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# A Practical Synthesis of (±)-α-Isosparteine from a Tetraoxobispidine Core†

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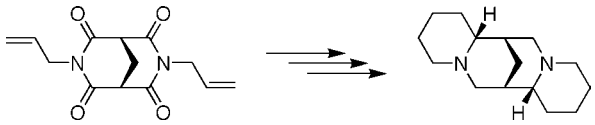
## ABSTRACT



**The title alkaloid was synthesized in racemic form from 3,7-diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (7) by a regioselective diallylation reaction followed by double ring-closing olefin metathesis and exhaustive reduction. Tetraoxobispidine 7 was itself prepared in three simple operations from dimethyl malonate. The entire sequence to α-isosparteine was conducted on a multigram scale and proceeded without recourse to chromatography.**

The sparteine subgroup of lupine alkaloids are 3,11-diazatetracyclo[7.7.1.0.$^{3,8}$0$^{11,16}$]heptadecanes which exhibit a range of useful biological and physical properties.[1,2] Three relative stereochemical configurations for this tetracycle are geometrically possible, and each diastereomeric form is naturally occurring (Figure 1).[3] The eponymous sparteine group alkaloid (**2**), abundant as its levorotatory enantiomorph in a number of common papilionaceous plants,[4] is distinguished by an asymmetrical *exo-endo* arrangement of bridgehead hydrogen atoms at C6 and C11 (sparteine numbering). α-Isosparteine (**1**)[5] and *β*-isosparteine (**3**)[6] represent the two $C_2$-symmetric forms of the parent ring system and display *exo-exo* and *endo-endo* bridgehead hydrogen atom configurations, respectively.

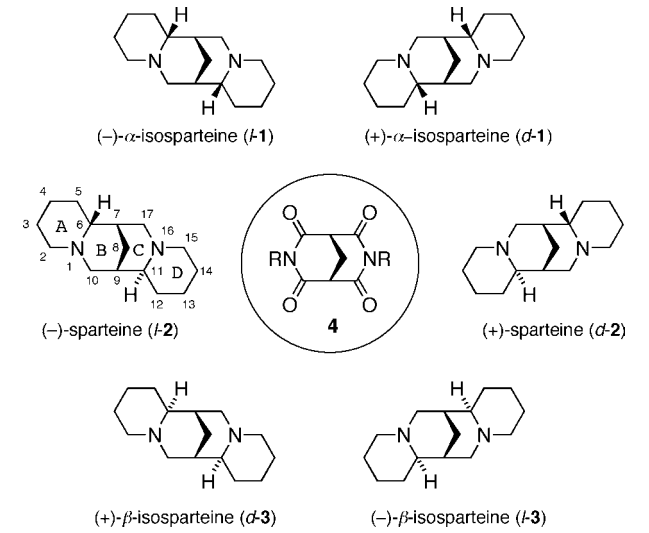



**Figure 1.** Six stereoisomers of 3,11-diazatetracyclo[7.7.1.0.$^{3,8}$0$^{11,16}$]-heptadecane (**1**−**3**) and tetraoxobispidines **4**.

† Dedicated to Professor Emeritus James D. White on the occasion of his 70th birthday.

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(1) Reviews: (a) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. (b) Ohmiya, S.; Saito, K.; Murakoshi, I. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 47, p 1. See also earlier reviews in the same series.

(2) Biological activity: (a) Schmeller, T.; Wink, M. In *Alkaloids: Biochemistry, Ecology, and Medicinal Applications*; Roberts, M. F., Wink, M., Eds.; Plenum Press: New York, 1998; p 435. (b) Seeger, R.; Neumann, H. G. *Inst. Pharmakol. Toxikol.* **1992**, *132*, 1577.

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(−)-Sparteine (*l*-**2**), which is commercially available, and (−)-α-isosparteine (*l*-**1**), conveniently obtained from *l*-**2** by isomerization,[7] have found widespread use as chiral ligands in asymmetric synthesis.[8−10] At present, all enantioselective methods based on these diamines are inherently limited due to the lack of a readily available source of sparteine bases in dextrorotatory form.[11,12]

A practical stereocontrolled entry to all six stereoisomers of the characteristic sparteine skeleton is a desirable goal and would extend the versatility of existing asymmetric methods which rely on these intriguing compounds. Numerous racemic syntheses of the sparteine bases have appeared,[13−15] but few of these approaches are efficient[16] and no obvious methods exist to render enantioselective the routes which are genuinely practical. Notwithstanding the plethora of known racemic routes to **1**−**3**, two enantioselective syntheses of sparteine itself have now been reported.[17] Arguably, neither of these asymmetric approaches is simple enough in its execution or of sufficient brevity to compete effectively with resolution based protocols to (+)-sparteine (*d*-**2**) and (+)-α-isosparteine (*d*-**1**).

Pursuant of an efficient and unified strategy for the stereocontolled elaboration of all members of the sparteine group, we identified $C_{2v}$-symmetric tetraoxobispidines **4** as pivotal synthons for this purpose. Bisimides **4** provide the central sparteine BC-ring bispidine system in a form amenable for the regio- and stereocontrolled annulation of rings A and D. Furthermore, the enantioselective desymmetrization of prochiral imides has been well demonstrated,[18] and we felt confident that suitable dissymmetric reagents would be available to effectively discriminate between pairs of enantiotopic carbonyl groups within **4** when required. Herein, we report our initial forays in this area and describe an annulation strategy based on ring-closing olefin metathesis (RCM)[19] to convert allyl-substituted tetraoxobispidine **7** to (±)-α-isosparteine (*dl*-**1**).

Our new approach to the sparteine alkaloids required an efficient synthesis of tetraoxobispidines **4**. Tetraoxobispidines substituted on the methylene bridge are a well-known class of compounds,[20] commonly referred to as "Guareschi imides" in regard to their usual manner of construction via Guareschi condensation.[21,22] By contrast, tetraoxobispidines unsubstituted on the methylene bridge are scarcely known; indeed, only the parent compound (**6**) has appeared in an isolated report by Guthzeit.[23] Since it proved impossible to prepare **6** by Guareschi condensation, or by a related tactic,[24] we elected to reexamine Guthzeit's long neglected synthesis of **6** from tetraamide **5**.

Compound **5** was prepared by way of the Knoevenagel condensation adduct formed from dimethyl malonate and paraformaldehyde.[25] This tetraester was not isolated but treated directly with concentrated aqueous ammonia to afford

(4) (−)-Sparteine (lupinidine), a cardiac stimulant easily extracted from the weed Scotch broom (*Cytisus scoparius*), was first isolated in 1851 by Stenhouse and its structure correctly elucidated 82 years later by Clemo and Raper; see: Clemo, G. R.; Raper, R. *J. Chem. Soc.* **1933**, 644.

(5) (−)-α-Isosparteine (genisteine) was first obtained semi-synthetically from (−)-sparteine but later found naturally occurring in *Lupinus caudatus*, see: Marion, L.; Turcotte, F.; Ouellet, J. *Can. J. Chem.* **1951**, *22*, 29.

(6) (−)-*β*-Isosparteine has also been known as *l*-spartalupine and pusilline and occurs in a variety of *Lupinus* species; see: Greenhalgh, R.; Marion, L. *Can. J. Chem.* **1956**, *34*, 456.

(7) (a) For isomerization with $AlCl_3$, see: Galinovsky, F.; Knoth, P.; Fischer, W. *Monatsh. Chem.* **1955**, *86*, 1014. (b) For isomerization by oxidation/reduction, see: Okamoto, Y.; Suzuki, K.; Kitayama, T.; Yuki, H.; Kageyama, H.; Miki, K.; Tanaka, N.; Kasai, N. *J. Am. Chem. Soc.* **1982**, *104*, 4618.

(8) For a review of sparteine/alkyllithium reagent pairs in synthesis, see: Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

(9) Recent representative synthetic applications of (−)-sparteine: (a) Vrancken, E.; Alexakis, A.; Mangeney, P. *Eur. J. Org. Chem.* **2005**, 1354. (b) Caupene, C.; Boudou, C.; Perrio, S.; Metzner, P, *J. Org. Chem.* **2005**, *70*, 2812. (c) Kocienski, P. J.; Christopher, J. A.; Bell, R.; Otto, B. *Synthesis* **2005**, 75. (d) Martinez, M. M.; Hoppe, D. *Org. Lett.* **2004**, *6*, 3743. (e) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353. (f) Metallinos, C.; Szillat, H.; Taylor, N. J.; Snieckus, V. *Adv. Synth. Catal.* **2003**, *345*, 370. (g) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057

(10) Recent representative synthetic applications of (−)-α-isosparteine: (a) Allen, B. D.; Cintrat, J.-C.; Faucher, N.; Berthault, P.; Rousseau, B.; O'Leary, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 412. (b) Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Tetrahedron* **2003**, *59*, 9719. (c) Muller, P.; Patrice, N.; Bernardinelli, G. *Eur. J. Org. Chem.* **2001**, *21*, 4137. (d) Hodgson, D. M.; Cameron, I. D.; Christlieb, M.; Green, R.; Lee, G. P.; Robinson, L. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, *18*, 2161.

(11) O'Brien has introduced a (+)-sparteine surrogate derived from (−)-cytisine which goes some way to addressing this issue, see: (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (b) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789.

(12) (+)-Sparteine has been obtained from natural (±)-lupanine by resolution followed by reduction, see: Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm. (Weinheim)* **1989**, *322*, 399.

(13) Syntheses of (±)-sparteine: (a) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1948**, *70*, 2298. (b) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316. (c) Clemo, G. R.; Raper, R.; Short, W. S. *J. Chem. Soc.* **1949**, 663. (d) van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 7372. (e) Bohlmann, F.; Müller, H.-J.; Schumann *Chem. Ber.* **1973**, *106*, 3026. (f) Takatsu, N.; Noguchi, M.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, *35*, 4990. (g) Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1996**, *61*, 5581. (h) Butler, T.; Fleming, I.; Gonsior, S.; Kim, B.-H.; Sung, A.-Y.; Woo, H.-G. *Org. Biomol. Chem.* **2005**, *3*, 1557.

(14) Syntheses of (±)-α-isosparteine: (a) Sorm, F.; Keil, B. *Collect. Czech. Chem. Commun.* **1948**, *13*, 544. (b) Tsuda, K.; Sato, T. *Chem. Pharm. Bull.* **1954**, *2*, 190. (c) Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2593. See also ref 13b.

(15) Syntheses of (±)-*β*-isosparteine: Carmack, M.; Douglas, B.; Martin, E. W.; Suss, H. *J. Am. Chem. Soc.* **1955**, *77*, 4435. See also refs 14b and 13 g.

(16) Notable exceptions include the very first synthesis of sparteine and α-isosparteine by Leonard and Beyler (two steps, ref 13ab) and the elegant three-step approach to α-isosparteine by Kakisawa et al (ref 14c).

(17) The following enantioselective syntheses by Aubé and O'Brien could each be used in principle to prepare either (+)- or (−)-sparteine: (a) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577. (b) Hermet, J.-P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830.

(18) Speckamp and Hiemstra have made seminal contributions in this area; see: Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773.

(19) Review: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(20) By tetraoxobispidine we imply 2,4,6,8-tetraoxo-3,7-diazabicyclo-[3.3.1]nonane. A substructure search of Scifinder Scholar retrieved 188 examples of this ring system mono- or disubstituted at position 9.

(21) The Guareschi condensation is a Knoevenagel-type three-component coupling reaction between a cyanoacetate, a carbonyl compound and ammonia; the initially generated α,α'-dicyanoglutarimides cyclize to tetraoxobispidines upon treatment with sulfuric acid; see: (a) Guareschi, I. *Gazz. Chim. Ital.* **1919**, *49*, 126. (b) Kon, G. A. R.; Thorpe, J. F. *J. Chem. Soc.* **1919**, 686. (c) Vogel, A. I. *J. Chem. Soc.* **1934**, 1758.

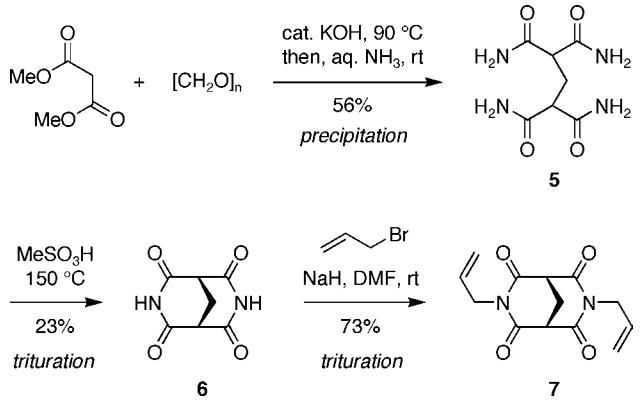
(22) Guareschi imides have been used as precursors to bispidines having antiarrhythmic properties; see: Schön, U.; Antel, J.; Brückner, R.; Messinger, J. *J. Med. Chem.* **1998**, *41*, 318.

(23) Guthzeit, J. *J. Prakt. Chem.* **1902**, *2*, 11.

(24) Acidic hydrolysis of 1,1,3,3-tetracyanopropane failed to produce bisimide **6**. For the preparation of 1,1,3,3-tetracyanopropane, see: Bell, R. A.; Brown, B. E.; Duarte, M.; Howard-Lock, H. E.; Lock, C. J. L. *Can. J. Chem.* **1987**, *65*, 261.

(25) Gogoll, A.; Johansson, C.; Axén, A.; Grennberg, H. *Chem. Eur. J.* **2001**, *7*, 396.

**Scheme 1.** Synthesis of *N*,*N*′-Diallyltetraoxobispidine **7**




a precipitate of the amide product **5** (Scheme 1). Following filtration, subsequent drying of the material afforded a 56% yield of **5** from over one mole of paraformaldehyde as limiting reagent. The easy isolation of **5** in pure form by simple filtration set the trend for the entire synthesis of *dl*-**1** as it turned out that not a single compound en route to this initial target required chromatographic purification (vide infra). Guthzeit's preparation of **6** called for pyrrolysis of **5** at reduced pressure.[23] In our hands, brief heating of **5** at 250 °C and 20−50 mmHg (water aspirator) resulted in melting with vigorous gas evolution. Upon cessation of bubbling, the resinous dark brown pyrrolyte was allowed to cool and subsequent trituration and recrystallization from ethanol permitted quantities of **6** to be isolated in low yield (4−6%). Notwithstanding the poor efficiency of this transformation, it proved impossible to execute reliably from any more than single gram quantities of **5**, either in conventional apparatus or in a microwave reactor. Reasoning that some sort of activation of **5** might allow for a less torturous conversion to **6**, we investigated a modification of the Guthzeit condensation process in acidic media. After some experimentation, it was discovered that methanesulfonic acid served this purpose very well, presumably by facilitating the generation of acylium cations from **5** while also sequestering liberated ammonia. In the event, heating a mechanically stirred paste composed of finely ground **5** and methanesulfonic acid, resulted in dissolution followed by copious gas evolution. After cooling, bisimide **6** was isolated in 23% yield by simple trituration of the pale oily residue with methanol followed by washing of the resulting solid with water. The modest yield for this transformation was offset by its operational simplicity, its reproducibility over a range of scales (near identical yields at 5, 100, and 300 mmol) and the extreme ease of product isolation.

With the establishment of a robust and convenient tetraoxobispidine synthesis, our approach to α-isosparteine continued uneventfully by electrophilic alkylation of both nitrogen-atoms of **6** with allyl bromide. Owing to the insolubility of bisimide **6** in most organic solvents, the allylation reaction was conducted in DMF. Following a standard workup procedure, crystalline *N*,*N*′-diallyltetraoxobispidine **7** was obtained in pure form by trituration with hexanes. An X-ray crystallographic analysis of **7** provided unequivocal proof of structure and indicated the well-distinguished *exo* and *endo* faces of this bicyclo[3.3.1]nonane system (Figure 2).

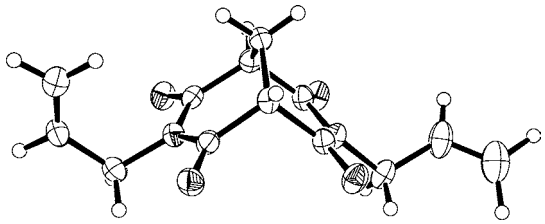
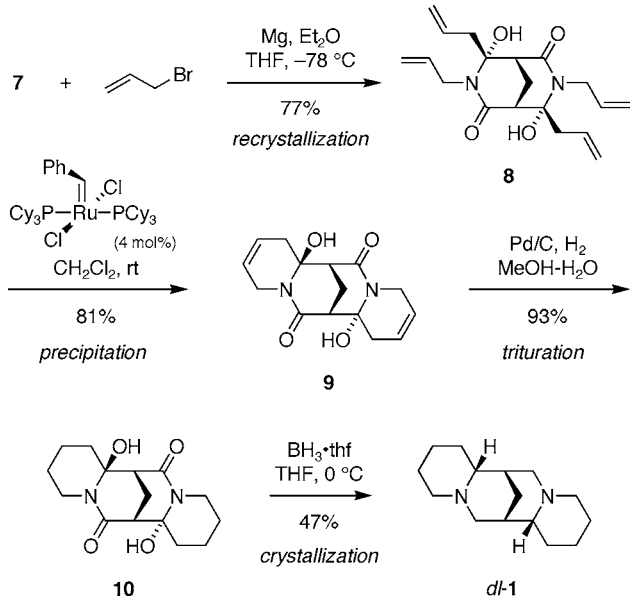


**Figure 2.** ORTEP diagram for **7**. 50% probability ellipsoids are plotted for non-hydrogen atoms.

Our plan next called for the nucleophilic introduction of two further allyl moieties with the intention of forging the A and D rings of *dl*-**1** via double RCM. Allyl bromide was again used as the carbon source, but this time converted to allylmagnesium bromide in diethyl ether to effect the desired reactivity umpolung (Scheme 2). Rapid addition of an excess

**Scheme 2.** Synthesis of (±)-α-Isosparteine (*dl*-**1**) from **7**




of the Grignard reagent to **7** in chilled THF solvent resulted in a remarkably regioselective diallylation reaction and afforded a tetraene compound (**8**) which was adjudged to be $C_2$-symmetric on the basis of NMR analysis.[26] No other isomers were evident in the crude product mixture and recrystallization from hexanes gave **8** in 77% yield. Double

(26) Whether the hydroxyl groups in **8** are both *exo* or both *endo* has not been determined; however, we presume that they are configurated *endo* as illustrated based on steric considerations.

RCM of the tetraene **8** was sluggish, requiring over 24 h and the portionwise addition of 4 mol % of Grubbs' first-generation ruthenium alkylidene catalyst,[27] but eventually delivered sparteine derivative **9** in an acceptable yield on a 10 mmol scale.[28] The tetracyclic product precipitated as it was formed and was isolated directly by filtration of the reaction mixture. Interestingly, while NMR spectral analysis suggested that this material had retained the $C_2$-symmetry of its parent, X-ray analysis indicated otherwise, and revealed an asymmetric configuration for **9** in the solid state (Figure 3).[29]

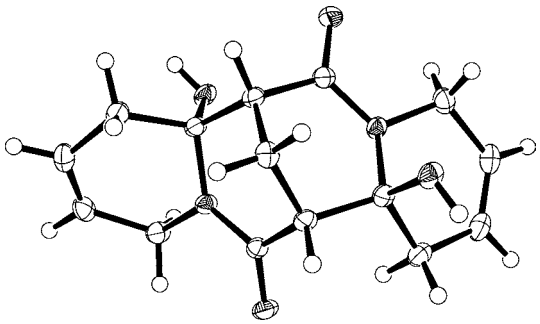


**Figure 3.** ORTEP diagram for **9**. 50% probability ellipsoids are plotted for non-hydrogen atoms.

Hydrogenation of diene **9** in aqueous methanol resulted in saturation of its olefinic moieties and gave the expected product (**10**) in high yield. In this case, NMR analysis clearly indicated an asymmetric anomeric configuration for the bishemiaminal which was isolated as a single isomer by trituration. An attempt to fashion **10** more directly from **8** by tandem olefin metathesis/hydrogenation[30] failed to proceed beyond intermediate **9** due to the poor solubility of this rigid tetracycle in 1,2-dichloroethane.

Finally, (±)-α-isosparteine (*dl*-**1**) was generated from **10** by exhaustive reduction with borane tetrahydrofuran complex. The free-base of *dl*-**1** was isolated as a hydrate which readily crystallized from an alkaline solution during workup. The identity of our synthetic material was confirmed by comparison to literature data reported for *dl*-**1**[31] and *l*-**1**.[32] The stereochemical outcome of the concluding step in our synthesis was anticipated on the basis that acyl iminium ions generated by formal loss of hydroxide from **10** would suffer *exo* attack from exogenous hydride species.[33]

In summary, a racemic synthesis of α-isosparteine (*dl*-**1**) from an easily prepared tetraoxobispidine derivative **7** has been demonstrated. The alkaloid was ultimately fabricated from three inexpensive carbon sources (dimethyl malonate, paraformaldehyde, and allyl bromide) by a short sequence of simple synthetic operations, none of which required a chromatographic purification stage. Efforts to access sparteine and $\beta$-isosparteine along similar lines are in progress,[34] as are studies directed at the enantiocontrolled desymmetrization of tetraoxobispidines for the purpose of rendering these novel alkaloid syntheses enantioselective.

We predict that tetraoxobispidines **4** will find further applications as versatile synthons for the preparation of other valuable target molecules containing bispidine nuclei.

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**Supporting Information Available:** Experimental procedures, characterization data, and $^1$H NMR spectra for all compounds. CIF files for **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(28) It is worth noting that tetracycle **9** could potentially be generated in enantioenriched form by kinetic resolution of **8** using a chiral metathesis catalyst. For an example of enantioselective olefin metathesis, see: van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.

(29) The $^{13}$C NMR spectrum (75 MHz) for **9** collected in DMSO-$d_6$ at ambient temperature showed eight peaks, as expected for a symmetric structure. The $^1$H NMR spectrum for **9** (300 MHz, DMSO-$d_6$) was broad, but also suggestive of $C_2$-symmetry (see the Supporting Information). The apparent discrepancy between solution- and solid-state structures for **9** is explicable by a number of arguments. Either a symmetric anomer of **9** equilibrates to the asymmetric form only upon crystallization or the two (indistinguishable) asymmetric forms for **9** are in rapid dynamic equilibrium in solution. A third possibility, that NMR is a poor indicator of molecular symmetry for this molecule, seems less likely.

(30) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

(31) *dl*-**1**: mp 74−75 °C ($H_2O$) [lit.[14c] mp 76−79 °C]. *dl*-**1**·$C_6H_3N_3O_7$ (monopicrate salt): mp 124−125 °C (EtOH) [lit.[13b] mp 132.5−133.5 °C (EtOH)].

(32) $^{13}$C NMR data for *dl*-**1** prepared from **7** were essentially identical to those reported for *l*-**1** by Galasso et al.; see: Galasso, V.; Asaro, F.; Berti, F.; Kovac, B.; Habus, I.; Sacchetti, A. *Chem. Phys.* **2003**, *294*, 155.

(33) Harrison and O'Brien have observed that related bispidine-type acyl iminium ions experience nucleophilic attack exclusively from their open *exo* faces; see: Harrison, J. R.; O'Brien, P. *Tetrahedron Lett.* **2000**, *41*, 6167.

(34) Strategic reversal in allylation and reduction of **7** leads in principle to $\beta$-isosparteine stereochemistry. Isomerization of $\beta$-isosparteine to sparteine is known; see ref 15.