A New Synthetic Approach to Unusually Electron Rich α-Amino Acids

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An electron rich dihydrobenzoxazine based α-amino acid has been synthesized using the Schollkopf chiral auxiliary giving a new adaptation of the standard C_α–C_β bond formation strategy, as required by the electron rich nature of the side chain.

The development of new methodologies enabling the synthesis of unusual amino acids plays a significant role in the interface between medicine, biology and chemistry. A steady increase in the literature[1] devoted to amino acid research demonstrates that the possible number of unusual amino acids is evidently unlimited. Surprisingly, none of the synthetic groups involved in amino acid synthesis report methods applicable to highly electron rich and electron deficient amino acids. In connection with our ongoing project to study the electronic interactions of donor and acceptor moieties in conformationally restricted peptides, we needed to synthesize an electron rich α-amino acid **1** and its derivatives in optically active form. The most common methods of α-amino acid syntheses involve asymmetric derivatization of glycine **3**. Although a number of chiral auxiliaries have become available in recent years which address this issue,[1] the Schollkopf bislactim ether **10** method has enjoyed unrivalled popularity owing to its simplicity and reliability.[2,3] In this communication we report a unique application of Schollkopf's technique for

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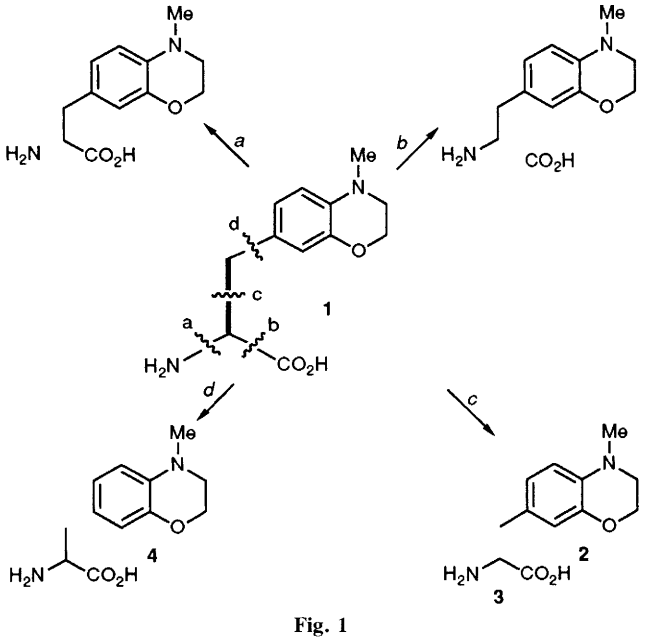
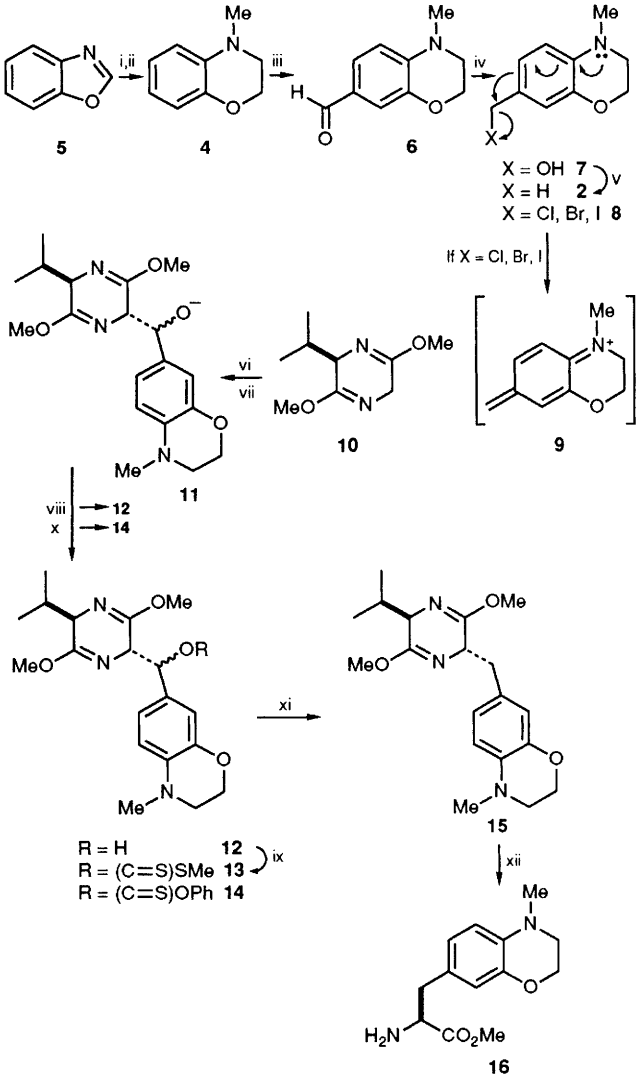


Fig. 1

the asymmetric derivatization of glycine, as applied to electron rich amino acid synthesis. The synthetic method adopted here paves an effective and potentially valuable way to the synthesis of unusual α-amino acids.

Bond disconnection analysis of **1** identifies four possible paths (Fig. 1*a–d*) for its assembly. Paths *a* and *b* generate predecessors whose synthesis require multistep sequences. Path *c* involves the alkylation of a glycine enolate equivalent with an appropriate electrophile **8**. Alternatively, Williams' electrophilic glycine technique[4] can also be adopted. Path *d* implies, for example, the displacement of serine hydroxy with compound **4** as an aromatic nucleophile.[5]

Initially, compound **2**‡ was prepared by modification of a known literature procedure,[6a] but failed to brominate at the benzylic position under different reaction conditions. Only a very low yield of a ring brominated compound was obtained under strong conditions. An alternative route to **8** *via* **6** or **7** appeared to be logical (Scheme 1). The required aldehyde **6** was made quickly in multigram quantities starting from commercially available benzoxazole by a reduction[6b] and alkylation sequence followed by Vilsmeier formylation[7] (55%). The regiochemistry of the aldehyde group in **6** was established by its conversion into **2** *via* **7**,[6c] which was also obtained by an independent synthesis[6a] from 2-amino-5-methylphenol. All attempts to prepare **8** *via* **7** or **6** using boron, sulfur, silicon, selenium and phosphorus based reagents were unsuccessful.[8] The generation of **8** or its equivalents under exceptionally mild conditions also proved to be futile.[9] It is highly probable that the electron donating nature of the nitrogen induces a facile fragmentation leading to a highly reactive intermediate **9** as shown by arrows in Scheme 1. At this point it was decided to use aldehyde **6** instead of **8** to proceed directly towards **15** (*via* **12**). The aldehyde **6** was treated with the mono-anion of bislactim ether **10** at −78 °C and quenched with water giving **12** in 100% yield as a mixture of epimeric alcohols (1 : 1). In an attempt to prepare **15** from **12** by hydrogenolysis, only retro-aldol or decomposed products were observed. Next, the hydroxy compound **12** was converted into xanthate **13** in 30% yield along with some unwanted side products. Under Barton's radical deoxygenation conditions[10] compound **15** was obtained from **13** in 60% yield as a single isomer. Acidic



Scheme 1 *Reagents and conditions*: i, $NaBH_4$–AcOH; ii, $BrCH_2CH_2Br$, K_2CO_3; iii, $POCl_3$–dimethylformamide; iv, $NaBH_4$; v, $NaBH_4$–trifluoroacetic acid; vi −78 °C, Bu^nLi; vii, compound **6**; viii, H_2O; ix, NaH, CS_2, MeI; x, PhO(C=S)Cl; xi, $(Bu^n)_3SnH$, azoisobutyronitrile; xii, 0.25 mol dm^{-3} HCl

hydrolysis of **15** gave **16**. The overall yield of **16** *via* this xanthate route is 4.6%; $[\alpha]_D^{25}$ −7.9 (*c* 0.11, $CHCl_3$). The two low yielding steps in the present synthesis are xanthate formation and its removal. In order to avoid xanthate **13** preparation, trapping of the intermediate **11** with carbon disulfide–iodomethane was attempted but gave no desired product. Robins' deoxygenation[11] proved to be a much more efficient variant than the xanthate method, but attempts to convert **12** into **14** were also not successful. Finally, direct trapping of the intermediate **11** with phenyl chlorothionoformate gave **14** from **6** and **10** in one pot. As expected, deoxygenation of **14** gave better yields. Starting from **6**, compound **15** was thereby prepared in 50% overall yield in two steps. Using this thionoformate route, the dihydrobenzoxazine α-amino acid derivative **16** (68% from **15**) was prepared in six steps with an overall yield of 18.6%.

In conclusion our successful synthesis of the highly electron rich amino acid derivative **16**‡ demonstrates the utility of the two-step route developed here from readily available aromatic aldehydes to the amino acid adduct (*e.g.* **15**). This strategy further augments the flexibility of the highly practical Schollkopf method. Our progress using this amino acid in peptides of novel design will be reported in due course.

‡ $E_{1/2}$ for the oxidation of **2** was found to be 0.61 V *vs.* SCE in MeCN (0.1 mol dm^{-3} tetrabutylammonium perchlorate). Derivatives of **1** also have similar values.

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3 The bislactim ether used in this study is (2*R*)-(−)-2,5-dihydro-3.6-dimethoxy-2-isopropylpyrazine and was obtained from Merck Schuchardt, Dr Theodor Schuchardt + Co, 8011, Hohenbrunn. Germany.

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