A Two-Directional Synthesis of (+)-β-Isosparteine

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A Two-Directional Synthesis of (+)-β-Isosparteine

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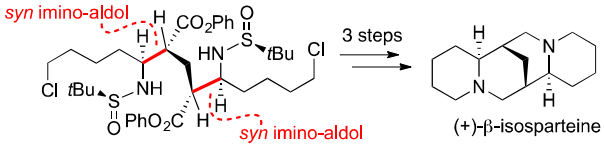
Supporting Information Placeholder



ABSTRACT: A two-directional synthesis of (+)-*β*-isosparteine is described in 5 steps from glutaric acid, where the entire carbon and nitrogen backbone of the alkaloid, possessing the requisite relative and absolute stereochemistry at its four stereogenic centers, is assembled using a double imino-aldol reaction.

Sparteine alkaloids represent a sub-set of a larger group of quinolizidine-containing alkaloids known as lupinus or lupin alkaloids due to their widespread occurrence as secondary metabolites in lupins.[1] Both enantiomeric forms of sparteine (**(–)-1** and **(+)-1**) are present in nature,[2] as are the less abundant C_2 symmetrical diastereoisomers (–)-*α*- and (–)-*β*-isosparteine (**2** and **3**, respectively, Figure 1).[3] The enantiomers of sparteine are valued by organic chemists for a diversity of applications as chiral diamines in asymmetric synthesis,[4] although supply issues have stimulated interest in the development of surrogates.[4e,5] Reported bioactivity is also dominated by the more available stereoisomer,[1d] and (–)-sparteine even found clinical applications, for example as an oxytocic agent,[6,7] although its FDA approved drug status was withdrawn due to safety concerns. Comparatively less is known about the more scarce C_2 symmetrical isomers either in terms of pharmacology,[8] or synthetic applications as ligands.[4f,9] There have been racemic total synthesis of α- and *β*-isosparteine, and enantiomerically enriched α- and *β*-stereoisomers have been obtained from synthetic conversions of other sparteine alkaloids.[10–12]

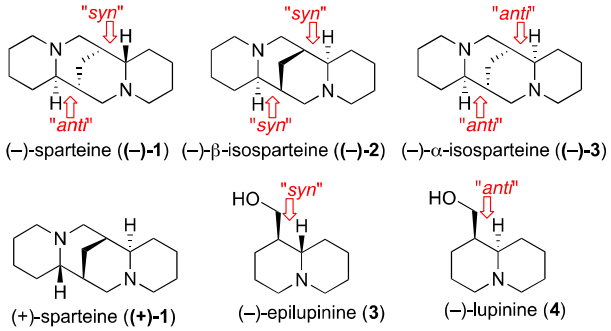


Figure 1. Structures of sparteine stereoisomers and simple quinolizidine alkaloids

We have shown that simple quinolizidine alkaloids, such as epilupinine **3**, possessing a "*syn*" relationship are conveniently accessible using *syn*-selective imino-aldol reactions wherein control of absolute stereochemistry is enabled through use of *tert*-butanesulfinyl auxiliaries.[13–15] Stereochemically, the possible diastereoisomeric sparteine alkaloids **1**–**3** may also be considered to posses "*syn*" or "*anti*" relationships between adjacent stereogenic centers based upon their synthetic origin from amino-aldols (Figures 1 and 2). For example, C6/C7 and C9/C11 have "*syn*" and "*anti*" relationships in sparteine, while the relative relationships are both "*syn*" in (+)-*β*-isosparteine (**(+)-2**). Here we show how a two-directional, *syn*-selective, double imino-aldol reaction can be applied to achieve a short synthesis of (+)-*β*-isosparteine.

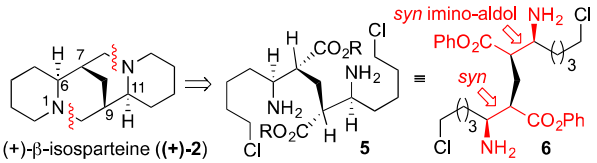
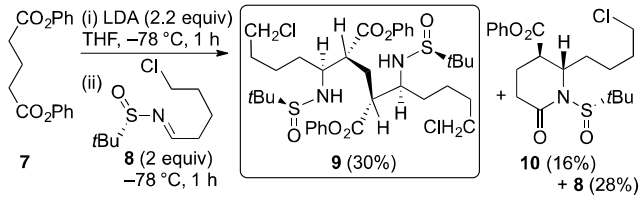


Figure 2. Two-directional synthesis approach to (+)-*β*-isosparteine

Previous studies from our laboratory involving imino-aldol reactions of *tert*-butanesulfinimines showed that lithium enolates of phenyl esters underwent addition to alkyl- and alkenyl-substituted *tert*-butanesulfinimines with good to excellent diastereoselectivity.[13] Furthermore, these imino-aldol reactions tolerated a reasonable variety of functionalization in both ester and sulfinimine substrates. Our starting point for the current work was to explore whether this methodology could be used in a two-directional approach to the C_2-symmetrical tetracyclic lupin alkaloid (+)-*β*-isosparteine. Deprotonation of

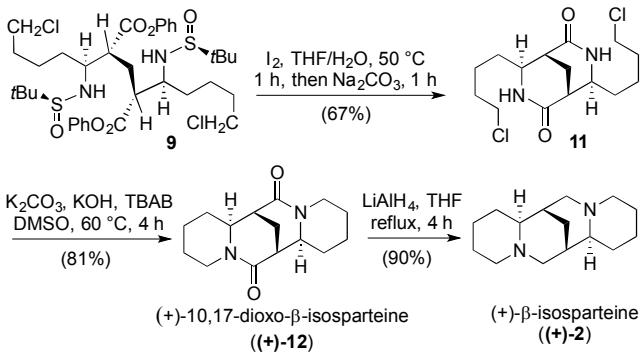
diphenyl glutarate (**7**) with 2.2 equivalents of LDA in THF at –78 °C (Scheme 1), followed by treatment with 2 equivalents of *tert*-butanesulfinimine **8** yielded the anticipated double imino-aldol **9**, isolated in diastereoisomerically pure form in 30% yield, and containing the entire skeleton of (+)-*β*-isosparteine with the requisite relative and absolute stereochemistry. Other reaction components included a cyclized single *syn* imino aldol **10** (16%), and an unseparated mixture of cyclized and uncyclized minor double imino aldol stereoisomers. Further details and stereochemical assignments for the minor components can be found in Supporting Information.

Scheme 1. Double imino-aldol reaction of diphenyl glutarate giving the acyclic carbon skeleton of (+)-β-isosparteine



Stereochemical assignment of double imino-aldol **9** was confirmed by X-ray structure determination of an intermediate later in the synthesis (Figure 3), and ultimately through its conversion to (+)-*β*-isosparteine (Scheme 2). The structure of lactam **10** was confirmed directly using X-ray crystallography, and the configuration of the newly formed stereogenic centers in both compounds is consistent with a six-centered chair-like transition state model.[13,15b] Thus far we have not been able to improve upon the yield of the double imino-aldol **9**, although the conditions could be biased to produce *N*-sulfinyl δ-lactam **10** in 51% yield when the bis enolate of **7** was reacted with a reduced quantity of imine **8** (0.8 equiv).

Scheme 2. Total syntheses of (+)-10,17-dioxo-*β*-isosparteine and (+)-*β*-isosparteine



In view of the fact that the complete acyclic carbon skeleton of (+)-*β*-isosparteine had been created in a single reaction, along with all of its stereochemical complexity, we considered the somewhat modest yield of **9** satisfactory for progression with the total synthesis. In fact, only 3 steps were required to access (+)-*β*-isosparteine from **9** (Scheme 2). Cleavage of the *tert*-butanesulfinyl groups from double imino-aldol **9** and cyclization was effected using molecular iodine followed by neutralization with bicarbonate to give the enantiomerically enriched 2,6-dioxobispidine **11**. Under basic conditions, and in the presence of tertabutylammonium bromide (TBAB), (+)-10,17-dioxo-*β*-isosparteine (**(+)-12**) was formed in 81% yield as a crystalline solid. Single crystal X-ray analysis allowed confirmation of the structure **12**.

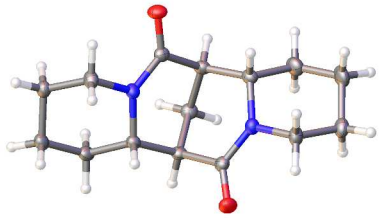


Figure 3. X-ray structure of (+)-10,17-dioxo-*β*-isosparteine (**(+)-12**).

The natural product, (+)-*β*-isosparteine, was obtained in high yield following $LiAlH_4$ reduction of bis lactam **(+)-12**. It was also possible to obtain (+)-*β*-isosparteine directly from **11**, by $LiAlH_4$ reduction, although the isolation of pure product was complicated by the presence of byproducts arising from reduction of the chloroalkyl groups. Hence, the two-step protocol was favored, providing the synthetic (+)-*β*-isosparteine with physical and spectroscopic data in good agreement with reported values.

In conclusion, we have reported a short synthesis of the C2-symmetrical alkaloids (+)-10,17-dioxo-*β*-isosparteine and *β*-isosparteine over 4 and 5 steps, respectively, from glutaric acid. The carbon framework with all four stereogenic centres was created in a single reaction step through implementation of a two-directional double imino-aldol reaction of diphenyl glutarate with *tert*-butanesulfinimine **8**.

ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, compound characterization data, stereochemical assignment, X-ray structural data for **10**, **(+)-12**, **SI1**, **SI5** and copies of ^1H and ^{13}C NMR spectra for all new compounds.

The Supporting Information is available free of charge on the ACS Publications website.

SI file is attached as pdf

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

Any additional relevant notes should be placed here.

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