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Total Synthesis of (±)-α-Isosparteine, (±)-β-Isosparteine, and (±)-Sparteine from a Common Tetraoxobispidine Intermediate†

Neil R. Norcross,§ John P. Melbardis,‡ Margarita Ferris Solera,§ Mark A. Sephton,‡ Colin Kilner,§ Lev N. Zakharov,‡ Peter C. Astles,⊥ Stuart L. Warriner,§ and Paul R. Blakemore*,‡

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003, School of Chemistry, University of Leeds, Leeds, West Yorkshire LS2 9JT, United Kingdom, and Eli Lilly & Co. Ltd., Lilly Research Centre, Erl Wood Manner, Windlesham, Surrey, GU20 6PH, United Kingdom

paul.blakemore@science.oregonstate.edu

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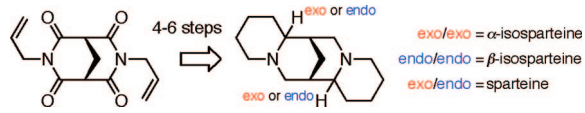

The three title alkaloids were separately prepared in stereocontrolled fashion from a common tetraoxobispidine precursor, 3,7-diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (**16**). Bisimide **16** was generated from malonate via acid promoted cyclization of the Knoevenagel condensation adduct 1,1,3,3-propanetetracarboxamide. (±)-α-Isosparteine (*dl*-**2**) was elaborated from **16** in 28% overall yield by a two-directional synthetic sequence composed of four reactions: double addition of allylmagnesium bromide, ring-closing olefin metathesis (RCM), hydrogenation, and borane mediated reduction. (±)-β-Isosparteine (*dl*-**3**) was targeted along similar lines by a strategic reversal in allylation and reduction operations on the core synthon. Thus, **16** was advanced to *dl*-**3** in five steps and 12% overall yield by a reaction sequence commencing with sodium borohydride mediated reduction and followed by double Sakurai-type allylation of the resulting bishemiaminal. The synthesis of *dl*-**3** was concluded by RCM and then global reduction (H_2, Pd/C; $LiAlH_4$). The final target, (±)-sparteine (*dl*-**1**), was secured in six steps and 11% overall yield from **16** by monoreduction and Sakurai allylation, followed by allyl Grignard addition and then RCM and global reduction as before. Reasons for the inherent C_2-type regioselectivity of net double nucleophilic additions to tetraoxobispidines are discussed and enantioselective oxazaborolidine mediated reduction of the *N*,*N*′-dibenzyl congener of **16** is reported.

Introduction

The lupine alkaloids constitute a structurally diverse group of quinolizidine bases found in a variety of leguminous plant and tree species, including broom, lupin, gorse, and laburnum.[1] The sparteine subgroup of lupine alkaloids are identified by a shared 3,11-diazatetracyclo[7.7.1.0^{3,8}.0^{11,16}]heptadecane ring system characterized by a bispidine nucleus with peripheral quinolizidine motifs flanking its core.[2] Three diastereomeric forms for this inherently chiral tetracyclic array are geometrically accessible, and each possible isomeric variation is represented by a naturally occurring alkaloid (e.g., **1**−**3**, Figure 1).[3] The eponymous and most abundant sparteine alkaloid (**1**), prevalent as the levorotatory enantiomorph in many common papilionaceous plants (e.g., Scotch broom *Cytius scoparius*), is distinguished by a nonsymmetric *exo*−*endo* arrangement of hydrogen atoms at C6 and C11 (sparteine numbering). Stenhouse described the original isolation of (−)-sparteine (lupinidine, *l*-**1**) in 1851 and was the first to determine its molecular formula (as $C_{15}H_{26}N_2$).[4] Building on the work of Ing,[5] Winterfeld,[6] and others,[2] the intriguing tetracyclic structure of sparteine was correctly deduced by Clemo and Raper some 82 years later,[7]

† Dedicated to the memory of Professor Nelson J. Leonard (1916−2006) on the occasion of the 60th anniversary of the Leonard−Beyler synthesis of sparteine.

‡ Oregon State University.

§ University of Leeds.

⊥ Eli Lilly & Co. Ltd.

(1) Reviews: (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191–222. (b) Ohmiya, S.; Saito, K.; Murakoshi, I. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 47, pp 1−114. See also earlier reports in both of these regular series.

(2) For definitive accounts of the early history of the sparteine subgroup, see: (a) Leonard, N. J. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1953; Vol. 3, pp 119−200. (b) Leonard, N. J. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. 7, pp 253−317.

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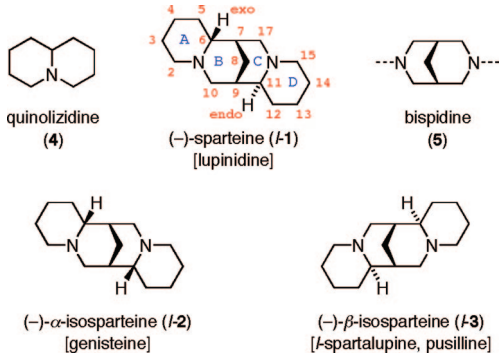

FIGURE 1. Three naturally occurring levorotatory lupine alkaloids of the sparteine subgroup (*l*-**1**, *l*-**2**, *l*-**3**) and embedded structural motifs (**4**, **5**) found within these molecules.

while stereochemical detail for this compound (and related C15 lupine alkaloids) was only finally clarified by Marion and Leonard a century after its first isolation.[8,9] It is a popular misconception that the dextrorotatory enantiomorph of sparteine is not a natural product; however, although more narrowly distributed than its better known and commercially available antipode, (+)-sparteine (pachycarpine, *d*-**1**) is biosynthesized by numerous plant species (e.g., *Cytisus caucasicus*).[10,11] Traditionally, (+)-sparteine (*d*-**1**) has been most conveniently obtained from natural (±)-lupanine (2-oxosparteine), extracted from the seeds of *Lupinus albus*,[12] by classical resolution followed by reduction of the resulting (−)-lupanine.[13]

The remaining two diastereomeric forms of the parent sparteine ring system, α-isosparteine (**2**) and β-isosparteine (**3**), are C_2-symmetric and differ by a respective *exo*−*exo* and *endo*−*endo* configuration of hydrogen atoms at C6 and C11. (−)-α-Isosparteine (genisteine, *l*-**2**) was first unequivocally obtained by Winterfeld via semisynthesis from (−)-sparteine (*l*-**1**),[14] and only later found to be a naturally occurring substance (in *Lupinus caudatus*) by Marion and co-workers.[15] Interestingly, (+)-α-isosparteine (*d*-**2**) has yet to be identified as a natural plant alkaloid. (−)-β-Isosparteine (*l*-spartalupine, pusilline, *l*-**3**) belongs to the same enantiomorphic series as (+)-sparteine (*d*-**1**) and was originally isolated (as "pusilline") from *Lupinus pusillus* (also a source of *d*-**1** and (−)-lupanine) by Marion and Fenton but mis-identified at that time as a dihydrosparteine.[16] Carmack and co-workers later obtained the same compound from *Lupinus sericeus* (as "*l*-spartalupine") and correctly identified it as the final stereoisomer in the sparteine series.[17] The equivalence of pusilline and *l*-spartalupine was established soon thereafter by Marion and Greenhalgh thus removing earlier confusion in the literature.[18] More recently, (+)-β-isosparteine (*d*-**3**) has been found in a variety of *Lupinus* species.[19] Various chemical methods for interconversion between sparteine diastereoisomers within a given enantiomeric series have been reported.[20,21]

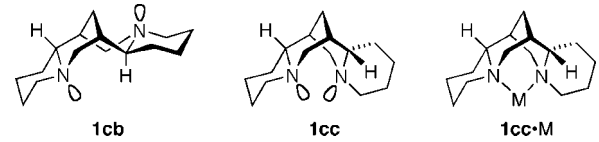

FIGURE 2. Significant conformations of sparteine (**1**) and as bidentate metal ligand.

Applications. The biological activity of the sparteine alkaloids is limited, but not insignificant.[22] (−)-Sparteine (*l*-**1**) is a cardiac agent with moderate toxicity[23] and it has been investigated as a potential drug for the management of arrhythmias[24] and as an agent for the induction of uterine contractions.[25] Although of little medicinal importance, (−)-sparteine (*l*-**1**), and to a lesser extent (−)-α-isosparteine (*l*-**2**), nevertheless elicit intense interest because of their deployment as uniquely effective chiral ligands in a wide variety of metal-mediated enantioselective synthetic methods.[26] It was recognized early on that the "chair−chair" conformer of sparteine (**1cc**), calculated (by DFT) to be 3.4 kcal mol^{-1} higher in energy than its ground state "chair-boat" conformation **1cb**,[27] could behave as a bidentate metal ligand (Figure 2). Within the resulting metal complexes **1cc**·M, the metal ion is partially encapsulated by the chiral alkaloid framework and provided with a dissymmetric coordination sphere suitable for the promotion of enantioselective transformations. In this regard, now rarely cited seminal reports

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(11) At the time of writing, at least two U.S. chemical companies list (+)-sparteine (as pachycarpine) in their catalogues (100 g quantities) at a price ca. three times greater than that typical for (−)-sparteine.

(12) More recently, (+)-sparteine itself has been discovered to be a minor alkaloid of *Lupinus albus*, see: Wysocka, W. *Sci. Legumes* **1995**, *2*, 137–140.

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(20) Mercuric ion oxidation of (−)-sparteine (*l*-**1**) leads successively to (−)-Δ^5-dehydrosparteine and (−)-$\Delta^{5,11}$-didehydrosparteine. Reduction of the former enamine regenerates *l*-**1**, while reduction of the latter affords (−)-α-isosparteine (*l*-**2**). (+)-β-Isosparteine (*d*-**3**) is similarly oxidized to the same enamine intermediates and is therefore a viable synthetic progenitor to either *l*-**1** or *l*-**2**. See ref 14 and: Leonard, N. J.; Thomas, P. D.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 1552–1558.

(21) A mixture of (−)-α-isosparteine (*l*-**2**) (major) and (+)-β-isosparteine (*d*-**3**) (minor) is obtained by heating (−)-sparteine (*l*-**1**) with $AlCl_3$ at 180−230 °C, see: (a) Galinovsky, F.; Knoth, P.; Fischer, W. *Monatsh. Chem.* **1955**, *86*, 1014–1023. (b) Winterfeld, K.; Bange, H.; Lalvani, K. S. *Ann. Chem.* **1966**, *698*, 230–234.

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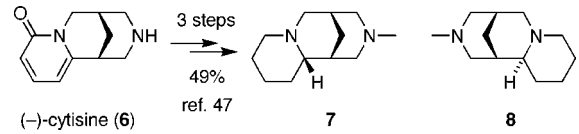
by Nozaki et al.,[28] and others,[29] first highlighted a wealth of possibilities for asymmetric induction using sparteine diamines in the presence of all manner of organometallic reagents.

Pioneering contributions from Hoppe[30,31] and Beak[32,33] have since led to the introduction of highly enantioselective transformations employing complexes of (−)-sparteine (*l*-**1**) and alkyllithium reagents. These complexes are typically used to effect enantioselective deprotonation (via either kinetic control or "dynamic thermodynamic" resolution)[34] leading to scalemic carbanionic species that are quenched with electrophiles to generate enantioenriched products of interest.[35] Many significant implementations of this concept have been reported, including homoaldol[30a] and related reactions of allylic carbamates,[31c] enantioselective transformations of oxiranes[36] and *N*-Boc azacycles,[37] synthesis of enantioenriched ferrocenes,[38] and asymmetric chain extension of boronic esters.[39] Other recent developments have seen the use of (−)-sparteine (*l*-**1**) as a ligand for palladium in the Sigman−Stoltz enantioselective oxidative resolution of 2° alcohols,[40,41] and as a ligand for magnesium in the asymmetric ring-opening of cyclic meso anhydrides by aryl Grignard reagents.[42] (−)-Sparteine (*l*-**1**) is also the ligand of choice in the Crimmins variant of the Ti-mediated Evans aldol reaction; however, in this application it does not play a stereodirecting role.[43]

SCHEME 1. O'Brien's (+)-Sparteine Surrogate (7) and a BCD-Ring Analogue of (−)-Sparteine (8)



(−)-α-Isosparteine (*l*-**2**) is also employed in enantioselective synthesis but this C_2-symmetric diamine is only rarely found to be a superior chiral ligand to its nonsymmetric counterpart (−)-sparteine (*l*-**1**).[44] Metal complexes of *l*-**2** (i.e., *l*-**2cc**·M analogous to *l*-**1cc**·M above) are more sterically encumbered than those of *l*-**1** and this facet compromises their kinetic competence and stability.[45]

The limited availability of both (+)-sparteine (*d*-**1**) and (+)-α-isosparteine (*d*-**2**) restricts the scope of asymmetric methodologies which rely on sparteine alkaloids as stereoinduction elements. Accordingly, there has been a long standing interest in either a concise asymmetric synthesis of *d*-**1**, or else, a readily accessible equivalent to this privileged ligand. O'Brien's recently introduced diamine **7** (Scheme 1), a structurally simplified tricyclic analogue of (+)-sparteine (*d*-**1**) that mimics its ABC-ring motif, offers a practical solution to this problem.[46] Diamine **7**, obtained via semisynthesis from the abundant lupine alkaloid (−)-cytisine (**6**),[47,48] has now been evaluated as a complementary pseudoenantiomeric ligand to (−)-sparteine (*l*-**1**) in many asymmetric transformations and shown to offer similar enantioselectivity but in the opposite sense.[49] Interestingly, an isomeric diamine (**8**) that mimics instead the BCD-ring system of (−)-sparteine (*l*-**1**) was significantly inferior to **7** in the enantioselective lithiation/silylation of *N*-Boc-pyrrolidine.[50] These results suggest that the sparteine D-ring plays a relatively minor role in stereoinduction; moreover, recent work by Kozlowski and co-workers has clarified the importance of an intact A-ring moiety for high enantioselectivity in the application of sparteine-like diamines.[51]

To the best of our knowledge, neither enantiomorph of β-isosparteine (**3**) has received documented attention as a chiral

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(51) Phuan, P.-W.; Ianni, J. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 15473–15479.

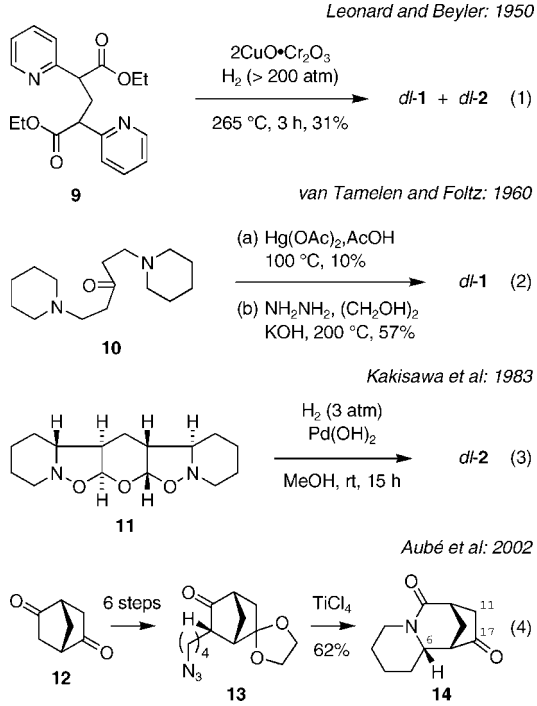

FIGURE 3. Salient features of four notable synthetic approaches to sparteine group alkaloids.

ligand for enantioselective synthesis. However, given that (+)-β-isosparteine (*d*-**3**) is configurationally related to the ineffectual BCD-tricyclic analogue of (−)-sparteine (**8**), it is unlikely to offer useful levels of enantioselectivity in typical applications employing chiral diamine ligands.

Existing Total Syntheses. The first total synthesis of (±)-sparteine (*dl*-**1**) was described by Leonard and Beyler in 1948.[52,53] Since that time, many other efforts toward sparteine and its isomers have been disclosed; however, none match the synthetic brevity of the original two-step synthesis. In common with the Leonard−Beyler approach, a significant majority of known sparteine syntheses may be loosely categorized as "outside-in" strategies, wherein the central B- and C-rings of the tetracyclic nucleus are fabricated from compounds replete with pre-existing A- and D-ring substructure (Figure 3). For example, in a second generation variant of their original procedure, Leonard and Beyler transformed 2,4-dipyrid-2-yl glutarate **9** (available from ethyl 2-pyridylacetate via Knoevenagel condensation with paraformaldehyde) directly into a mixture of (±)-sparteine (*dl*-**1**) and (±)-α-isosparteine (*dl*-**2**) by high-pressure hydrogenative reductive cyclization over a copper chromite catalyst (eq 1 in Figure 3).[52b] Closely related contemporaneous efforts by other groups led to similarly nonstereoselective syntheses of the sparteine bases,[53,54] including the first recognized preparation of (±)-β-isosparteine (*dl*-**3**).[55,56] Recently, stereodefined 2,4-dipiperid-2-yl glutarate precursors analogous to the Leonard−Beyler intermediate **9** have featured in two stereocontrolled elaborations of sparteine.[57,58]

The biosynthetic theory of Robinson[59] inspired a number of early "biomimetic" approaches to the sparteine nucleus in which Mannich-type processes were used to forge C6−C7/C9−C11 or C9−C10/C7−C17 bonds from suitable iminium ion precursors. The first ostensibly viable route to (±)-sparteine (*dl*-**1**) along these lines, and analogous to Robinson's landmark tropinone synthesis,[60] was reported by Anet, Hughes, and Ritchie in 1950;[61] however, the veracity of the synthesis was called into question.[2b,62] An unambiguous "biogenetic-type" route to *dl*-**1** was later reported by van Tamelen and Foltz, in which double Mannich adduct **10** was further converted to (±)-8-oxosparteine, and hence the target alkaloid itself, by oxidative cyclization followed by Wolff−Kishner reduction (eq 2 in Figure 3).[63] Similar approaches have been disclosed,[64,65] but the more recent work of Koomen and Wanner, in which both (±)-sparteine (*dl*-**1**) and (±)-β-isosparteine (*dl*-**3**) were elaborated from tetrahydroanabasine,[66] represents the most truly biomimetic synthesis of these alkaloids described to date.[67]

The C_2-symmetric isomers of sparteine have rarely been the deliberate targets of total synthesis. A notable exception is a remarkably concise synthesis of (±)-α-isosparteine (*dl*-**2**) reported by Kakisawa and co-workers in 1983 (eq 3 in Figure 3).[68] Again, an "outside-in" strategy was employed and pentacycle **11**, formed diastereoselectively via consecutive nitrone−olefin cycloadditions between 2 equiv of 2,3,4,5-tetrahydropyridine-*N*-oxide and 4*H*-pyran, gave the target molecule directly upon reductive cyclization (in an unspecified yield).

In 2002, Aubé and co-workers described an enantioselective total synthesis of (+)-sparteine (*d*-**1**) that highlighted the utility

(52) (a) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1948**, *70*, 2298–2299. (b) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316–1323.

(53) Clemo and co-workers succeeded in preparing 17-oxosparteine by a related multi-step route as early as 1936, but could not convert this material into sparteine itself with the reducing reagents available at the time. The same group later completed a true total synthesis of sparteine following the introduction of $LiAlH_4$, see: (a) Clemo, G. R.; Morgan, W. McG.; Raper, R. *J. Chem. Soc.* **1936**, 1025–1028. (b) Clemo, G. R.; Raper, R.; Short, W. S. *J. Chem. Soc.* **1949**, 663–665.

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(55) Tsuda, K.; Satoh, Y. *Pharm. Bull.* **1954**, *2*, 190–193.

(56) Carmack and co-workers later repeated the Sorm−Keil synthesis of sparteine (ref 54) and succeeded in converting one of the 10,17-dioxosparteine isomers produced by that approach into (±)-β-isosparteine via $LiAlH_4$ reduction, see ref 17.

(57) O-Brien's recently reported elaboration of (−)-sparteine (*l*-**1**) is the second enantiocontrolled synthesis of this important alkaloid, see: Hermet, J.-P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830–1831.

(58) (a) Buttler, T.; Fleming, I. *Chem. Commun.* **2004**, 2404–2405. (b) Buttler, T.; Fleming, I.; Gonsior, S.; Kim, B.-H.; Sung, A.-Y.; Woo, H.-G. *Org. Biomol. Chem.* **2005**, *3*, 1557–1567.

(59) (a) Robinson, R. *J. Chem. Soc., Trans.* **1917**, *111*, 876–899. (b) Robinson, R. *The Structural Relations of Natural Products*; Oxford University Press: London, UK, 1955.

(60) Robinson, R. *J. Chem. Soc., Trans.* **1917**, *111*, 762–768.

(61) (a) Anet, E.; Hughes, G. K.; Ritchie, E. *Nature* **1950**, *165*, 35–36. (b) Anet, E. F. L. J.; Hughes, G. K.; Ritchie, E. *Aust. J. Sci. Res.* **1950**, *3*, 635–641.

(62) Schöpf, C. L.; Benz, G.; Braun, F. R.; Hinkel, H.; Rokohl, R. *Angew. Chem.* **1953**, *65*, 161–162.

(63) (a) van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1960**, *82*, 2400. (b) van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 7372–7377.

(64) (a) Bohlmann, F.; Müller, H.-J.; Schumann, D. *Chem. Ber.* **1973**, *106*, 3026–3034. (b) Takatsu, N.; Noguchi, M.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, *35*, 4990–4992.

(65) Somewhat related recent elaborations of (±)-anagyrine and (±)-thermopsine by Gallagher and Gray constitute formal syntheses of (±)-sparteine, (±)-α-isosparteine, and (±)-β-isosparteine, see: Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419–2423.

(66) Tetrahydroanabasine is biosynthesized from cadaverine, the known natural precursor of sparteine, see: (a) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1985**, *63*, 2707–2718. (b) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1988**, *66*, 1734–1748. (c) Brown, A. M.; Rycroft, D. S.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2353–2355.

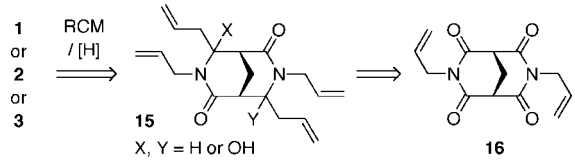
(67) Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1996**, *61*, 5581–5586.

(68) (a) Oinuma, H.; Dan, S.; Kakisawa, H. *Chem. Commun.* **1983**, 654–655. (b) Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2593–2597.

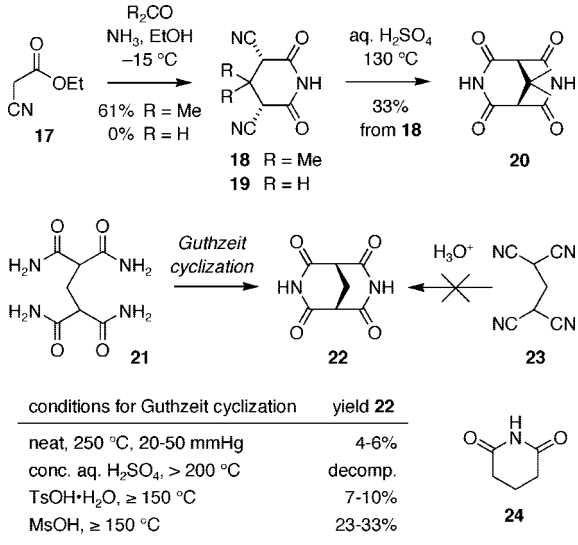
(69) (a) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577−2579. For preliminary studies, see: (b) Wendt, J. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 1531–1534.

(70) For a commentary on this work, see: Iyengar, R.; Gracias, V. *Chemtracts* **2004**, *17*, 92–96.

SCHEME 2. A Retrosynthetic Analysis of the Sparteine Group Alkaloids (1−3)



SCHEME 3. Synthesis of 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonane (22) and Related Studies



conditions for Guthzeit cyclization	yield **22**
neat, 250 °C, 20-50 mmHg	4-6%
conc. aq. H_2SO_4, > 200 °C	decomp.
$TsOH{\cdot}H_2O$, ≥ 150 °C	7-10%
MsOH, ≥ 150 °C	23-33%

of the alkyl Schmidt reaction.[69,70] Remarkably, this 21st century work constituted the first ever asymmetric synthesis of any alkaloid of the sparteine subgroup and, prior to our studies (vide infra), it was further distinguished by being the only known effort to deviate from the traditional "outside-in"-type strategy. Rather, the outer A- and D-rings were successively annulated on to a bicyclic template representing the central BC-rings of the target in an "inside-out" fashion. Thus, scalemic C_2-symmetric diketone **12**, wrought from achiral norbornadiene by enantioselective desymmetrization via a three-step hydrosilylation/oxidation sequence,[71] was advanced to alkyl azide **13** as a prelude to a stereospecific Schmidt-type nitrenoid insertion yielding tricycle **14** (eq 4 in Figure 3).[72] Stereochemistry at C6 (sparteine numbering) was set by hydrogenation of an exocyclic olefin en route to **13**, and ketone **14**was further converted into (+)-sparteine (*d*-**1**) by an 8-step sequence incorporating diastereoselective exo face alkylation at C11 and an unusual photo-Beckmann rearrangement to effect a second net formal nitrene insertion into C11−C17.

Synthetic Plan. Given the historical and practical relevance of the sparteine alkaloids, we sought a concise synthetic scheme capable of targeting any member of this special group of molecules in a stereocontrolled fashion. As highlighted above, many "outside-in" approaches to the sparteine bases had been previously evaluated and we felt that an "inside-out" strategy conceptually akin to the Aubé synthesis of (+)-sparteine (*d*-**1**),[69] and progressing via sequential desymmetrization of an initially achiral C_{2v}-symmetric core synthon, would offer greater

(71) Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259–266.

(72) For a notable recent application of the intramolecular alkyl Schmidt reaction, see: (a) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731–734. (b) Clayden, J.; Moran, W. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7118–7120.

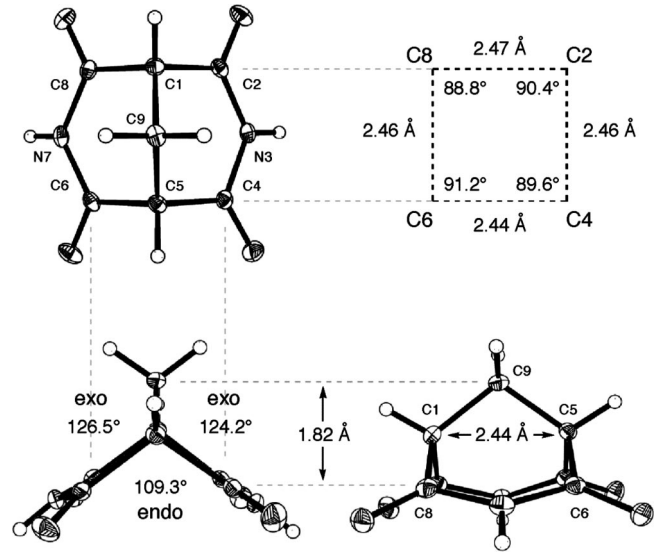


FIGURE 4. Orthographic views of the ORTEP diagram for 2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (**22**) with parameters of interest. Indicated "exo" and "endo" angles are appropriate intersection angles between the three least-squares fitted planes containing {C1,C2,N3,C4,C5}, {C5,C6,N7,C8,C1}, and {C1,C9,C5}. Fifty percent probability ellipsoids are plotted for non-hydrogen atoms.

opportunities for novel discoveries. Retrosynthetic analysis guided by this consideration led to the identification of a tetraoxobispidine (such as **16**) as an ideal platform from which to elaborate all principal lupine alkaloids of the sparteine group (Scheme 2). Thus, it was recognized that bisimide **16**, representing the central sparteine BC-rings, is potentially amenable to the controlled annulation of rings A and D via nucleophilic allylation processes followed by ring-closing olefin metathesis (RCM) and thence exhaustive reduction from intermediate tetraallyl compounds **15** of appropriate oxidation level and stereochemistry. From the outset, exo face selective additions to the bicyclic and tetracyclic intermediates of interest were anticipated; however, the regiochemical outcome of successive nucleophilic additions to bisimides such as **16** was far less certain. In the event, reduction of this plan to practice was successful and accounts of our studies concerning the syntheses of (±)-α-isosparteine (*dl*-**2**)[73] and (±)-*β*-isosparteine (*dl*-**3**)[74] were previously communicated. Herein, we report full details for these two efforts with new improvements, the first disclosure of a synthesis of (±)-sparteine (*dl*-**1**) along similar lines, and also preliminary work directed at rendering this kind of approach enantioselective.[75]

Results and Discussion

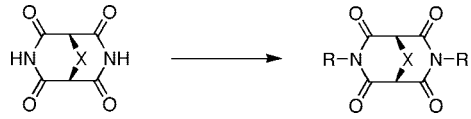
Synthesis of Tetraoxobispidines. The viability of our proposed synthetic scheme hinged on securing access to pivotal tetraoxobispidine intermediates such as **16**. Tetraoxobispidines (i.e., 2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonanes) substituted at the methylene bridge are well described in the literature, and have been used as precursors to bispidines with antiarrhythmic

(73) Blakemore, P. R.; Kilner, C.; Norcross, N. R.; Astles, P. C. *Org. Lett.* **2005**, *7*, 4721–4724.

(74) Blakemore, P. R.; Norcross, N. R.; Warriner, S. L.; Astles, P. C. *Heterocycles* **2006**, *70*, 609–617.

(75) Blakemore, P. R.; Norcross, N. R.; Astles, P. C. Presented in part at the 232nd ACS National Meeting, San Francisco, CA, September 10−14, 2006: *Abstracts of Papers*; American Chemical Society: Washington, DC, 2006; ORGN#751.

TABLE 1. *N,N′*-Dialkylation of Tetraoxobispidines **20** and **22**



entry	starting material	X	reaction conditions	product	R	yield, %
1	**22**	CH_2	allyl-Br, K_2CO_3, acetone, Δ	**16**	allyl	29
2	**22**	CH_2	allyl-Br, K_2CO_3, MeCN, Δ	**16**	allyl	43
3	**22**	CH_2	allyl-Br, K_2CO_3, MeOH, Δ	**16**	allyl	dec
4	**22**	CH_2	allyl-Br, NaOMe, MeOH, rt	**16**	allyl	dec
5	**22**	CH_2	allyl-OH, DIAD, PPh_3, THF, rt	**16**	allyl	61
6	**22**	CH_2	allyl-Br, NaH, DMF, rt	**16**	allyl	83
7	**22**	CH_2	BnBr, NaH, DMF, rt	**25**	Bn	83
8	**22**	CH_2	crotyl-Br, NaH, DMF, rt	**26**	crotyl	46
9	**22**	CH_2	prenyl-Br, NaH, DMF, rt	**27**	prenyl	51
10	**20**	CMe_2	BnBr, K_2CO_3, acetone, Δ	**28**	Bn	63

properties;[76] however, at the outset of our studies, the parent compound **22** had featured in only a single century old report by Guthzeit and Jahn.[77] The bisimides of interest are traditionally prepared by acidic hydrolysis of α,α′-dicyanoglutarimides ("Guareschi imides" e.g., **18**), which are in turn conveniently synthesized by the Guareschi condensation: a Knoevenagel-type three-component coupling reaction involving coalescence of a cyanoacetate, a carbonyl compound, and ammonia.[78] We found this procedure entirely acceptable for the synthesis of known 9,9-dimethyltetraoxobispidine (**20**),[76] via meso Guareschi imide **18**,[79] but attempts to extend the same process to the synthesis of **22** where wholly unsuccessful (Scheme 3). Thus, the previously undescribed Guareschi imide **19** was not an identifiable component of the reaction mixtures that were obtained from addition of either formalin or paraformaldehyde to ethyl cyanoacetate (**17**) in ethanolic ammonia. The failure of this transformation was attributed to the high reactivity of the putative α-cyanoacrylic intermediates which readily polymerize. Other attempts to synthesize **19** along similar lines via the Clemens variant of the Guareschi condensation were equally fruitless,[80] as was a related direct cyano-group hydrolysis route to **22** from the malononitrile derived tetracyanide **23**.[81] In this case, exposure of **23** to acidic media (including aq AcOH, HCl, or H_2SO_4) gave no reaction at low-to-moderate temperatures, but caused decomposition to volatile byproducts under more forcing conditions (≥100 °C) with simple ammonium salts making up the reaction residue.

Guthzeit's long neglected synthesis of **22** via direct pyrrolysis of tetraamide **21** presented an obvious solution to the problem at hand. Indeed, given the extreme ease with which **21** may be prepared from dimethyl malonate,[82] we had initially regarded this approach to **22** as attractive, but preliminary results were not encouraging. Following the originally prescribed protocol,[77] brief heating of **21** beyond its melting point at subambient pressure (20−50 mmHg) instigated the vigorous evolution of a gaseous stream clearly containing both NH_3 and H_2O, the latter indicating that competitive undesired cyclization modes to isoimide forms of **22** were potentially in operation. Upon cessation of bubbling, the darkly colored resinous pyrrolyte was allowed to cool and subsequent trituration and recrystallization from EtOH allowed small quantities of the crystalline bisimide **22** to be isolated (4−6%). Glutarimide (**24**), the undoubted result of retro-Claisen-type bond scissions en route to **22**, was consistently identified as a significant component of the mass balance (ca. 10−40% depending on duration of heating), but the formation of other simple molecules (e.g., urea) during this crude transformation cannot be discounted. Notwithstanding the poor efficiency of the cyclocondensation, it proved impossible to reliably execute beyond single gram quantities of **21**, either by conventional heating or in a focused microwave reactor. Reasoning that the presence of liberated free ammonia would be deleterious to the survival of **22**, and that some sort of electrophilic activation would facilitate cyclization of **21** in the desired manner, an acid mediated variant of the Guthzeit cyclization was explored. Sulfuric acid proved unsatisfactory for this purpose, but reasonable results were obtained by fusing **21** with toluenesulfonic acid (7−10% **22**), or (better) by heating a mechanically stirred paste prepared from this amide and methanesulfonic acid (23−33% **22**). The still modest yield of the transformation in MsOH is offset by its operational simplicity, reproducibility over a range of scales (essentially identical results at 5, 100, and 300 mmol), and the ease with which the desired bisimide product may be conveniently isolated from the reaction mixture in pure form by simple trituration with MeOH.

As one might anticipate given its highly symmetrical cage-like structure, the parent tetraoxobispidine (**22**) is a beautifully crystalline material and good quality colorless needles are readily generated upon recrystallization from H_2O (mp 295 °C, dec). X-ray crystallographic analysis of **22** was performed for the first time and revealed only a slight deviation from perfect C_{2v}-symmetry (Figure 4). Near planar imide subunits with well-differentiated *exo* and *endo* faces are clearly evident, with the

(76) Schön, U.; Antel, J.; Brückner, R.; Messinger, J. *J. Med. Chem.* **1998**, *41*, 318–331.

(77) Guthzeit, M.; Jahn, C. *J. Prakt. Chem.* **1902**, *66*, 1–15. For an English language abstract, see: *J. Chem. Soc., Abstr.* **1902**, *82* (I), 658−659.

(78) The early discoveries of Guareschi were later followed and more extensively explored by Thorpe and Vogel, see: (a) Guareschi, I. *Gazz. Chim. Ital.* **1919**, *49*, 124–133. (b) Kon, G. A. R.; Thorpe, J. F. *J. Chem. Soc.* **1919**, 686–704. (c) Vogel, A. I. *J. Chem. Soc.* **1934**, 1758–1765.

(79) Holder, R. W.; Daub, J. P.; Baker, W. E.; Gilbert, R. H.; Graf, N. A. *J. Org. Chem.* **1982**, *47*, 1445–1451.

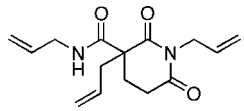
(80) The Clemens variant of the Guareschi reaction calls for base mediated condensation of a pre-formed (β-substituted) α-cyanoacrylate with cyanoacetamide; however, given the instability of β-unsubstituted α-cyanoacrylates, the isolable dicyclohexylamine salt of α-cyanoacrylic acid (ref 80c) was utilized in our attempts to access **19** via this route, see: (a) McElvain, S. M.; Clemens, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 3915–3923. (b) McElvain, S. M.; Clemens, D. H.; Parham, W. E.; Kirklin, P. W.; Noland, W. E. *Org. Synth.* **1959**, *39*, 52–53. (c) Krawczyk, H. *Synth. Commun.* **2000**, *30*, 657–664.

(81) Bell, R. A.; Brown, B. E.; Duarte, M.; Howard-Lock, H. E.; Lock, C. J. L. *Can. J. Chem.* **1987**, *65*, 261–270.

(82) See the Experimental Section for details concerning an improvement to our earlier method (ref 73) for the preparation of propane-1,1,3,3-tetracarboxamide (**21**). See also: Gogoll, A.; Johansson, C.; Axén, A.; Grennberg, H. *Chem. Eur. J.* **2001**, *7*, 396.

former some 16° more open than the latter. Of further interest, the four carbonyl carbon atoms of **22** lie in a common plane and constitute a virtually flawless molecular square (as illustrated); the C9 bridge atom lies 1.82 Å above the exact center of this square. The NMR spectral signature of **22** (in d_6-DMSO) is in accord with expectation: the ^{13}C NMR spectrum exhibits three signals only (δ_C 166.9, 47.2, and 22.8 ppm), while the small magnitude of mutual scalar coupling (t, $J^3 = 2.8$ Hz) between anisochronous methylene bridge (δ_H 2.59 ppm) and methine ring-junction (δ_H 3.64 ppm) protons in the ^1H NMR spectrum is consistent with geometrically imposed fixed dihedral angles of 60(±0.3)°.

The conversion of bisimide **22** into various *N*,*N*′-dialkyl derivatives of potential utility en route to the sparteine alkaloids was next investigated (Table 1). These studies further highlighted the propensity of tetraoxobispidines unsubstituted at the (C9) bridge position to suffer base-promoted decarboxylative fragmentation. For example (entry 1), treatment of **22** with allyl bromide in the presence of K_2CO_3 in refluxing acetone gave a poor yield of the desired product **16** (29%), which was accompanied (among other unidentified minor decomposition products) by glutarimide **29** (10%). The identity of this byproduct reveals that once the bicyclic bisimide core has been opened, enolization of any remaining β-dicarbonyl moieties may readily occur. Analogous C-alkylation of intact tetraoxobispidines is precluded because formation of the necessary enolate species would violate Bredt's rule.[83,84]

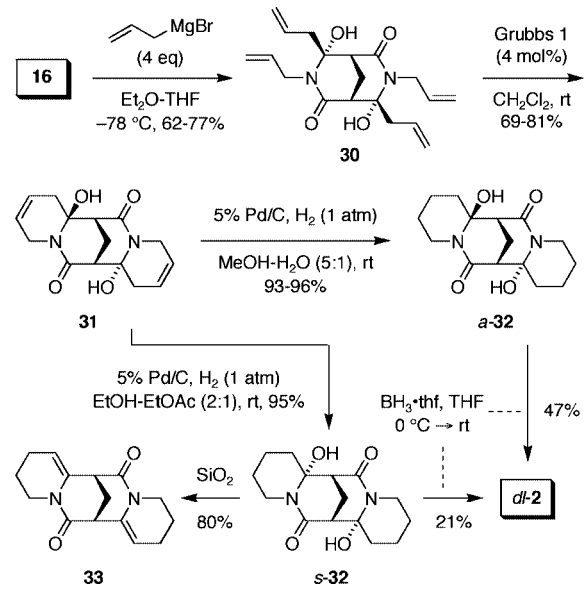


29

Given the low solubility of **22** in acetone, similar alkylations were conducted in more polar solvents; however, it was evident that methoxide was inimical to the desired process (entries 2−4). A Mitsunobu dehydrative coupling[85] between **22** and allyl alcohol in THF gave better results (entry 5), but ultimately it was discovered that allylation of **22** was best and most simply performed in the traditional manner by employing NaH as base and DMF as solvent (entry 6). Following this procedure, key synthon **16** was isolated in pure form by trituration and without recourse to chromatography in 83% yield.[86] Benzyl (**25**), crotyl (**26**), and prenyl (**27**) derivatives of **22** were similarly prepared (entries 7−9). By contrast to the parent tetraoxobispidine (**22**), alkylation of the 9,9-dimethyl congener (**20**) was less problematic and proceeded as indicated without significant decomposition (entry 10). Presumably, nucleophilic attack on the carbonyl groups of bisimide **20** is retarded by the presence of flanking methyl substituents on the bridge.

With a satisfactory and scalable route to *N*,*N*′-diallyltetraoxobispidine (**16**) and related bisimides successfully developed,

SCHEME 4. Synthesis of (±)-α-Isospartine (*dl*-2) from Tetraoxobispidine 16



attention was next directed to advancing these materials into the three different diastereomeric forms of the sparteine ring system.

Synthesis of (±)-α-Isosparteine. According to the prescribed plan (Scheme 2), a successful synthesis of (±)-α-isosparteine (*dl*-**2**) would necessitate regiocontrolled double nucleophilic allylation of bisimide **16**, followed at some later juncture by exo face selective reduction of a bishemiaminal intermediate (i.e., **15**, X = Y = OH, or an RCM derived adduct thereof). Pleasingly, after some experimentation, it was discovered that addition of excess allylmagnesium bromide to bisimide **16** generated a bishemiaminal product (**30**) of the desired symmetry type in an efficient manner (Scheme 4). Unwanted C_s-type regioisomers were not significant components of the crude product mixture (<5% by NMR analysis), and bicycle **30** was directly isolated as a single diastereoisomer by recrystallization.[87] Since the first report of this transformation,[73] an X-ray crystallographic analysis has confirmed our original assumption that both hydroxyl groups within **30** are endo (α) configurated (see the Supporting Information). It should be noted, however, that the now established stereochemical assignment for **30** does not necessarily imply that allylation of **16** occurred with exo face kinetic diastereoselectivity. Epimerization of the anomeric stereogenic centers in **30** is a mechanistic possibility, and indeed, later compounds in the synthetic sequence en route to α-isosparteine showed a propensity for such behavior.

Double ring-closing olefin metathesis (RCM) of tetraene **30** with Grubbs' first generation catalyst ("Grubbs 1")[88] occurred without incident to afford the tetracyclic sparteine congener **31** as an insoluble solid. Spontaneous precipitation of **31** from the reaction mixture allowed for its easy isolation by means of filtration. NMR spectral analysis of **31** suggested that the compound retained the C_2-symmetry of its precursor;[89] however,

(83) (a) Köbrich, G. *Angew. Chem.* **1973**, *85*, 494–503. (b) Buchanan, G. L. *Chem. Soc. Rev.* **1974**, *3*, 41–63.

(84) Successful α-metalation at bridge-head positions in related [3.3.1] systems is possible in the presence of stronger bases, see: Giblin, G. M. P.; Kirk, D. T.; Mitchell, L.; Simpkins, N. S. *Org. Lett.* **2003**, *5*, 1673–1675, and references cited therein.

(85) (a) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656. (c) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(86) For X-ray crystallographic analyses of compounds **16** and **31**, see ref 73.

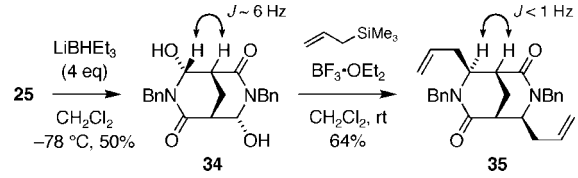
(87) Attempted purification of **30** by column chromatography (SiO_2) led to significantly reduced yields, possibly due to the generation of acyl iminium ions and thence decomposition.

(88) Herein, "Grubbs 1" = $(Cy_3P)_2Cl_2Ru{=}CHPh$; "Grubbs 2" = $(Cy_3P)(H_2IMes)Cl_2Ru{=}CHPh$. For recent reviews of olefin metathesis with these catalysts, see: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (b) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003.

an X-ray diffraction analysis of the crystalline form of **31** indicated an exo/endo arrangement of hydroxyl groups in the solid state.[86] These data are not incompatible and are consistent with the existence of a solution phase dynamic equilibrium between **31** anomers that is perturbed upon selective deposition of the illustrated nonsymmetrical isomer during crystallization. Lending credence to this hypothesis, subsequent hydrogenative saturation of the olefinic moieties within **31** revealed the possibility for interconversion between epimeric 6,11-dihydroxy-10,17-dioxosparteines (**32**) under mild conditions. Thus, the polarity of the hydrogenation reaction medium was noted to markedly affect the final isomeric ratio for the isolated reduction product. In a very polar solvent mixture (MeOH−H_2O, 5:1), hydrogenation of **31** over Pd/C (at 1 atm) gave the nonsymmetric bishemiaminal *a*-**32** as a single isomer in near quantitative yield following its isolation by trituration. By contrast, execution of an otherwise identical procedure in a less polar solvent combination (EtOH−EtOAc, 2:1) afforded the symmetric product *s*-**32** with endo configurated hydroxyl groups (as supported by both NMR and X-ray crystallographic analysis, see the Supporting Information). Yet another hydrogenation reaction of **31** in EtOH (not illustrated) gave a 1:1 mixture of *a*-**32** and *s*-**32**. In no example were alkoxy groups incorporated at the anomeric positions of the product and it is therefore evident that epimerization involved ring-opened amido keto tautomers rather than the formation of acyl iminium ions. The latter species were, however, implicated in the unexpectedly facile dehydration of diol *s*-**32** to enamide **33** upon its exposure to silica gel during a (superfluous) chromatographic purification operation. Attempts to reduce this new compound to 10,17-dioxo-α-isosparteine by analogy to the known conversion of (−)-$\Delta^{5,11}$-didehydrosparteine to *l*-**2**[20] did not meet with immediate success and were not further pursued.[90] The more direct conversion of **30** to **32** by a tandem RCM/hydrogenation procedure was also briefly entertained, but failed due to the insolubility of diene **31** in 1,2-dichloroethane.[91]

Conclusion of the total synthesis of (±)-α-isosparteine (*dl*-**2**) required deoxygenation of *a*-**32** or *s*-**32** with stereocontrolled exomode introduction of hydride at C6 and C11. In the event, this objective was successfully accomplished from either anomer by the action of a large excess of borane tetrahydrofuran complex. Presumably, identical transient acyl iminium ions were generated during the course of both transformations, with exogenous hydride delivery occurring in the desired and anticipated manner.[92] The reduction was significantly more efficient from *a*-**32** than *s*-**32**, but in each case, the free base of *dl*-**2** spontaneously crystallized as its hydrate from alkaline solution during workup, greatly facilitating isolation of the racemic alkaloid target. The identity of the crystalline material obtained was confirmed by comparison to spectroscopic and physical data previously recorded from both natural and synthetic samples of α-isosparteine.[93]

Synthesis of (±)-β-Isosparteine. A two-directional approach to (±)-β-isosparteine (*dl*-**3**) was pursued along similar lines to the synthesis of its symmetry related congener, (±)-α-isosparteine (*dl*-**2**). To target the alternate *endo*−*endo* configuration of C6/C11 hydrogen atoms presented by *dl*-**3**, a strategic reversal in the order of introduction of allyl and hydride nucleophiles onto a tetraoxobispidine template was called for. Accordingly, following a preliminary survey of potentially suitable reducing reagents, it was observed that reaction of *N*,*N*′-dibenzyl bisimide **25** with an excess of lithium triethylborohydride (Super Hydride)[94] proceeded in the desired regiochemical mode to afford bishemiaminal **34** as the double α-anomer. Other hydride sources, including diisobutylaluminum hydride (DIBAL-H) and sodium bis(methoxyethoxy)aluminum hydride (Red-Al), gave inferior results and intractable byproduct, while simple boranes (9-BBN and catecholborane) failed to react. Exposure of bishemiaminal **34** to boron trifluoride etherate in the presence of allyltrimethylsilane resulted in an *exo*-face selective double Sakurai-type allylation process affording bislactam **35**. The stereochemical outcome of this transformation, evident from the low magnitude of scalar coupling between vicinal bridgehead and CHN methine protons (<1 Hz, as indicated),[95] is a further testament to the predictable nature of nucleophilic addition to acyl iminium cations derived from constrained bispidine systems.



With a viable strategy in place for setting the desired regio- and stereochemistry, extension of the same two-step protocol to *N*,*N*′-diallyl bisimide **16**, a precursor better suited for eventual advancement to the akaloid of interest, was attempted. In the event, **16** proved to be a significantly less robust substrate than **25** (possibly due to the absence of sterically encumbering groups on imide N-atoms) and its exposure to excess lithium triethylborohydride gave complex mixtures from which only traces of the desired *N*,*N*′-diallyl bishemiaminal **38** could be identified (≤11% yield). As previously outlined, this problem was initially solved by resorting to a circuitous four-step sequence (two iterations of $LiBHEt_3$ monoreduction/mono-Sakurai allylation) that yielded **39** in 9−14% overall yield from **16**.[74] It has since been discovered that **39** can be obtained from bisimide **16** more directly via sodium borohydride mediated reduction followed by Sakurai allylation of the resulting cocktail of unpurified hemiaminals **36** and **38** (Scheme 5). This step-saving protocol afforded a mixture of triene **37** and tetraene **39** in higher net yield (33% and 16%, respectively) than the less convenient four-step sequence. Accordingly, that the mixture of **37** and **39**

(89) The ^{13}C NMR (75 Hz, d_6-DMSO) spectral signature of **31** comprises eight signals and is compatible with a (static or time-averaged) C_2-symmetric bishemiaminal structure. The ^1H NMR (300 MHz, d_6-DMSO) spectrum for **31** exhibits significant line broadening, but is also suggestive of net C_2-symmetry.

(90) Bisenamide **33** proved resistant to hydrogenation as catalyzed by either Pd/C or $Pd(OH)_2$/C (albeit at 1 atm pressure of H_2), and was likewise recovered unchanged following treatment with $NaBH(OAc)_3$ or $NaBH_3CN$ in AcOH.

(91) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.

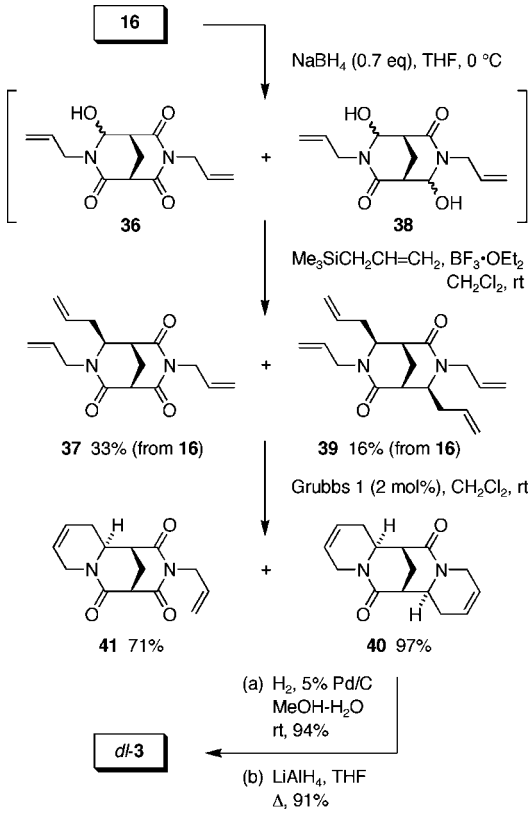
(92) Exo-face selective addition of Grignard reagents to acyl iminium ions derived from *N*-acyl bispidines has been previously observed, see: Harrison, J. R.; O'Brien, P. *Tetrahedron Lett.* **2000**, *41*, 6167–6170.

(93) For compiled ^{13}C NMR spectral data for sparteine alkaloids **1**−**3**, see: (a) Galasso, V.; Asaro, F.; Berti, F.; Kovac, B.; Habus, I.; Sacchetti, A. *Chem. Phys.* **2003**, *294*, 155–169. (b) Mikhova, B.; Duddeck, H. *Magn. Reson. Chem.* **1999**, *36*, 779–796.

(94) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671.

(95) The Karplus relation predicts a very low *J* value in this case as a consequence of a near 90° dihedral angle between the bridgehead proton and endo-configurated CHN methine proton in bislactam **35**. A significantly larger *J* value is expected for isomeric compounds wherein the same CHN methine proton is exo-configurated, e.g., as observed for bishemiaminal **34**. For a review of the Karplus relation, see: Minch, M. J. *Concept. Maget. Reson.* **1994**, *6*, 41–56.

SCHEME 5. Synthesis of (±)-β-Isosparteine (*dl*-3) from Tetraoxobispidine 16

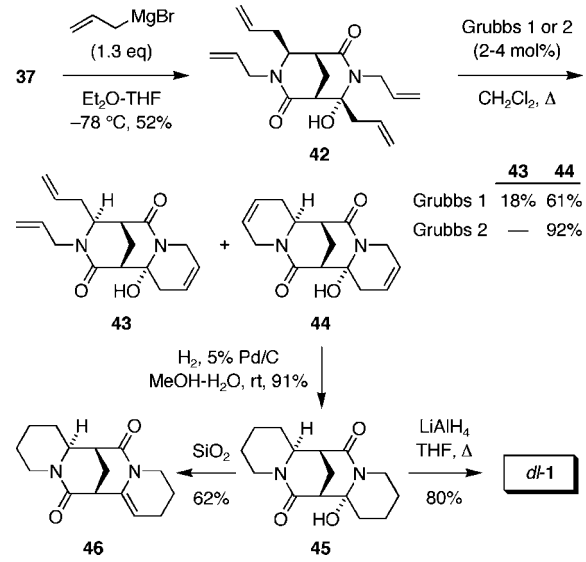


generated in this manner proved difficult to separate, was viewed as only a minor detraction of the new process. Exposure of a two component mixture of alkenes **37** and **39** to Grubbs' first generation metathesis catalyst[88] gave the expected (and easily separated) RCM adducts **41** and **40**. Exhaustive reduction of the latter resulted in its high-yielding transformation to the target alkaloid (*dl*-**3**) of immediate interest. The identity of the synthetic (±)-β-isosparteine (*dl*-**3**) generated by the described five-step route from **16** was confirmed by comparison of ^{1}H and ^{13}C NMR spectral data with those previously reported for this relatively obscure member of the sparteine family.[67,74,93]

Synthesis of (±)-Sparteine. With a hoard of knowledge gained from the successful tetraoxobispidine based elaborations of (±)-α-isosparteine (*dl*-**2**) and (±)-β-isosparteine (*dl*-**3**), an assault on the parent alkaloid (*dl*-**1**) was approached with confidence. The nonsymmetrical nature of sparteine precluded an obvious wholly two-directional approach from bisimide **16**, although one such strategy was devised and briefly entertained before its abandonment.[96] A way forward presented itself when it was discovered that imidolactam **37**, the intermediate encountered en route to *dl*-**3**,[74] received allylmagnesium chloride in a regioselective manner (Scheme 6). The resulting pseudo-C_2-symmetric addition adduct **42** was obtained as a single stereoisomer, presumably with an endo configurated hydroxyl group (cf. **56**, vide infra), following its isolation by chromatography. Tetraene **42** was converted to the final target molecule

(96) It was envisioned that ionic reduction of a bis(diethylsilyl) hydride (2 × $OSiEt_2H$) derivative of diol **31** (or related compounds **32**) would proceed via a successive combination of intramolecular (endo selective) and intermolecular (exo selective) hydride additions to acyl iminium ions generated in the presence of a Lewis acid and external silane (Et_3SiH). This plan stalled when the requisite silyl ether derivatives could not be generated.

SCHEME 6. Synthesis of (±)-Sparteine (*dl*-1) from Imidolactam 37



via essentially the same sequence of steps used previously to convert **39** to (±)-β-isosparteine (*dl*-**3**). In this case, however, the double RCM reaction could not be coaxed to completion by the action of the first generation Grubbs metathesis catalyst (up to 30 mol% of "Grubbs 1"), presumably due to a product inhibition effect. The problem was circumvented by use of the more reactive second generation Grubbs catalyst instead ("Grubbs 2"),[88] which gave the desired tetracyclic diene **44** in an excellent yield. An X-ray crystallographic analysis secured the structural assignment for **44** (see the Supporting Information) and subsequent hydrogenation led to the expected oxygenated sparteine derivative **45**. The illustrated α-anomeric configuration of **45** was established by further X-ray diffraction work that also revealed a hydrogen-bonded heteroenantiomeric dimer for the crystalline racemic amido alcohol (see the Supporting Information). Hemiaminal **45** showed similar acid catalyzed instability to *s*-**32** and upon prolonged exposure to silica gel gave a dehydration adduct (**46**) analogous to **33**. Even brief contact of **45** with SiO_2 resulted in anomerization (leading to $\alpha{:}\beta = 2{:}3$) and so chromatographic purification was best avoided. Finally, reduction of **45** with lithium aluminum hydride gave (±)-sparteine (*dl*-**1**) in 80% yield (after Kugelrohr distillation), indistinguishable from a commercial sample of natural (−)-sparteine (*l*-**1**) by IR and NMR spectral analysis.

Enantioselective transformations. During the course of our studies, it was discovered that sequential net double nucleophilic additions to C_{2v}-symmetric tetraoxobispidine intermediates typically afford (inherently chiral) C_2-type rather than (potentially meso) C_s-type regioisomers; however, a priori no such intrinsic substrate bias was anticipated. In fact, it was initially believed that chiral reagent control would be required to target the desired C_2-type addition adducts (**49**) by repeated recognition of the shared local prochirality of a given pair of homotopic carbonyl groups within bisimides **47** (Figure 5). The tactic of employing chiral reagent control to influence *regioselectivity* in this manner has been but rarely applied in synthesis.[97] On the basis of our observations, the two remaining imide carbonyl groups in imidolactam intermediates of type **48** (and even those lacking a formal alkoxide moiety, e.g., **37**) are evidentally sufficiently electronically differentiated to allow for their regioselective transformation

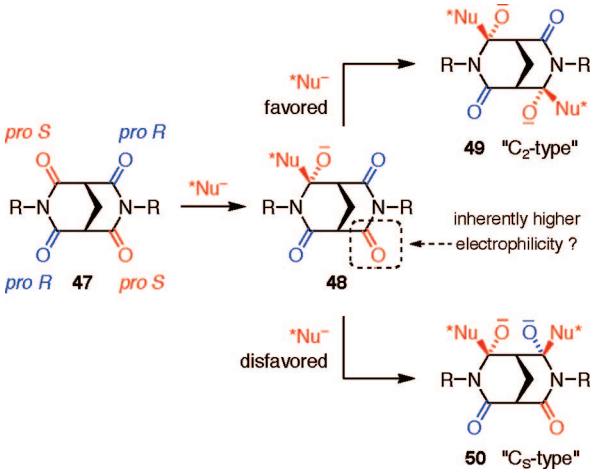
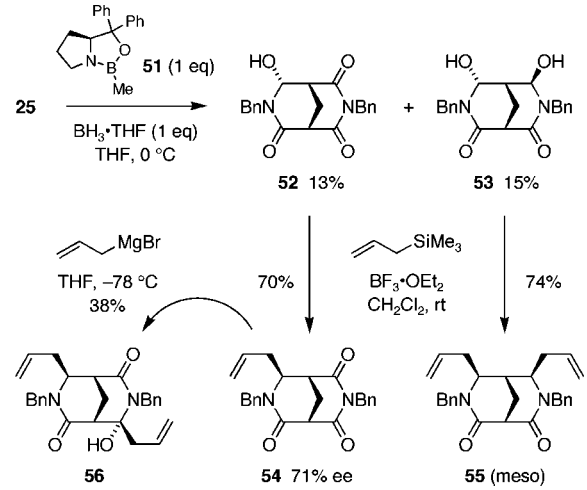


FIGURE 5. Conceptualized enantioselective addition to C_{2v}-symmetric tetraoxobispidines **47**. Nu* represents a generic enantioselective nucleophilic addition process that preferentially recognizes imide carbonyl groups with local *pro S* enantiotopicity.

without the need for subtle absolute stereorecognition effects. The apparent enhanced electrophilicity of the imide carbonyl group diagonally opposite from the first addition point is tentatively attributed to the inductive effect of the proximal lactam carbonyl group. Even a cursory inspection of molecular models reveals that steric factors are highly unlikely to be the cause of the substrate regioselectivity bias.

While chiral reagent control was ultimately not necessary to gain access to bisimide addition adducts of the desired regiochemistry, this paradigm (ideally in a catalytic enantioselective guise) would provide the most efficient way to target nonracemic sparteine alkaloid targets from tetraoxobispidines. For example, an enantioselective addition of a single hydride anion equivalent to bisimide **16** would be sufficient to obtain scalemic samples of both β-isosparteine (**3**) and sparteine (**1**) via the routes already described. Likewise, α-isosparteine (**2**) could be secured from **16** in optically active form via an initial enantioselective allyl anion addition event (or alternatively by isomerization of **1** or **3**).[20] Numerous methods for the enantioselective allylation[98] and reduction[99] of aldehydes and ketones are available but very few of these protocols have been successfully extended to transformation of carbonyl groups at the less electrophilic carboxyl oxidation level.[100] Notable contributions from Speckamp and Hiemstra,[101] among others,[102,103] have shown that chiral oxazaborolidine catalyzed borane reduction[104] is an effective tool for the differentiation of enantiotopic carbonyl groups within prochiral cyclic imides. Accordingly, we elected to evaluate the

SCHEME 7. Enantioselective Reduction of Tetraoxobispidine 25



viability of this precedented desymmetrization tactic for the enantioselective reduction of our tetraoxobispidine synthons.

Initial studies focused on borane reduction of *N*,*N*′-diallyl bisimide **16** catalyzed by Corey's (*S*)-diphenylprolinol derived oxazaborolidine **51** (the "CBS" catalyst).[104b,c] Hydroboration of the alkenyl moieties in **16** competed with imide reduction when borane tetrahydrofuran complex was used as a terminal reductant and application of catecholborane in the same role proved ineffectual.[105] Comparable reactions from the crotyl and prenyl analogues of **16** were also unsuccessful: alkene hydroboration and decomposition plagued attempted CBS-reduction of dicrotyl bisimide **26**, while the sterically encumbered diprenyl derviative **27** was wholly unreactive. More promising results were obtained from dibenzyl bisimide **25**, a compound that had earlier been shown to give isolable hemiaminal derivatives upon its reduction (e.g., **25** → **34**). However, it became immediately evident that double reduction of **25** as mediated by BH_3•THF and promoted by oxazaborolidine **51** led to the undesired C_s-type regiochemistry (Scheme 7). Compounding this problem, the potentially valuable monoreduction product **52** could not be secured in a truely useful yield because further reduction of (the borane complex of) this compound occurred at a rate greater than that for initial hydride delivery to bisimide **25**. Thus, after considerable optimization experiments, imidolactam **52** was obtained in at best a 13% isolated yield, accompanied by 15% of the essentially meso bishemiaminal **53**, following the treatment of bisimide **25** with equimolar quantities of CBS "catalyst" **51** and BH_3•THF.

The opposite regiochemical outcomes for bisimide double reduction with use of a monohydride donor (such as $LiBHEt_3$) versus a multiple hydride donor (such as BH_3•THF) is readily understood when considering the possibility of intramolecular delivery of the second hydride equivalent in the latter case. Following exo face selective monoreduction of **25** with BH_3•THF (or with BH_3•**51**; the enantiodetermining step), the resulting borate complex **57** is perfectly poised to add hydride to the adjacent imide carbonyl group from the endo face (i.e.,

(97) Hayashi's enantioselective hydrosilylation of norbornadiene (ref 71), utilized by Aubé to access diketone **12** en route to (+)-sparteine (Figure 3, eq 4), owes its (C_2-symmetric) regioselectivity to this phenomena. For elaboration on the concept as it relates to the regiodivergent conversion of enantiomers within a racemic mixture by a chiral reagent, see: Kagan, H. B. *Croat. Chem. Acta* **1996**, *69*, 669–680.

(98) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.

(99) Itsuno, S. *Org. React.* **1998**, *52*, 395–576.

(100) Carboxylic acid anhydrides represent the best studied substrate class, see: Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683–5712.

(101) (a) Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 1087–1090. (b) Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773–1789.

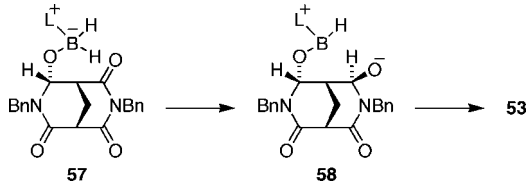
(102) (a) Shimizu, M.; Nishigaki, Y.; Wakabayashi, A. *Tetrahedron Lett.* **1999**, *40*, 8873–8876. (b) Jones, S.; Dixon, R. A. *Tetrahedon: Asymmetry* **2002**, *13*, 1115–1119. (c) Barker, M. D.; Dixon, R. A.; Jones, S.; Marsh, B. J. *Tetrahedron* **2006**, *62*, 11663–11669. (d) Barker, M. D.; Dixon, R. A.; Jones, S.; Marsh, B. J. *Chem. Commun.* **2008**, 2218–2220.

(103) For related work using a chiral thiazazincolidine catalyst, see: Kang, J.; Lee, J. W.; Kim, J. I.; Pyrun, C. *Tetrahedron Lett.* **1995**, *36*, 4265–4268.

(104) (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315–317. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. Review: (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(105) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614.

57 → **58**). The exact regio- and stereochemical identity of **53** is predicated on this basis, and supported by the fact that the isolated material was optically active when the reduction was controlled by **51**. If thermodynamic configurational equilibration of anomeric stereogenic centers in **53** was the principle origin of relative stereochemistry, then the product would be be racemic.



Sakurai-type allylation of **52** and **53** with excess allyltrimethylsilane converted each compound to the expected product in good yield. Bishemiaminal **53** gave the true meso compound **55**, the C_s-symmetry of which was obvious from its ^{1}H NMR spectral signature, while imidolactam **52** gave an allylated adduct (**54**) analogous to the intermediate (**37**) used earlier to access (±)-sparteine (*dl*-**1**). HPLC analysis of **54** on a chiral stationary phase (Daicel Chiralcel OD-RH column) revealed an enantiomeric excess of 71%, the absolute sense of which was not established.[106] Addition of allylmagnesium bromide to **54** proceeded in a like manner to that observed previously for **37** (Scheme 6), and an X-ray crystallographic analysis confirmed the exact nature of the resulting pseudo-C_2-symmetric product **56**. While synthetic possibilities clearly exist for the conversion of intermediates **54** and **56** to sparteine diamines, given the low efficiency of the conversion of **25** to **52**, generation of the optically active target alkaloids along these lines was deemed to hold no practical value and was not further pursued. Nevertheless, the above studies serve a useful purpose in establishing proof-of-principle for reagent controlled enantioselective addition to a tetraoxobispidine platform.

Conclusion

In summary, a new "inside-out" strategy for the preparation of lupine alkaloids of the sparteine subgroup has been successfully demonstrated. All three diastereomeric variants of the parent sparteine tetracyclic skeleton were individually targeted by appropriate synthetic manipulations of a pivotal *N*,*N*′-diallyltetraoxobispidine intermediate (**16**) prepared from malonate via a modified Guthzeit cyclization. Racemic alkaloids, (±)-α-isosparteine (*dl*-**2**), (±)-*β*-isosparteine (*dl*-**3**), and (±)-sparteine (*dl*-**1**), were each concisely elaborated from this common bisimide precursor in good overall yield (i.e., 28%, 12%, and 11%, respectively). Throughout, nucleophilic additions to tetraoxobispidine derived bicyclic electrophiles were found to be exo face selective, and sequential net double additions to such templates gave predominantly C_2-type rather than C_s-type regiomers. The predictable nature of these reactions bodes well for the wider deployment of bisimide synthons such as **16** for the controlled fabrication of other types of nitrogenous heterocycles (e.g., piperidines and bispidines, or tricyclic compounds such as cytisine (**6**) and sparteine surrogate **7**). Various tactics for differentiating the two pairs of enantiotopic carbonyl groups within prochiral C_{2v}-symmetric tetraoxobispidines are potentially available and one such method (chiral oxazaborolidine mediated borane reduction) was shown to offer a useful level of enantioselectivity, albeit in low yield. An entirely satisfactory asymmetric rendering of the alkaloid syntheses described herein awaits a more thorough evaluation of enantioselective additions to bisimides.

Finally, it is sobering to reflect on the fact that in the 60 years since the publication of Leonard and Beyler's total synthesis of (±)-sparteine,[52] no other purely artificial preparation of this important alkaloid (including the work herein) has come close to matching the simple elegance and brevity of that seminal effort. Despite continuing advances,[107] sparteine retains its position as the ligand of choice for a great many metal mediated enantioselective methods and yet a genuinely practical asymmetric synthesis of this long known diamine system that can compete with natural supply remains elusive.

Experimental Section

Propane-1,1,3,3-tetracarboxamide (21). 21 was synthesized by a higher yielding modification of an earlier method.[73] A stirred mixture of dimethyl malonate (300 mL, d = 1.15, 345 g, 2.61 mol) and paraformaldehyde (19.8 g, 0.660 mol) at 75 °C was treated with KOH (3.0 mL, 10 wt % in MeOH) and the resulting solution heated to reflux (ca. 95 °C) for 6 h. The mixture was allowed to cool to rt and shaken with saturated aq NH_4Cl (50 mL). The organic phase was separated and dried (Na_2SO_4), and excess dimethyl malonate was removed by distillation at reduced pressure (water aspirator, bp 80−90 °C, ca. 30 mmHg). The residual tetramethyl 1,1,3,3-propanetetracarboxylate was treated with conc aq NH_4OH (400 mL) and the initially biphasic mixture stirred vigorously for 15 h at rt. During this time a colorless precipitate formed. The insoluble solid was removed by filtration, triturated with EtOAc−MeOH (2:1, 500 mL), and dried in vacuo to afford tetraamide **21** (102.5 g, 0.474 mol, 72%) as a colorless powder: mp 256−257 °C (MeOH); IR (KBr) 3385, 3188, 1656, 1419, 1383, 1346, 615 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.18 (4H, s), 7.05 (4H, s), 2.95 (2H, t, J = 7.5 Hz), 2.00 (2H, t, J = 7.4 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 170.7 (4C, 0), 50.3 (2C, 1), 28.3 (2) ppm; MS (ES) m/z 239 (M + Na)$^+$, 217 (M + H)$^+$; HRMS (ES) m/z 239.0755 (calcd for $C_7H_{12}N_4O_4Na$ 239.0756).

2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonane (22). 22 was synthesized by a higher yielding modification of an earlier method.[73] A 1 L round-bottomed flask was charged with tetraamide **21** (22.8 g, 105 mmol) and MsOH (21.4 mL, d = 1.48, 31.7 g, 330 mmol) and the resulting paste was manually stirred with a metal spatula while a "cool" (yellow-blue) Bunsen burner flame was applied for 10 min. During heating, an initial period of intense effervescence was observed, which subsided to leave a gently boiling homogeneous yellow liquid (internal temp 170−180 °C). The liquid was allowed to cool to rt and triturated with MeOH (100 mL) to induce crystallization, then the resulting suspension stirred for 12 h. The solid was filtered off, pulverized, then suspended in fresh MeOH (100 mL) and heated at reflux for 1 h to dissolve additional residual ammonium mesylate. The suspension was allowed to cool to rt, then filtered to yield bisimide **22** (6.77 g, 95 wt % with NH_4OMs, 35.3 mmol, 33%) as a colorless solid: mp 295 °C dec (H_2O); IR (KBr) 3257, 2838, 1740, 1714, 1339, 1274, 1201, 833, 800, 768 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 11.44 (2H, s), 3.64 (2H, t, J = 2.8 Hz), 2.59 (2H, t, J = 2.8 Hz) ppm; ^{13}C NMR (75 MHz,

(106) The illustrated enantiomer of **52** is that anticipated on the basis of the standard Corey model (ref 104c) assuming that only exo-face addition of hydride to **25** is possible, and that the *N*-benzyl moiety is the more sterically demanding group (as advocated by Speckamp and Hiemstra for related bicyclic mono-imides, ref 101b). Almost identical results were obtained with Jones' aminoindanol derived oxazaborolidine (ref 102c) in place of the more common CBS-catalyst **51**. In this case, reduction of **25** with the *B*-methyl oxazaborolidine derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol gave the opposite enantiomer of **52** to that generated from the (*S*)-prolinol derived catalyst **51**, but also in ca. 70% ee.

(107) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409–1412.

d_6-DMSO) δ 166.9 (4C, 0), 47.2 (2C, 1), 22.8 (2) ppm; MS (EI) m/z 182 $M^{+\bullet}$. Crystals suitable for X-ray diffraction analysis (Figure 4) were obtained by recrystallization from H_2O.

3,7-Diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (16). **16** was synthesized by a higher yielding modification of an earlier method.[73] A vigorously stirred suspension of bisimide **22** (17.2 g, 94.4 mmol) in anhydrous DMF (180 mL) at 0 °C under Ar was treated portionwise with NaH (9.11 g, 60 wt % disp. in oil, 228 mmol). The ensuing gas evolution ceased within 2 min. The resulting solution was stirred for 3 min and then treated dropwise with neat allyl bromide (19.3 mL, d = 1.43, 27.6 g, 228 mmol). The mixture was warmed to rt and stirred for an additional 2 h. After this time, saturated aq NH_4Cl (50 mL) was added and the quenched reaction mixture was partitioned between H_2O (160 mL) and EtOAc (240 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed successively with H_2O (2 × 80 mL) and brine (35 mL) and then dried (Na_2SO_4) and concentrated in vacuo. The resulting solid residue was triturated with hexanes (65 mL), filtered-off, and sucked dry to afford the pure diallylated product **16** (20.5 g, 78.2 mmol, 83%) as a colorless crystalline solid: mp 130−132 °C (EtOAc); IR (KBr) 3006, 1699, 1361, 1328, 1190, 982, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (2H, ddt, J = 16.8, 10.5, 5.9 Hz), 5.14 (2H, dq, J = 10.5, 1.2 Hz), 5.13 (2H, dq, J = 16.6, 1.2 Hz), 4.36 (4H, dt, J = 5.9, 1.3 Hz), 4.07 (2H, t, J = 2.9 Hz), 2.57 (2H, t, J = 2.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (4C, 0), 130.7 (2C, 1), 119.0 (2C, 2), 48.5 (2C, 1), 42.5 (2C, 2), 22.6 (2) ppm; MS (ES) m/z 263 $(M + H)^+$; HRMS (ES) m/z 263.1027 (calcd for $C_{13}H_{15}N_2O_4$ 263.1032).

Direct Synthesis of (±)-(1*R,5*S**,6*R**)-3,6,7-Triallyl-2,4,8-trioxo-3,7-diazabicyclo[3.3.1]nonane (37) and (±)-(1*R**,4*S**,5*R**,8*S**)-2,6-Dioxo-3,4,7,8-tetraallyl-3,7-diazabicyclo[3.3.1]nonane (39).** A well-stirred solution of bisimide **16** (2.70 g, 10.3 mmol) in anhydrous THF (45 mL) at 0 °C was treated with $NaBH_4$ (274 mg, 7.21 mmol, 0.70 equiv). The resulting mixture was stirred for 4.5 h and then aq HCl (8 mL, 4 M) was added to quench excess borohydride reagent. Following cessation of effervescence (5 min), the mixture was warmed to rt and partitioned between EtOAc (40 mL) and H_2O (20 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 40 mL). The combined organic phases were then washed with saturated aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 2.30 g of a residual pale yellow oil containing a complex mixture of hemiaminals. A stirred solution of the residue (2.30 g) in anhydrous CH_2Cl_2 (25 mL) at rt under Ar was treated with allyltrimethylsilane (4.16 mL, d = 0.719, 2.99 g, 26.2 mmol), followed by the dropwise addition of $BF_3 \cdot OEt_2$ (1.64 mL, d = 1.15, 1.89 g, 13.3 mmol). The mixture was stirred for 40 h at rt, and then diluted with CH_2Cl_2 (30 mL), washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue (2.55 g) was purified by column chromatography (SiO_2, eluting with 0−2% MeOH in CH_2Cl_2) to afford, in order of elution, pure triene **37** (829 mg, 2.88 mmol, 28%) and a mixture of **37** and tetraene **39** [640 mg, **37**:**39** = 22:78 mol: effectively, **37** (134 mg, 0.465 mmol, 5%), **39** (506 mg, 1.61 mmol, 16%)], as colorless oils. Data for **37**: IR (neat) 3082, 2949, 1739, 1684, 1455, 1357, 1194, 995, 922, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78−5.66 (2H, m), 5.65−5.54 (1H, m), 5.24−5.06 (6H, m), 4.51 (1H, dm, J = 15.2 Hz), 4.37−4.25 (2H, m), 3.70 (1H, dm, J = 9.6 Hz), 3.67−3.64 (1H, m), 3.49 (1H, dd, J = 15.3, 7.4 Hz), 3.13−3.09 (1H, m), 2.71 (1H, dm, J = 14.5 Hz), 2.37 (1H, ddd, J = 13.8, 3.2, 2.1 Hz), 2.29−2.20 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (0), 168.1 (0), 163.0 (0), 132.8 (1), 132.0 (1), 131.4 (1), 120.0 (2), 119.0 (2), 118.2 (2), 58.7 (1), 48.3 (1), 47.8 (2), 42.1 (2), 39.9 (1), 36.7 (2), 19.8 (2) ppm; MS (EI) m/z 288 ($M^{+\bullet}$, 6%), 247 (100%), 193 (20%), 164 (32%), 136 (36%); HRMS (EI) m/z 288.1478 (calcd for $C_{16}H_{20}N_2O_3$ 288.1474). The authenticity of **39** was confirmed by comparison to spectral data collected previously from a pure sample obtained via the multistep conversion sequence.[74]

(±)-(1*R,2*R**,5*R**,6*S**)-4,8-Dioxo-2-hydroxy-2,3,6,7-tetraallyl-3,7-diazabicyclo[3.3.1]nonane (42).** A vigorously stirred solution of triene **37** (405 mg, 1.40 mmol) in anhydrous THF (11 mL) at −78 °C under Ar was treated dropwise with allylmagnesium bromide (2.47 mL, 0.74 M in Et_2O, 1.83 mmol). After 25 min at −78 °C, saturated aq NH_4Cl (5 mL) was added and the quenched reaction mixture was partitioned between EtOAc (20 mL) and H_2O (20 mL). The layers were then separated and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was further purified by column chromatography (SiO_2, eluting with 0−50% EtOAc in hexanes) to yield tetraene **42** (240 mg, 0.727 mmol, 52%) as a colorless oil: IR (neat) 3329, 3071, 2972, 1643, 1613, 1432, 1157, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80−5.43 (4H, m), 5.32 (1H, d, J = 1.9 Hz), 5.07−4.88 (8H, m), 4.25 (1H, ddt, J = 15.2, 4.9, 1.6 Hz), 4.01 (1H, ddm, J = 14.9, 6.6 Hz), 3.76 (1H, ddm, J = 14.9, 5.2 Hz), 3.55−3.43 (2H, m), 2.75−2.62 (3H, m), 2.54 (1H, dm, J = 14.6 Hz), 2.24 (1H, ddd, J = 14.3, 9.7, 1.8 Hz), 2.13 (1H, dt, J = 14.4, 9.6 Hz), 1.99 (2H, t, J = 3.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (0), 169.1 (0), 134.7 (1), 133.0 (1), 132.6 (1), 131.5 (1), 118.8 (2C, 2), 118.1 (2), 116.4 (2), 87.2 (0), 58.8 (1), 47.6 (2), 43.1 (2), 42.8 (2), 42.5 (1), 39.0 (1), 35.8 (2), 16.8 (2) ppm; MS (EI) m/z 330 ($M^{+\bullet}$, <5%), 289 (100%), 206 (20%); HRMS (EI) m/z 330.1946 (calcd for $C_{19}H_{26}N_2O_3$ 330.1944).

(±)-$\Delta^{3,13}$-Didehydro-10,17-dioxo-6-hydroxy-β-isosparteine (44). A solution of tetraene **42** (465 mg, 1.41 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt under N_2 was treated with $(Cy_3P)(H_2IMes)Cl_2Ru{=}CHPh$ (22 mg, 0.026 mmol)[88] and the resulting mixture was stirred at reflux for 7 h. After this time, the mixture was cooled to rt and concentrated in vacuo, then the residue was purified by column chromatography (SiO_2, eluting with 1% MeOH in CH_2Cl_2) to afford the unsaturated tetracycle **44** (354 mg, 1.29 mmol, 92%) as a colorless solid: mp 223−225 °C (EtOAc−MeOH); IR (KBr) 3270, 3036, 2916, 1620, 1429, 1255, 1201, 988, 896, 672 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 5.83−5.74 (1H, m), 5.72−5.58 (3H, m), 5.54 (1H, s), 4.75 (1H, dm, J = 18.7 Hz), 4.54 (1H, dm, J = 18.0 Hz), 3.56 (1H, dd, J = 11.2, 3.8 Hz), 3.47−3.27 (2H, m), 2.70 (1H, dt, J = 3.7, 1.9 Hz), 2.64 (1H, dm, J = 17.8 Hz), 2.58−2.53 (1H, m), 2.35 (1H, tm, J = 13.9 Hz), 2.20−1.99 (4H, m) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 169.0 (0), 165.4 (0), 124.7 (1), 124.3 (1), 123.5 (1), 122.7 (1), 82.9 (0), 54.8 (1), 47.3 (1), 41.6 (2), 40.6 (1), 38.1 (2), 37.1 (2), 31.1 (2), 18.3 (2) ppm; MS (EI) m/z 274 ($M^{+\bullet}$, 6%), 256 (28%), 146 (24%), 84 (100); HRMS (EI) m/z 274.1311 (calcd for $C_{15}H_{18}N_2O_3$ 274.1317). The identity of **44** was confirmed by X-ray diffraction analysis.

(±)-10,17-Dioxo-6-hydroxy-β-isosparteine (45). A mixture of unsaturated tetracycle **44** (125 mg, 0.456 mmol) and 10 wt % Pd/C (13 mg) in MeOH−H_2O (3:1, 8 mL) was stirred vigorously under 1 atm of H_2 at rt for 8 h. The active gas was then purged with N_2, and the mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a celite pad. The filter cake was washed with CH_2Cl_2 (2 × 10 mL) and the filtrate and combined washings dried (Na_2SO_4) and concentrated in vacuo to yield tetracycle **45** (116 mg, 0.417 mmol, 91%) as a colorless solid: mp 198−200 °C (Et_3N); IR (KBr) 3183, 2943, 1642, 1429, 1190, 1005, 634, 503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (1H, ddt, J = 13.1, 4.3, 1.9 Hz), 4.70 (1H, d, J = 1.0 Hz), 4.40 (1H, ddt, J = 12.8, 4.5, 2.2 Hz), 3.50 (1H, dm, J = 11.3 Hz), 3.18 (1H, td, J = 13.0, 3.1 Hz), 2.73 (1H, dt, J = 3.3, 2.7 Hz), 2.62−2.58 (1H, m), 2.52 (1H, td, J = 12.9, 2.8 Hz), 2.23−2.05 (3H, m), 2.00−1.93 (1H, m), 1.90−1.55 (8H, m), 1.47−1.30 (2H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (0), 167.4 (0), 84.2 (0), 59.9 (1), 47.0 (1), 43.8 (2), 42.6 (1), 37.7 (2), 37.5 (2), 32.0 (2), 25.4 (2), 25.1 (2), 24.9 (2), 20.2 (2), 19.4 (2) ppm; MS (EI) m/z 278 ($M^{+\bullet}$, <5%), 260 (100%); HRMS (EI) m/z 278.1635 (calcd for $C_{15}H_{22}N_2O_3$: 278.1631). Crystals suitable for X-ray diffraction analysis (see the Supporting Information) were obtained by recrystallization from Et_3N.

(±)-Sparteine (*dl*-1). *dl*-**1** was synthesized by a modification of O'Brien's method.[57] A stirred solution of bislactam **45** (55 mg, 0.198 mmol) in anhydrous THF (1.3 mL) at 0 °C under N_2 was treated with excess $LiAlH_4$ (79 mg, 2.08 mmol). The resulting suspension was heated to a gentle reflux and stirred for 16 h. The mixture was then cooled to rt and moistened Na_2SO_4 added portionwise until effervescence ceased. After being stirred for a further 30 min, the quenched reaction mixture was filtered through a shallow celite pad and the solids washed with $MeOH-CH_2Cl_2$ (1:9, 20 mL). The filtrate and combined washings were then dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to Kuglerohr distillation (130−140 °C, <5 mmHg) to yield the title alkaloid *dl*-**1** (37 mg, 0.158 mmol, 80%) as a colorless oil: IR (neat) 3395 (H_2O), 2927, 2856, 2758, 1647, 1446, 1353, 1288, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.76 (1H, dm, J = 12.2 Hz), 2.70−2.62 (2H, m), 2.51 (1H, dm, J = 10.9 Hz), 2.32 (1H, dd, J = 11.2, 3.5 Hz), 2.08−1.90 (4H, m), 1.82−1.77 (1H, m), 1.74−1.63 (3H, m), 1.60−1.15 (12H, m), 1.04 (1H, dt, J = 12.0, 2.4 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.7 (1), 64.5 (1), 62.1 (2), 56.4 (2), 55.5 (2), 53.6 (2), 36.2 (1), 34.5 (2), 33.2 (1), 29.5 (2), 27.8 (2), 26.0 (2), 25.8 (2), 24.9 (2), 24.8 (2) ppm; MS (ES) m/z 235 $(M + H)^+$; HRMS (ES) m/z 235.2161 (calcd for $C_{15}H_{27}N_2$ 235.2169). Essentially identical IR and NMR spectra were obtained from a commercial (Aldrich) sample of natural (−)-sparteine (*l*-**1**) recorded under the same conditions (nb. NMR signals show a slight concentration dependence).[93]

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Supporting Information Available: General methods and all other experimental procedures not previously described, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds, as well as CIF files for compounds **22**, **30**, *s*-**32**, **44**, **45**, and **56**.[86] This material is available free of charge via the Internet at http://pubs.acs.org.

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