixture of diastereomers; these intermediates were then transformed into the corresponding α-amino-γ-substituted adipic acids 7a–c, 8a–c.

The synthesis of modified and unnatural amino acids is a source of constant inspiration in organic chemistry.[1–3] In recent years glutamic acid, a major neurotransmitter in the mammalian brain, has received considerable attention from chemists involved in neurosciences.[4,5] During earlier studies on modified glutamates, we and others have found that the γ-substituted analogues of structure **1** are invaluable tools for the pharmacological exploration of excitatory amino acid receptors.[6,7] Interestingly it was found that the biological activity of such derivatives was largely confined to the 2*S*,4*S* diastereomers. For structure–activity studies devoted to this class of amino acids, we decided to synthesize compounds of type **2** in which the distal carboxylate is moved an additional methylene unit away from the α-amino acid group compared with **1**, generating γ-substituted α-amino adipic acids (Adi). As earlier observations have already demonstrated that Adi itself possesses good affinity for the glutamate receptors,[8] the introduction of different substituents on the Adi backbone may contribute to a better knowledge of steric demands at the receptor level.[9] Our goal was to employ an enantiospecific and diastereoselective synthesis which would provide analogues **2** in which the C-2 and C-4 substituents have the correct configuration for high biological activity. Since we have previously prepared modified glutamic acids using a conjugate addition of organocopper reagents,[10] we therefore proposed to submit compound **3** to a similar sequence, in the expectation that the presence of the C-2 carboxylate would provide facial selectivity.[11,12] We report herein our observations on the diastereoselectivity obtained in the 1,4-addition of organocuprate reagents to the α,β-unsaturated lactam **3**.



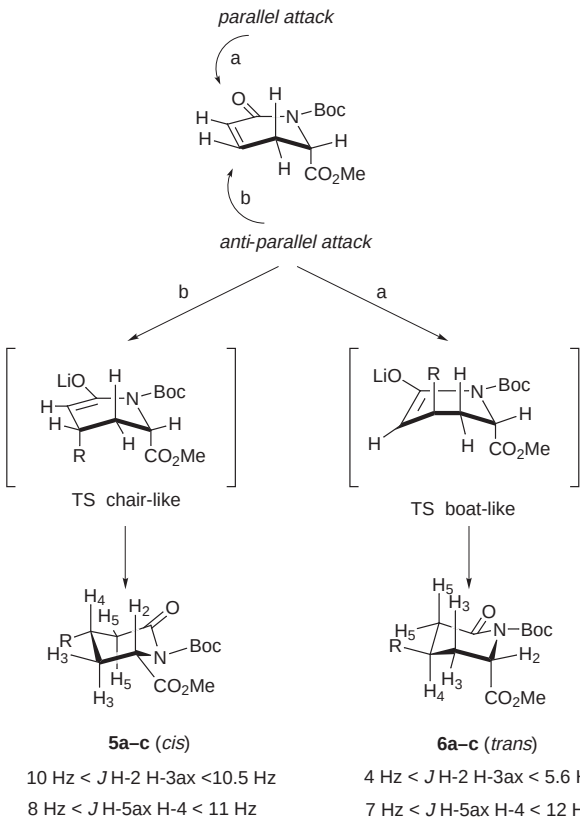
1 **2** **3**

The starting compound **3** was obtained from (*S*)-lysine in enantiomerically pure form *via* piperidone **4**, following literature reports.[13–15] The unsaturation was introduced by a sequence involving selenation and oxidative elimination, as decribed for the preparation of the corresponding benzyl ester (Scheme 1).[15] Since lactam **3** is potentially prone to nucleophilic attack, we were pleased to find that the reaction of this substrate in Et_2O with different organocuprates gave the expected adducts as mixtures of *cis/trans* diastereomers (**5a–c** and **6a–c**) in acceptable yields, and in moderate to good stereoselectivity.† Examination of the ^1H NMR (200 MHz) spectra of the crude mixtures revealed that each diastereomer has a well resolved signal (dd) between δ 4.5–4.8 for the hydrogen attached at C-2. Surprisingly, in analyzing these signals for the **5a**/**6a**, **5b**/**6b** and **5c**/**6c** mixtures, we observed that the intensity for the upfield signal (*trans* diastereomer) increases at the expense of the corresponding downfield one (*cis* diastereomer). These results indicate a change in the *cis* : *trans* ratio related to the structure of the transfered substituent. After purification, the pattern of the H-5ax proton was identified in each diastereomer as a doublet of doublets (B part of an ABX spin sytem) in which largest *J* value (around 17 Hz), corresponds to the geminal coupling H-5ax/H5eq. The smaller *J* value (around 11 Hz) arises from to the coupling between H-5ax and H-4, and these were of comparable value in all the compounds (**5a–c** and **6a–c**), consistent with an axial disposition of the proton at C-4. As a consequence the Me, Bu or Ph substituents attached at C-4 have an equatorial disposition in each diastereomer. For the protons attached at C-2 in **5a** and **6a** two sets of coupling constants were measured: J = 10 and 6 Hz, and J = 4 and 2 Hz, repectively. From these data it was clear that in the analogues **5a–c** the carboxylate adopts an equatorial disposition (large J values = axial orientation of the proton at C-2) whilst in contrast for derivatives **6a–c** the carboxylate has



Scheme 1 *Reagents and conditions*: i, LiHMDS (1.1 equiv.), PhSeCl (1. 2 equiv.), THF −78 °C, 2 h (78%); ii, MCPBA (2 equiv.), CH_2Cl_2, 25 °C, 12 h (72%); iii, for **5a**/**6a**: MeLi (2 equiv.), CuI (1 equiv.), Et_2O, −78 °C, 2 h, **5a** (68%) and **6a** (9%); for **5b**/**6b**: BuLi (2 equiv.), CuI (1 equiv.), −78 °C, 2 h , **5b** (35%) and **6b** (33%); for **5c**/**6c**: PhLi (2 equiv.), CuI (1 equiv.), Et_2O, −78 °C, 2 h , **6c** (48%); HCl in AcOH, reflux, 3 h (from 45 to 80%).

an axial orientation (small *J* values = equatorial orientation of the proton at C-2). These data are consistent with a chair conformation for all of the isolated compounds, in which the products **5a–c** have the substituents in a 1,3-*cis* arrangement, and **6a**–**c** in a 1,3-*trans* arrangement. In order to explain these findings, we performed calculations on lactam **3** (MOPAC out of SYBYL 6.3) which demonstrated that the conformer having the carboxylate at C-2 in an axial disposition is, by far, more stable (5 kcal mol^{-1}) than the corresponding equatorial conformer‡ (Scheme 1). This result is the obvious consequence of a strong $A^{1,3}$ strain between the carboxylate at C-2 and the Boc group on the nitrogen atom.[16] Based on these calculations and several literature reports on the stereoelectronic effects during conjugated addition in related α,β-unsaturated cyclohexanones or 2,3-dihydro-4-pyridones,[17,18] a strong axial bias was expected to operate during the addition of nucleophilic reagents to lactam **3**. Therefore one should observe the preferential formation of the *cis* adducts (**5a**–**c**) at the expense of the corresponding *trans* epimers (**6a**–**c**). Indeed for the smallest substituent (R = Me) an appreciable diastereoselectivity in favor of the *cis* adduct was observed (**5a** : **6a** = 5 : 1). However when the steric demand of the organocuprate was increased (R = Bu), the facial selectivity was lost (**5b** : **6b** = 1 : 1) or, for still bulkier groups (R = Ph) the facial steroselectivity was reversed, and the *trans* diastereomer was the only one detected (**5c** : **6c** = 1 : 30). Allinger has discussed a closely related example involving the 1,4-addition of Grignard reagents to 5-methylcyclohex-2-enone,[19] in which the importance of the conformation of the conjugated enolate (chair or boat) produced by parallel or anti-parallel attack was considered. As the carboxylate function in **3** is assumed to be axial, the major pathway for the reaction with Me_2CuLi_2I was *via* an anti-parallel attack to give the transient enolate of **5a.** This intermediate possesses a low energy chair-like conformation (TS chair), in spite of the 1,3-diaxial interaction between the carboxylate and the incoming methyl group. When the nucleophile is larger, such as in Bu_2CuLi_2I (**5b**/**6b**) or Ph_2CuLi_2I (**5c**/**6c**), the reaction pathway *via* parallel attack takes place preferentially due to a competing strong 1,3-diaxial interaction between the carboxylate and the bulky incoming nucleophile. This gives a transient, boat-like (TS boat) enolate, which collapses to the *trans* chair conformer. The final transformation of **5a**–**c** and **6a–c** into the desired substituted adipic acids was realized under hydrolytic conditions and the amino acids **7a,b** and **8a**–**c** were obtained as crystalline hydrochlorides.§



Scheme 2 Possible transition states and recorded values for coupling constants.

In conclusion, the diastereoselectivity observed for the conjugate addition of organocuprates to cyclic enamide **3** could be controlled by an appropriate choice of the transferable nucleophilic reagent. The significant $A^{1,3}$ strain inherent to the ring system and the size of the nucleophile are probably the key factors responsible for the diastereoselectivity observed in this conjugate addition reaction. Our findings demonstrate that α,β-unsaturated species **3** is an excellent substrate for the preparation of enantiomerically pure (2*S*,4*S*)- or (2*S*,4*R*)-2-amino-4-substituted adipic acids.

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Notes and references

† *Selected data* for **5a**: mp 60 °C; R_f 0.30 (hexanes–Et_2O = 5 : 5); $[\alpha]_D$ −66.2 (*c* 5, $CHCl_3$); δ_H(200 MHz, 30 °C) 4.51 (dd, *J* 10.2 and 6.2, 1 H), 3.74 (s, 3 H), 2.62 (dt, *J* 17 and 2.4, 1 H), 2.30 (m, 1 H), 2.10 (dd, *J* 17 and 10, 1 H), 2.15 (m, 1 H), 1.53 (m, 1 H),1.48 (s, 9 H), 1.02 (d, *J* 6, 3 H); δ_C(50 MHz) 172.1, 170.1, 151.9, 83.6, 58.6, 52.3, 42.7, 34.1, 28.3, 27.7, 26.3, 20.7. (Calc. for $C_{13}H_{21}NO_5$: C, 57.54; H, 7.80; N, 5.16. Found: C, 57.3; H, 7.9; N, 5.2%). For **6a**: oil; R_f 0.35 (hexanes–Et_2O = 6 : 5); $[\alpha]_D$ +20.1 (*c* 2, $CHCl_3$, 30 °C); δ_H(200 MHz) 4.71 (dd, *J* 4 and 1.8, 1 H), 3.80 (s, 3 H), 2.66 (ddd, *J* 16.3, 3.2 and 1.4, 1 H), 2.21 (dd, *J* 9.1, 4 and 1.4, 1 H), 2.09 (dd, *J* 16.3 and 9.6, 1 H), 1.96 (m, 1 H), 1.73 (m, 1 H), 1.51 (s, 9 H), 1.01 (d, *J* 4.2, 3 H); δ_C(50 MHz) 172.2, 169.9, 152.2, 83.6, 58.3, 52.6, 42.8, 33.5, 29.7, 27.9, 25.1, 21.1. (Calc. for $C_{13}H_{21}NO_5$: C, 57.54; H, 7.80; N, 5.16. Found: C, 57.6; H, 7.6; N, 5.1%).

‡ In compound **3**, the recorded coupling constant (dd, *J* 4.5) is consistant with an axial orientation of the carboxylate.

§ *Preparation* of **7a**: Lactam **5a** (96 mg, 0.35 mmol) was heated at reflux for 2 h in a mixture of concentrated HCl (2 ml) and AcOH (4 ml). The mixture was concentrated *in vacuo* and triturated with Et_2O, to provide a solid which was filtered to yield **7a** (60 mg, 81%) as a hygroscopic solid; mp 178 °C; $[\alpha]_D$ −79 (*c* 1, MeOH); *m/z* (FAB) 176 ($M + H^+$). For **8a**: mp 196 °C; $[\alpha]_D$ +26 (*c* = 1.8, MeOH); *m/z* (FAB) 176 ($M + H^+$).

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