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

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

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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 lupin or lupine alkaloids due to their widespread occurrence as secondary metabolites in lupins. Both enantiomeric forms of sparteine (–-1 and +-1) are present in nature, as are the less abundant C2 symmetrical diastereoisomers (–-α- and –-β-isosparteine (2 and 3, respectively, Figure 1). The enantiomers of sparteine are valued by organic chemists for a diversity of applications as chiral diamines in asymmetric synthesis, although supply issues have stimulated interest in the development of surrogates.

Reported bioactivity is also dominated by the more available stereoisomer, and (-)-sparteine even found clinical applications, for example as an oxytocic agent, although its FDA approved drug status was withdrawn due to safety concerns. Comparatively less is known about the more scarce C2 symmetrical isomers either in terms of pharmacology, or synthetic applications as ligands. 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.

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. Stereochemically, the possible diastereoisomeric sparteine alkaloids 1–3 may also be considered to possess “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. 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 C2-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-butanesulfonimine 8 yielded the anticipated double 
imino-aldol 9, isolated in diastereosomically pure form in 
30% yield, and containing the entire skeleton of (+)-β-
isoparteine with the requisite relative and absolute stereo-
chemistry. Other reaction components included a cyclized 
single syn imino aldol 10 (16%), and an unseparated mixture 
of cyclized and uncyclized minor double imino aldol stereo-
mers. Further details and stereochemical assignments for 
the minor components can be found in Supporting Informa-
tion.

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

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-isoparteine (Scheme 2). The structure of 
lactam 10 was confirmed directly using X-ray crystallography, 
and the configuration of the newly formed stereogenic 
centres in both compounds is consistent with a six-centered chair-li-
ke transition state model. 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-isoparteine 
and (+)-β-isoparteine

In view of the fact that the complete acyclic carbon skeleton 
of (+)-β-isoparteine 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-isoparteine from 9 (Scheme 2). Cleavage of the 
tert-butanesulfinyl groups from double imino-aldol 9 and 
cyclization was effected using molecular iodine followed by 
nitritiation with bicarbonate to give the enantiomerically 
enriched 2,6-dioxobispdine 11. Under basic conditions, and in 
the presence of tertbutyliammonium bromide (TBAB), (+)-
10,17-dioxo-β-isoparteine ((+)-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-isoparteine ((+)-
12).

The natural product, (+)-β-isoparteine, was obtained in 
high yield following LiAlH4 reduction of bis lactam (+)-12. It 
was also possible to obtain (+)-β-isoparteine directly from 11, 
by LiAlH4 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 pro-
tocol was favored, providing the synthetic (+)-β-isoparteine 
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-isoparteine and β-
isoparteine over 4 and 5 steps, respectively, from glutamic 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-butanesulfonimine 8.

ASSOCIATED CONTENT
Supporting Information
Experimental details and procedures, compound characterization 
data, stereochemical assignment, X-ray structural data for 10, (+)-
12, SI1, S15 and copies of 1H and 13C 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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