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Title: Total Synthesis of Sparteine Alkaloids from a Common Tetraoxobispidine Intermediate

Abstract approved:

Paul R. Blakemore

In previous work (Blakemore et al. *Org. Lett.* **2005**, *7*, 4721; *Heterocycles* **2006**, *70*, 609), successful elaborations of the lupine alkaloids (±)-$\alpha$-isosparteine (*dl*-**2**) and (±)-$\beta$-isosparteine (*dl*-**3**) were realized from a common tetraoxobispidine precursor, 3,7-diallyl -2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (**93**). Herein, the tetraoxobispidine approach to lupine alkaloids was extended to a total synthesis of (±)-sparteine (*dl*-**1**), a second generation improved route to (±)-$\beta$-isosparteine (*dl*-**3**) was established, and various novel synthetic manipulations of tetraoxobispidines were evaluated. The pivotal intermediate (**93**) was prepared in an optimized 16% overall yield (*c.f.* 9% previously reported) from dimethyl malonate and paraformaldehyde via acid-promoted cyclization of the

Knoevenagel condensation adduct 1,1,3,3-propanetetracarboxamide (**107**), followed by N,N´-diallylation of the resulting 2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (**108**). Bisimide **93** was advanced to (±)-sparteine (*dl*-**1**) in 12% overall yield via six operations: (a) monoreduction of the bisimide (**93**) with sodium borohydride, (b) Sakarai-type allylation of the hemiaminal (**97**), (c) nucleophilic addition of allylmagnesium bromide to the remaining imide (**98**), (d) double ring-closing olefin metathesis of the resulting tetraenyl bicyclic hydroxybislactam (**104**) to yield a tetracyclic diene intermediate (**126**), (e) hydrogenation of alkene moieties, and finally, (f) exhaustive reduction with lithium aluminum hydride. It was discovered that the sodium borohydride reduction [step (a)] also gave a $C_2$-symmetric bishemiaminal (**116**) as a minor by-product: double Sakarai-type allylation of this compound generated a tetraenylbislactam intermediate (**100**) identical to that employed in the original synthesis of (±)-$\beta$-isosparteine. As such, the tetraoxobispidine route to (±)-$\beta$-isosparteine was effectively shortened to just five net steps from bisimide **93** (*c.f.* seven steps previously). A variety of known methods for the enantioselective addition of hydride and allyl nucleophiles to aldehydes were applied to $C_{2V}$-symmetric bisimide **93** in an attempt to realize an efficient asymmetric synthesis of sparteine alkaloids. None of the methods investigated, which included Keck allylation and Noyori transfer hydrogenation, gave any trace of addition adducts, reflecting the comparatively low intrinsic reactivity of imides. Finally, the reduction of *N,N´*-dibenzyltetraoxobispidine (**149**) to *N,N´*-dibenzylbispidine

(**150**) was realized in 25% yield using sodium bis(methoxyethoxy)aluminum hydride (Red-Al). It was therefore established that tetraoxobispidines unsubstituted on the methylene bridge are viable precursors to potentially useful biologically active bispidines.

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# Total Synthesis of Sparteine Alkaloids from a Common Tetraoxobispidine Intermediate

by
John Melbardis

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APPROVED:

Major Professor, representing Chemistry

Chair of the Department of Chemistry

Dean of the Graduate School

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John Melbardis, Author

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# Total Synthesis of Sparteine Alkaloids from a Common Tetraoxobispidine Intermediate

## Chapter 1: Introduction

### 1.1 The sparteine subgroup of lupin alkaloids

The lupin alkaloids are various quinolizidine (**4**) bases found mostly in genera within the Leguminosae (Fabaceae) family; especially within the Papilionaceae (Faboideae) sub-family. Common legumes containing these alkaloids include Scotch broom (*Cytisus scoparius*), lupin (numerous species of the genus *Lupinus*), gorse (evergreen shrubs of the genus *Ulex*), and laburnum (*L. anagyroides* and *L. alpinum*).[1] Certain lupin alkaloids are also found in the families Chenopodiaceae, Berberidaceae, and Papaveracea.

An important set of lupin alkaloids is the sparteine subgroup, exemplified by a 3,11-diazatetracyclo[7.7.1.$0^{3,8}$.$0^{11,16}$]heptadecane framework which can take three diastereomeric forms (Figure 1).[2, 3] The most abundant of this kind is the eponymous sparteine (**1**) alkaloid (lupinidine), which contains an *endo-exo* placement of hydrogen atoms at C6 and C11 (sparteine numbering). This alkaloid is prevalent in nature as the levorotatory enantiomer, particularly among papilionaceous plants such as Scotch broom (*Cytisus scoparius*), from which it is readily extracted. The remaining two diastereomers are $C_2$-symmetric, with an *exo-exo* (α-isosparteine, **2**) or *endo-endo* (β-isosparteine, **3**) fusion at C6 & C11.

With the exception of (+)-α-isosparteine, all of the sparteine stereoisomers have been found to be naturally occurring.

The sparteine alkaloids contain two quinolizidine (**4**) rings (A-B & C-D of **1**) fused to form a central bispidine (**5**) core (B-C of **1**). Other alkaloids with this framework include lupanine (**13**) and anagyrine (**14**) (Scheme 1, p. 5), which can be used to semi-synthesize sparteine (*l*-**1**). Cytisine (**7**, Figure 2), which lacks the D-ring of this skeleton, is an important lupin alkaloid employed in the semi-synthesis of O'Brien's (+)-sparteine surrogate (**90**, Scheme 18, p. 26).

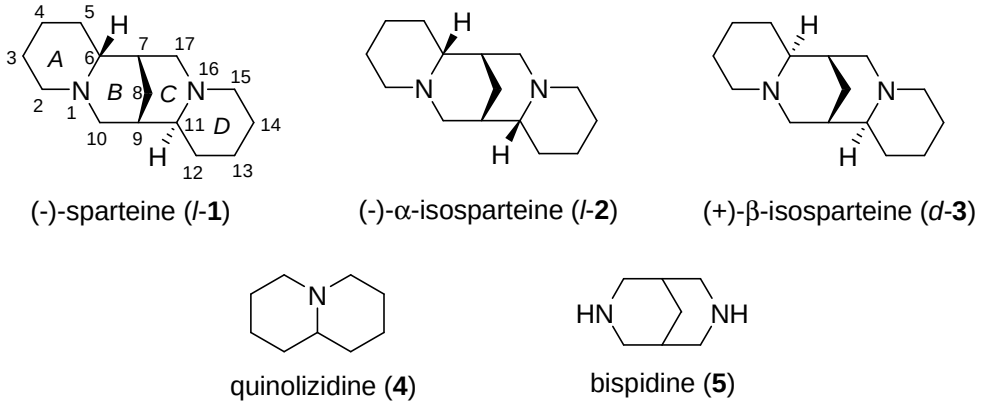
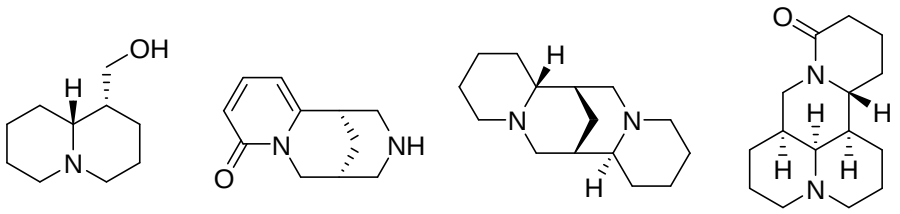



Figure 1: The three sparteine diastereomers
with their quinolizidine (**4**) and bispidine (**5**) cores

The sparteine series is one of four main subgroups of lupin alkaloids. These four consist of the common type of bicyclic alkaloids (lupinine (**6**) type), the tricyclic alkaloids (cytisine (**7**) type), and the tetracyclic alkaloids of the sparteine (**1**) and matrine (**8**) series.[4, 1]




lupinine (**6**) cytisine (**7**) sparteine (**1**) matrine (**8**)

Figure 2: Representative compounds from
the four main subgroups of lupine alkaloids

A number of more unusual structures makes up a fifth group (Figure 3), which are currently believed to be metabolites of lupine alkaloids and/or possible intermediates of other secondary metabolites in the plants.[5] This would suggest that the lupine alkaloids are not functionless waste products (as has previously been suggested),[3] but play a physiological role yet to be established.

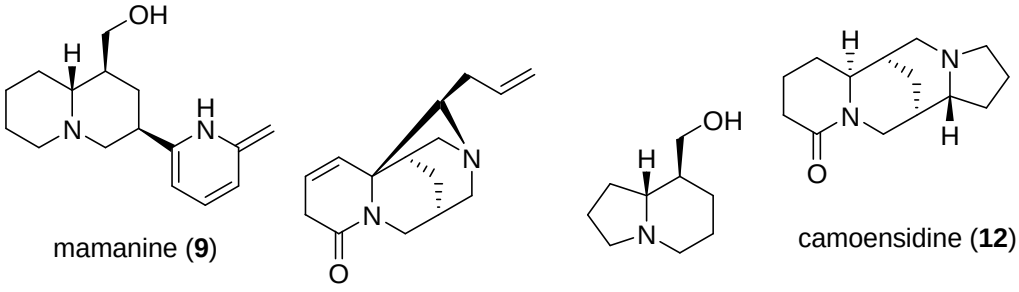



Figure 3: Representative compounds from
the anomalous fifth subgroup of lupine alkaloids

## 1.2 Sparteine

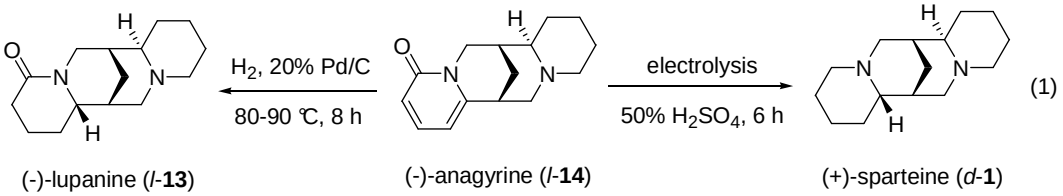
### 1.2.1 Isolation and identification

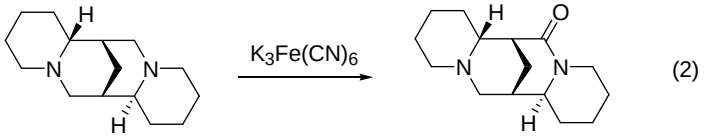
The eponymous and most abundant sparteine alkaloid (*l*-**1**) was first isolated in 1851 by Stenhouse, who also determined its molecular formula ($C_{15}H_{26}N_2$).[6] The correct tetracyclic structure, however, remained elusive for another 82 years. In 1903, Moureu and Valeur correctly postulated the presence of two tertiary nitrogen atoms and four rings,[7] but later incorrectly concluded sparteine (*l*-**1**) was a symmetrical compound with bridgehead nitrogen atoms.[8]

In 1928 Clemo and Leitch reported on the reduction of *dl*-lupanine (**13**) (an alkaloid found as a racemate in *Lupinus albus*, *Lupinus termis*, *Podalyria buxifolia*, *Podalyria sericea*, and *Virgilia capensis*) to "deoxylupanine",[9] later shown to be *dl*-sparteine (found as a racemate in *Cytisus proliferus*). At that time the structure of neither alkaloid was known, and the relationship between "deoxylupanine" and *dl*-sparteine remained unclear. Several years later Clemo, Raper, and Tenniswood succeeded in resolving *dl*-lupanine and reducing *d*- and *l*-lupanine to *l*- and *d*-sparteine, respectively, confirming the equivalence of *dl*-sparteine and "deoxylupanine".[10]

In 1933, Clemo and Raper finally confirmed the correct tetracyclic structure of sparteine,[11] supported by independent work from Ing involving anagyrine (**14**) and cytisine (**7**),[12, 13] extracted from the seeds of *Anagyris foetida*. Ing had shown tetra- and hexa-hydroanagyrine to be identical to *l*-lupanine and *d*-

sparteine, respectively, through exhaustive reduction of anagyrine (Scheme 1, equation 1).[14] This evidence, in addition to the alkaline ferricyanide oxidation of *dl*-sparteine to *dl*-oxosparteine (Scheme 1, equation 2),[15] proved to be key factors in determining the correct structure of *dl*-sparteine.




Scheme 1: Key transformations in the structural elucidation of sparteine (*dl*-**1**)

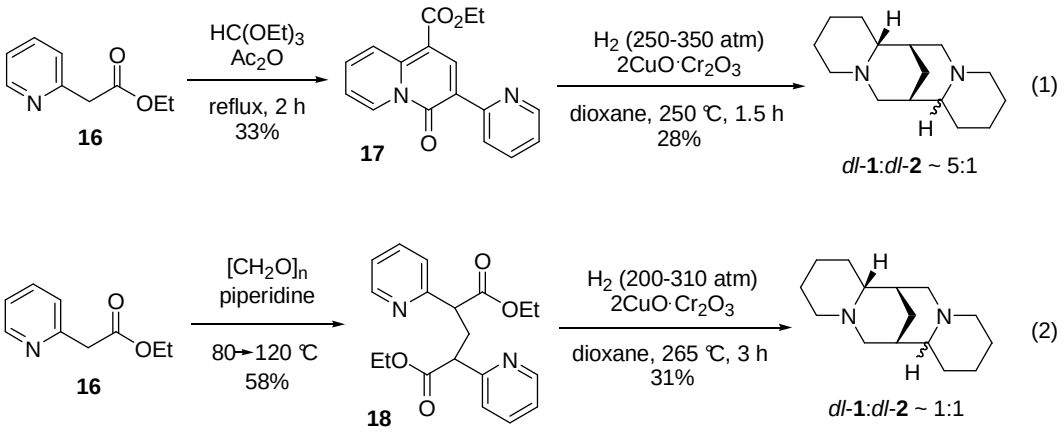
## 1.2.2 First total synthesis

The first total synthesis of *dl*-sparteine, and by far still the shortest to date, was a simple two-step procedure reported by Leonard and Beyler in 1948.[16] Proceeding from ethyl-2-pyridylacetate (**16**) according to the method of Clemo, Morgan, and Raper,[17] 1-carbethoxy-4-keto-3-(2'-pyridyl)-pyridocoline (**17**) was prepared through condensation with ethyl orthoformate in the presence of acetic anhydride (Scheme 2, equation 1). The second step was that of reductive cyclization, employing a procedure previously developed by Leonard for the synthesis of pyrrolizidines,[18] in which the pyridocoline (**17**) was hydrogenated

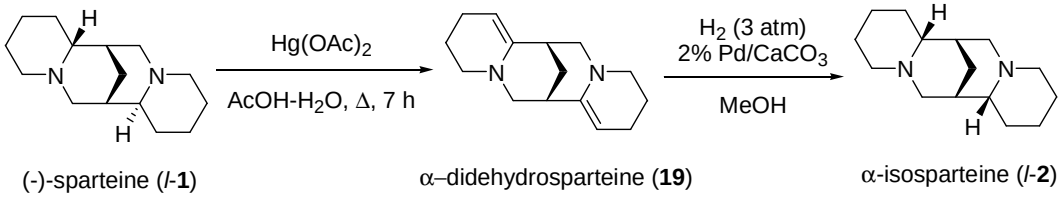
over catalytic copper chromite at 250 °C and 350 atm to afford synthetic sparteine (*dl*-**1**).

The following year, Leonard and Beyler announced the successful resolution of racemic sparteine with β-camphorsulfonic acid.[19] Full details of his sparteine synthesis were disclosed in 1950, which included the synthesis of *dl*-α-isosparteine (*dl*-**2**). An alternate route to sparteine through diethyl 2,4-di(α-pyridyl)-glutarate (**18**) was also specified (Scheme 2, equation 2). The condensation of two molecules of ethyl 2-pyridylacetate (**16**) with one formaldehyde was carried out according to the method of Sorm and Keil,[20] who had prepared the corresponding dimethyl ester. The previously described conditions for reductive cyclization of the glutarate were employed to yield a 1:1 mixture of sparteine (*dl*-**1**) and an "isosparteine".

This "isosparteine" was shown to be the racemate of the *l*-α-isosparteine obtained by Winterfeld and Rauch in 1934.[21] Repeating their isomerization procedure, natural *l*-sparteine (*l*-**1**) was dehydrogenated by the use of mercuric acetate and followed by addition of two molecules of hydrogen to the intermediate didehydrosparteine (Scheme 3). The product was identical to the levorotatory enantiomer of Leonard's "isosparteine".




Scheme 2: Leonard & Beyler first total synthesis of (±)-sparteine (*dl*-**1**)

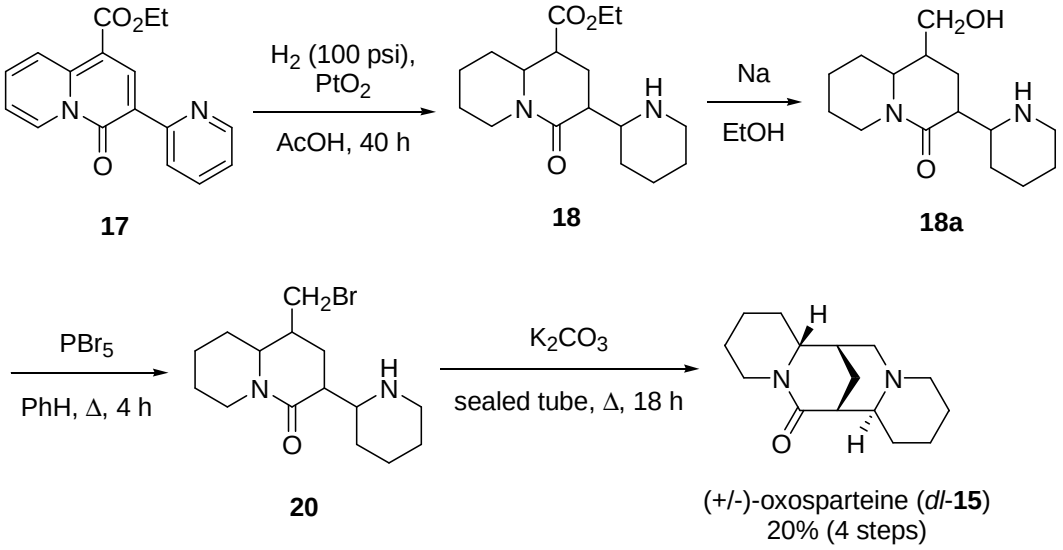



Scheme 3: Sequence to establish the equivalence
of Leonard's racemic "isosparteine" with (±)-α-isosparteine (*dl*-**2**)

## 1.2.3 Similar subsequent syntheses

Over a decade before communication of the Leonard-Beyler synthesis of sparteine, Clemo, Morgan, and Raper had prepared *dl*-oxosparteine (**15**) through a multi-step procedure from pyridocoline **17** (Scheme 4).[17] The pyridocoline (**17**) was prepared by Knoevenagel condensation of ethyl 2-pyridylacetate (**16**) with ethyl orthoformate, the same procedure later adopted by Leonard (Scheme 2).[16, 18] Electrolytic reduction of **17** failed to produce the desired *dl*-oxosparteine (**15**) directly, so a more circuitous approach was initiated by reduction to the

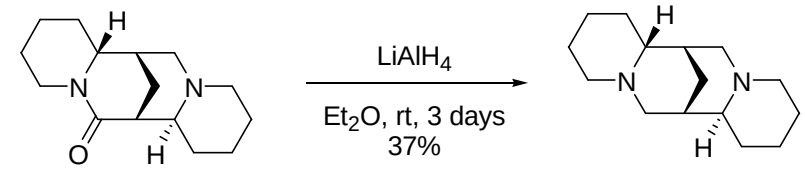
octahydropyridocoline **18** with Adams's catalyst. Submission to the Bouveault-Blanc reduction yielded the corresponding alcohol (**18a**), which upon treatment with phosphorus pentabromide gave the corresponding bromide (**20**). The crude residue carried through thus far was finally heated in a sealed tube with anhydrous potassium carbonate to give *dl*-oxosparteine (**15**) in 20% overall yield from pyridocoline **17**.




Scheme 4: Clemo, Morgan, & Raper's synthesis of *dl*-oxosparteine (**15**)

Although the carbonyl group in *dl*-oxosparteine (**15**) is structurally similar to that in *dl*-lupanine (**13**), the reduction of *dl*-oxosparteine (**15**) to *dl*-sparteine (**1**) could not be accomplished with reagents available at that time. However, the synthesis of *dl*-oxosparteine (**15**) served to establish its identity with the alkaline ferricyanide oxidation product of *dl*-sparteine (**1**) (Scheme 1, equation 2). In 1948, shortly after the appearance of Leonard & Beyler's first total synthesis of

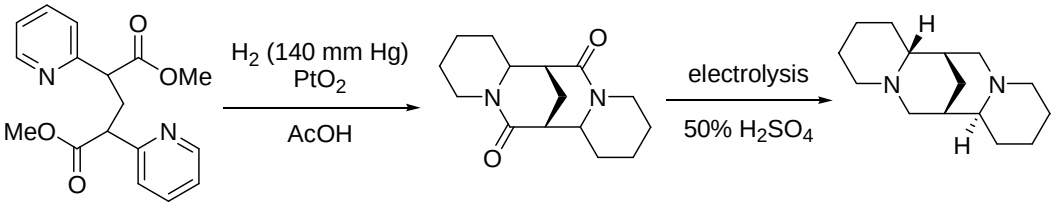
*dl*-sparteine (**1**), Clemo, Raper, and Short reported a successful reduction of *l*-oxosparteine (*l*-**15**) to *l*-sparteine (*l*-**1**) by means of lithium aluminum hydride (Scheme 5).[22, 23]




(-)-oxosparteine (*l*-**15**) (-)-sparteine (*l*-**1**)

Scheme 5: Clemo, Raper, & Short's successful reduction of *l*-oxosparteine (*l*-**15**) to *l*-sparteine (*l*-**1**)

Shortly thereafter, Sorm and Keil announced their own successful synthesis of sparteine (*dl*-**1**) through electrolytic reduction of a dioxosparteine (**22**) (Scheme 6).[24] In analogous fashion, 2,4-di-(2'-pyridyl)-dimethylglutarate (**21**) was subjected to hydrogenation in the presence of Adams's catalyst. A diastereomeric pair of dioxosparteines[25] was obtained, which were separately subjected to electrolytic reduction in 50% sulphuric acid with activated lead electrodes to give three $C_{15}H_{26}N_2$ bases, isolated as their dipicrates. The dipicrate of m.p. 205 °C was identified with racemic sparteine (*dl*-**1**).




**21** **22** (+/-)-sparteine (*dl*-**1**)

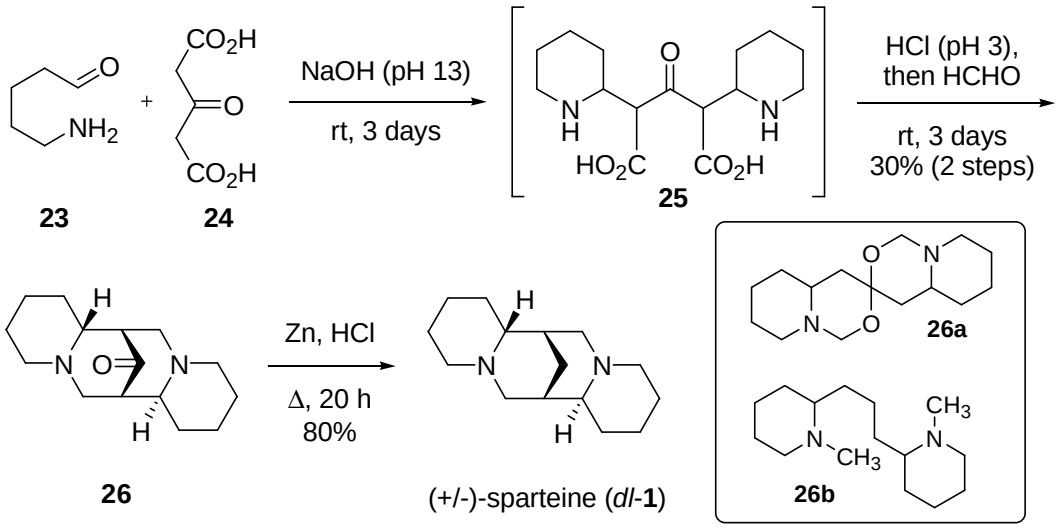
Scheme 6: Sorm & Keil synthesis of *dl*-sparteine (**1**)

### 1.2.4 Early "biomimetic" approaches

Robinson's 1917 theory[26, 27] on the phytochemical synthesis of certain alkaloids inspired a number of early "biomimetic" approaches to sparteine. The biosynthesis of "sparteine" suggested by Robinson was based on an incorrect conception of its structure: a bis-hydroxyquinuclidine, derived from the reduction of a bis-(hydroxyquinuclidyl)-ketone, in turn generated from condensation of three molecules of an acetone derivative, six of formaldehyde, and two of ammonia. However, these Mannich-type processes allowed for Robinson's landmark synthesis of tropinone,[28] the central figure to the tropane alkaloids (ie. atropine, scopolamine, cocaine).

The first ostensible route to *dl*-sparteine along these lines was reported by Anet, Hughes, and Ritchie in 1950 (Scheme 7).[29] A dilute aqueous solution of 5-aminopentanal (**23**) and acetonedicarboxylic acid (**24**) at pH 13 was allowed to stand for 3 days at rt. The solution was then acidified to pH 3 and formaldehyde added, giving *dl*-sparteine-8-one (**26**). Clemmensen reduction then gave *dl*-sparteine (**1**) in high yield. Minor variations in pH were reported to give substantially lower yield, or none, of ketone **26**. However, the synthetic *dl*-sparteine (**1**) obtained was identified only by a mixed melting point, and so this synthesis was discredited several years later by Schopf and co-workers.[30] The latter group suggested that the intermediate taken to be ketone **26** was actually **26a**, with melting point 133 ºC and formula $C_{15}H_{26}N_2O_2$ satisfying the recorded

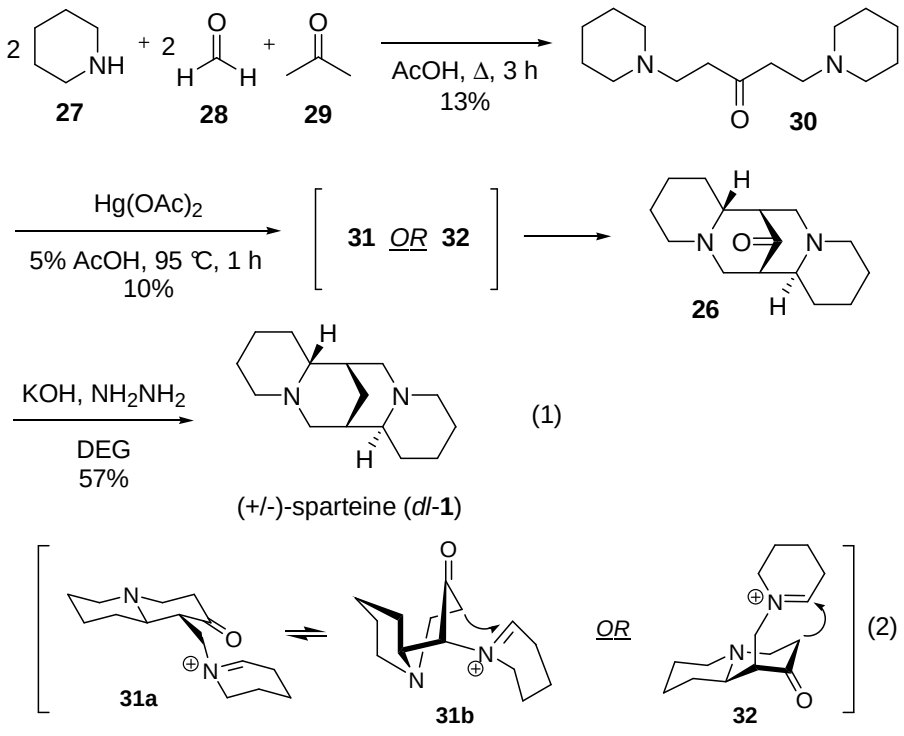
data.[31] The Clemmensen reduction product would then be 1,3-*bis*-(1'-methyl-2'-piperidyl)-propane (**26b**) rather than sparteine (**1**).




Scheme 7: Anet, Hughes, & Ritchie's purported "biomimetic" synthesis of *dl*-sparteine (**1**)

An unambiguously successful approach according to Robinson's prevailing biogenetic theory was reported by van Tamelen and Foltz in 1960[32, 33] (Scheme 8, equation 1). The key β,β'-di-(N-piperidino)-diethyl-ketone precursor (**30**) was prepared through application of a Mannich reaction between piperidine, formaldehyde, and acetone in refluxing glacial acetic acid. The activated diiminium ketone intermediate was prepared by mercuric acetate dehydrogenation of **30** to give *dl*-8-ketosparteine **26**, which was reduced according to the Huang-Minlon modification of the Wolf-Kishner conditions. The product (*dl*-**1**) in this case was identified by its IR spectrum and melting point of several of its salts.

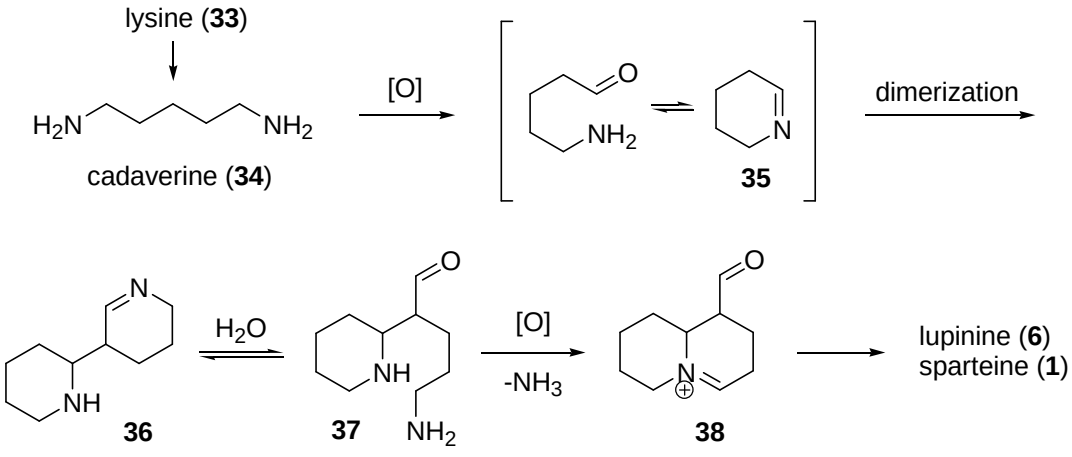
Interestingly, the 8-keto-sparteine (**26**) appeared to be the sole stereoisomer formed under these conditions; noteworthy since α-isosparteine (**2**) is known to be the most stable of the three forms. Consideration of the mechanism can shed some light on this observation, assuming that each new ring is formed in a sequential manner. If the pyridinyl substituent formed in the initially formed quinolizidine system were axial (**32**), epimerization to the more stable equatorial conformation (**31a**) should readily occur (Scheme 8, equation 2). The second ring closure would then have to occur through the less stable conformer (**31b**). Alternatively, cyclization from the less stable axial conformer (**32**) should also lead to the ketosparteine isomer (**26**) as shown.




Scheme 8: Van Tamelen & Foltz "biogenetic-type" *dl*-sparteine synthesis

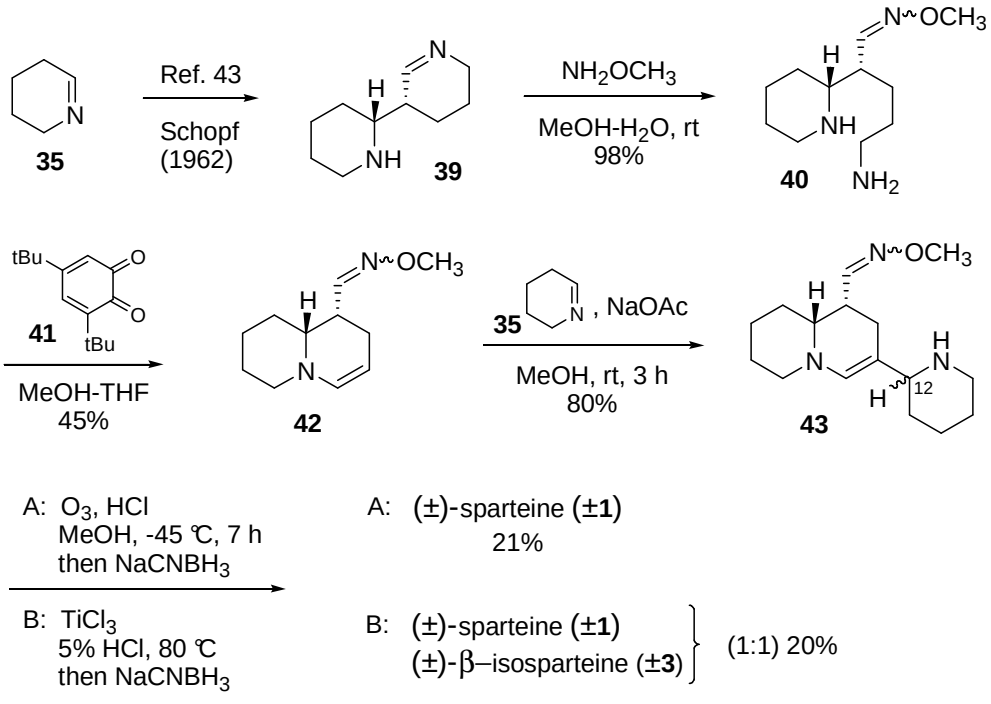
## 1.2.5 Wanner & Koomen's modern biomimetic approach

Other approaches to sparteine based on the Mannich approach were reported in the 70's and 80's.[34, 35] In recent decades an increasing number of lupin alkaloids were identified from various lupin species,[36] and greater attention was given to their biogenesis.[37, 38, 39, 40] Detailed labeling experiments led to the discovery that cadaverine (**34**), and thus lysine (**33**),[41] was the source of these alkaloids (Scheme 9). Diamine oxidase (DAO) catalyzed oxidative deamination of cadaverine (**34**) gives dehydropiperidine (**35**), which spontaneously dimerizes to form tetrahydroanabasine (**36**).[42] Further oxidative deamination proceeds through likely intermediate **37** to give quinolizidine **38**. This hypothetical precursor to sparteine and other lupin-type alkaloids is available in nature in its reduced form, lupinine (**6**).




Scheme 9: Modern biogenetic postulate for the lupin alkaloids

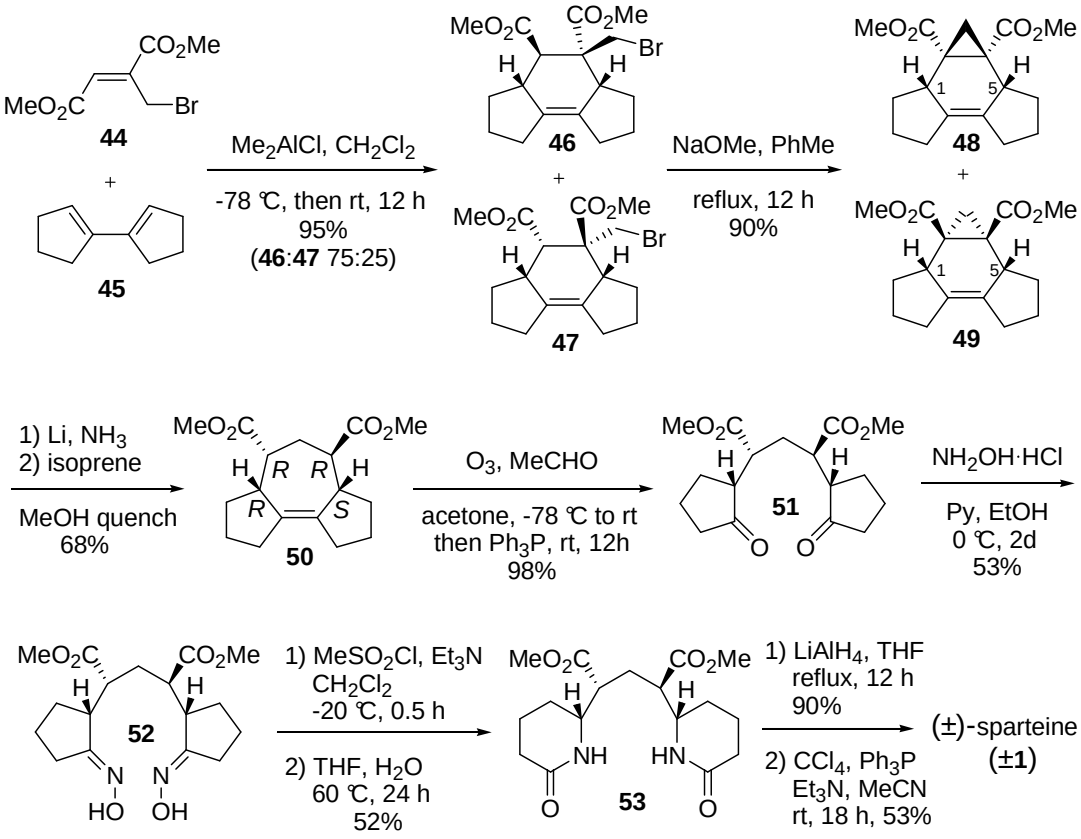
In 1996, Wanner & Koomen reported the first truly biomimetic approach to *dl*-sparteine (**1**) along these lines (Scheme 10).[43] Their common precursor was quinolizidine **42**, obtained in two simple steps from (±)-*trans*-tetrahydroanabasine (**39**), which in turn is easily derived from dehydropiperidine (**35**) trimer.[44] Condensation of **42** with *in situ* monomerized dehydropiperidine (**35**)[45] in buffered methanol proceeded efficiently to form 3-piperidylquinolizidine **43** as a mixture of epimers at C-12. Oxidative removal of the oxime with acidic ozone, however, was slow and incomplete, giving sparteine (*dl*-**1**) in only 21% yield (method A). Reductive hydrolysis at elevated temperature (80-90 °C) with $TiCl_3$/HCl gave similar yields, as a 1:1 mixture of sparteine (*dl*-**1**) and β-isosparteine (*dl*-**3**) (method B).




Scheme 10: Wanner & Koomen biomimetic synthesis of dl-sparteine

### 1.2.6 Butler & Fleming synthesis

Perhaps the most interesting, though lengthy, racemic synthesis of sparteine is Butler & Fleming's 2004 report (Scheme 11).[46, 47] Diels-Alder cycloaddition between dimethyl bromomesaconate (**44**) and diene **45** established the required sparteine stereochemistry at C-1 and C-5 (Scheme 11). Base induced cyclopropanation, followed by lithium-ammonia induced reductive ring expansion of the mixture of cyclopropanes **48** & **49**, gave a 68% yield of the *dis*symmetric R,R,S,S-diastereomer **50** (along with 21% of the corresponding *meso* R,S,R,S-diastereomer). Quenching with methanol was crucial to favor formation of the *dis*symmetric diastereomer **50** as opposed to the *meso* compound. With the relative stereochemistry established, **50** was subjected to ozonolysis in acetone, which was optimized to prevent epimerization of intermediate ketone oxide by the addition of acetaldehyde. Bisoxime (**52**) formation and Beckmann rearrangement gave the bispiperidine **53**, which on reduction with lithium aluminum hydride gave the corresponding bispiperidine diol. Treatment with triphenylphosphine/carbon tetrachloride allowed for double N-alkylation to proceed, giving (±)-sparteine (*dl*-**1**).



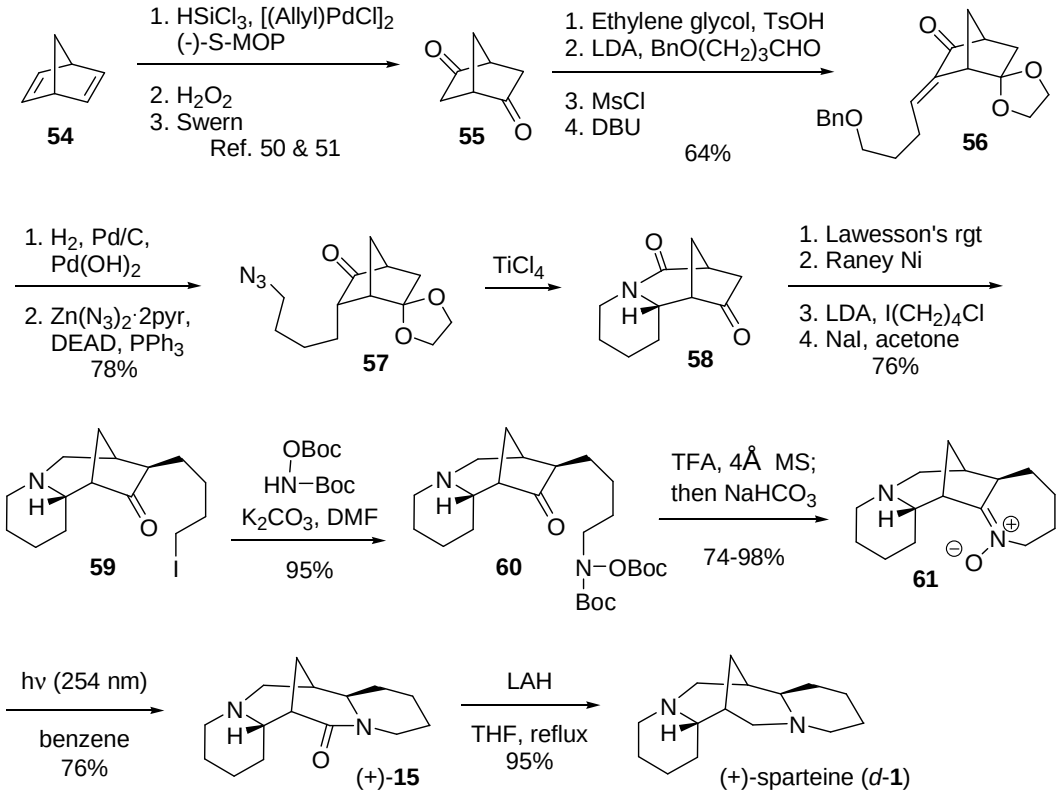

Scheme 11: Butler & Fleming synthesis of *dl*-sparteine

## 1.2.7 Asymmetric syntheses of sparteine

Although eight *racemic* total syntheses of sparteine have been described over the last 60 years,[48] there have been only two successful *asymmetric* syntheses to date – the first appearing only as recently as 2002.[49] As the importance of (-)-sparteine (*l*-**1**) as a ligand in asymmetric synthesis evolved in

the 70's and 80's (Section 1.2.9), interest in a concise preparation of its (+)-antipode mounted.

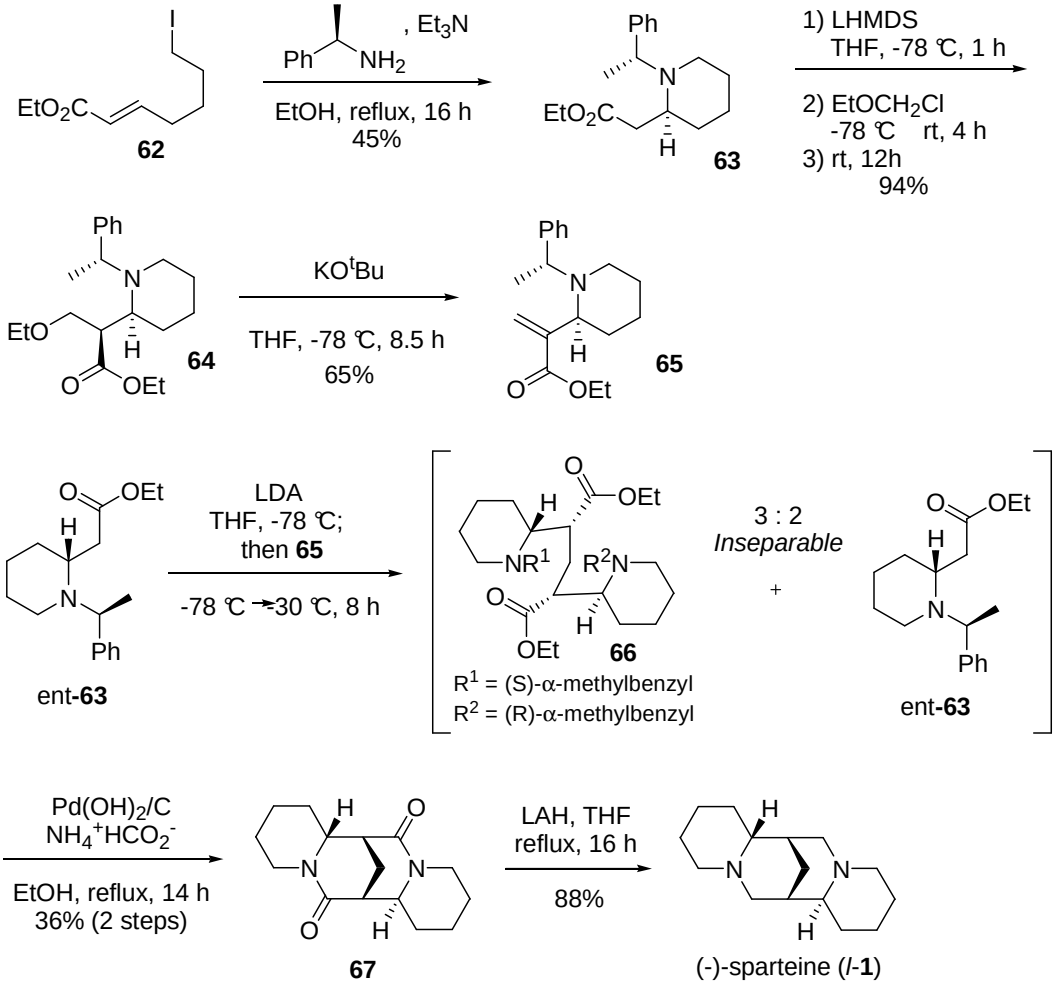
The first asymmetric total synthesis of sparteine was reported by Aubé in 2002,[49, 50] in which (+)-sparteine (*d*-**1**) was prepared from (+)-2,5-norbornadione (**55**) in 15 steps and 15.7% overall yield (Scheme 12). (+)-**55** was prepared from norbornadiene using previously established methods,[51, 52] then underwent aldol reaction with δ-benzyloxyaldehyde, followed by elimination, to give enone **56**. A modified Mitsunobu azidation[53] afforded **57**, which was treated with $TiCl_4$ to provide the intramolecular Schmidt product **58**. Alkylation of the corresponding amine was followed by BocNHOBoc displacement of the iodide in **59**, which upon deprotection gave nitrone **61** through intramolecular condensation. Photo-Beckmann rearrangement[54] afforded smooth conversion to (+)-oxosparteine (+**15**), which was reduced to (+)-sparteine (d-**1**) by the action of lithium aluminum hydride.




Scheme 12: Aubé asymmetric total synthesis of (+)-sparteine

In the most recent synthesis of the alkaloid to date, O'Brien and coworkers reported a concise synthesis of (-)-sparteine (*l*-**1**) in just six steps from ethyl 7-iodohept-2-enoate (**62**) (Scheme 13).[55] Featuring a connective Michael reaction as a key step, Michael acceptor **65** was prepared in three steps from heptenoate **62**. Cyclization of **62** in the presence of (R)-α-methylbenzylamine afforded β-amino ester **63**. A simple alkylation followed by elimination of ethoxide then gave the desired Michael acceptor **65**. The amino ester *ent*-**63** was prepared from (S)-α-methylbenzylamine according to the same method.

The key Michael reaction resulted in an inseparable mixture of desired diastereomer **66** with starting material (*ent*-**63**). However, hydrogenolysis of the mixture was accompanied by cyclization to give bislactam **67** in 36% yield over 2 steps from *ent*-**63**. Reduction with lithium aluminum hydride then gave (-)-sparteine (*l*-**1**).




Scheme 13: O'Brien asymmetric synthesis of (-)-sparteine

### 1.2.8 Biological Activity

(-)-Sparteine (*l*-**1**) saw limited use in the 60's and 70's as an investigational agent in the management of cardiac arrhythmias,[56, 57, 58, 59] as well as in the induction of uterine contractions.[60, 61] Its class 1a anti-arrhythmic activity and general effect on uterine and skeletal muscle appear to be due to a "stabilizing" effect on muscle cell membrane function.[62, 63, 64]

It was believed that this effect may be due to the ligand-metal binding properties of sparteine, which could directly interfere with the dynamic behavior of membrane-associated cations such as magnesium.[65] However, comparative studies with the mononitrate salt of sparteine and its free base in various solvents indicate that the free base binds calcium and magnesium, but the monoprotonated form does not.[66] Under physiological conditions of pH sparteine would exist in its monoprotonated form, indicating alternative mechanism(s) for its biological effects.

Sparteine is limited in potency and has moderate toxicity,[67] causing unpredictable side effects. At lower doses, increased blood pressure and diuretic effects are common, but dangerous heart rhythms and obstetrical complications are possible at moderately high doses. The FDA banned its use in 1979 as an anti-arrhythmic and oxytocic, but sparteine has since been used in human studies related to metabolism by the CYP2D6 enzyme.[68]

### 1.2.9 Applications in synthesis

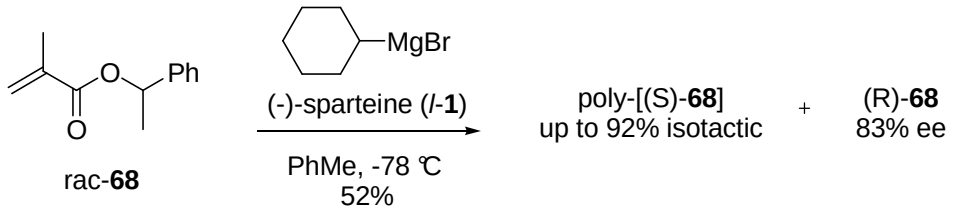
In the carbocyclic analog of (-)-sparteine (*l*-**1**), the A and D rings would be rigid as they are in trans-decalin. However, presence of the nitrogen atoms allows for a conformational change from **1a** to **1b** (the two lowest-energy conformations of (-)-sparteine) via inversion at the nitrogen center (Figure 4).[69] The magnitude of the barrier to this conformational change has been calculated by density functional theory to be only 6.5 kcal/mol, and **1b** (the *chair-chair* conformer) to be only 3.4 kcal/mol higher in energy than **1a** (the ground state *chair-boat* conformer).[70] The **1b** conformer thus makes an ideal bidentate pocket for metal ions – providing a dissymmetric framework for asymmetric transformations.


**1a** **1b**

Figure 4: Conformations of (-)-sparteine

In the years 1968-1970, Nozaki, Aratani, Toraya, and Noyori first studied the suitability of (-)-sparteine as a chiral additive in carbanion reactions,[71, 72, 73, 74, 75] such as asymmetric Grignard additions to benzaldehyde,[72] lithiation of isopropylferrocene and ethylbenzene,[73, 74] and rearrangements of cyclopropyl carbenoids.[71, 75] The enantiomeric excesses achieved at this time were rather low, but these studies established an important historical precedent. Further studies throughout the 70's and 80's met with limited success. Conjugate addition to

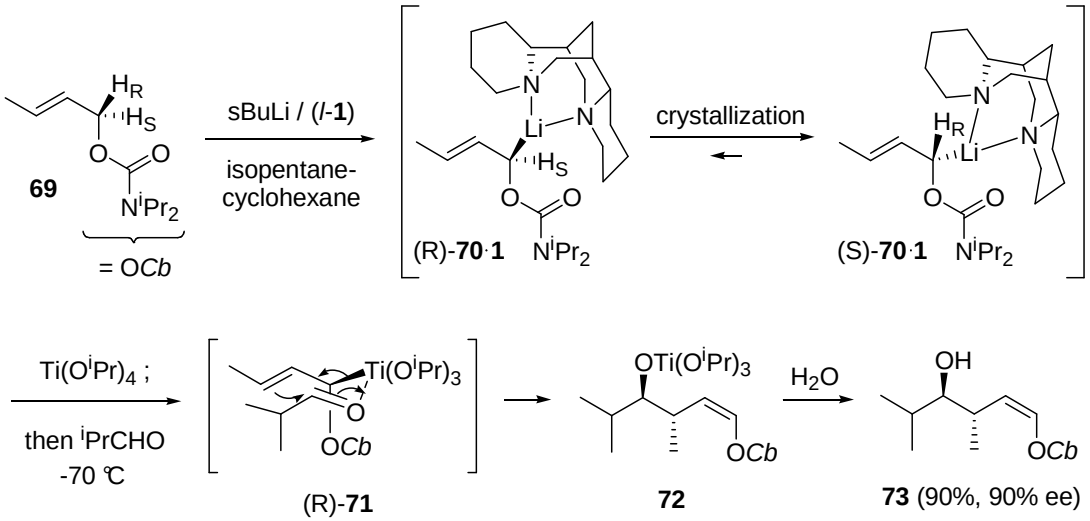
enones,[76] palladium-catalyzed allylation,[77] methyltitanium addition to aldehydes,[78] the Reformatzky reaction,[79, 80] and others were investigated as their (-)-sparteine-mediated asymmetric variants. Stereoselective anionic polymerization, however, did find early success through (-)-sparteine-mediated kinetic resolution. For example, racemic 1-phenylethyl methacrylate (rac-**68**) was transformed into isotactic poly(methacrylate) (poly-[(S)-**68**]) upon treatment with an alkylmagnesium complex in the presence of (-)-sparteine (*l*-**1**) (Scheme 14).[81, 82]




Scheme 14: (-)-Sparteine-mediated anionic polymerization

Not until the work of Hoppe in 1989 was the true potential of (-)-sparteine revealed.[83, 84, 85] Building on the precedent that alkenyl diisopropyl carbamates could be deprotonated with retention of configuration,[86] (E)-2-butenyl carbamate (**69**) was deprotonated in the presence of (-)-sparteine (*l*-**1**) (rather than TMEDA, the usual complexing agent) (Scheme 15). Trapping with tetra(isopropoxy)titanium followed by treatment with 2-methylpropanal led to the (Z)-anti-configured homoaldol adduct **73** in 90% yield and 90%ee. Interestingly, the selectivity here is *not* achieved through kinetic depronation in the first step, but through dynamic thermodynamic resolution of (R)- and (S)-**70•1**. The (S)-

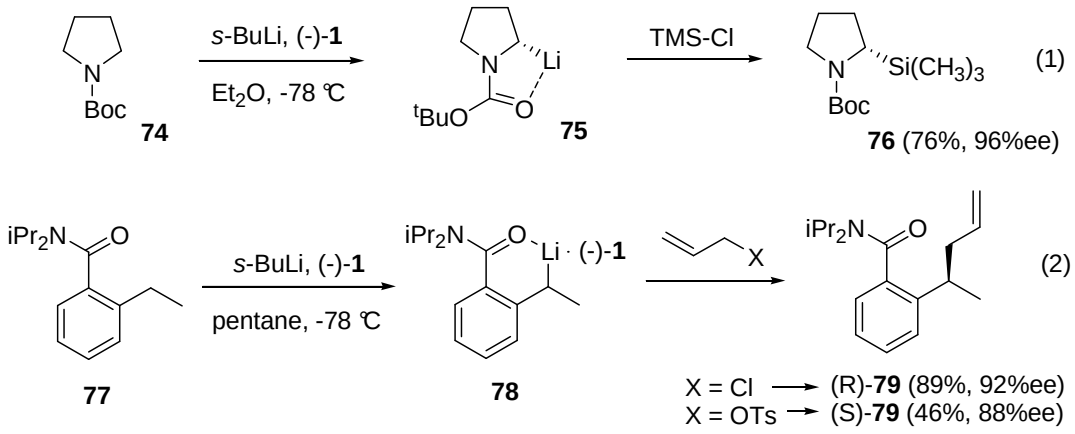
isomer crystallizes preferentially out of the equilibrium mixture of (R)-**70•1** and (S)-**70•1**. It is also possible to trap the intermediate titanium complex with a trialkyl tin chloride, with retention of configuration (through an anti-$S_E$' displacement), producing storable chiral homoenolate reagents.[87]




Scheme 15: Asymmetric homoaldol through
(-)-sparteine-induced dynamic thermodynamic resolution

In the 1990's, Beak and coworkers demonstrated other highly enantioselective transformations involving (-)-sparteine/alkyllithium complexes.[88, 89, 90] Synthesis of 2-substituted pyrrolidines (**76**) through (-)-sparteine-mediated asymmetric deprotonation followed by treatment with electrophiles generated numerous enantioenriched products with ee's greater than 95% (Scheme 16, equation 1).[89] In addition to asymmetric deprotonation and dynamic thermodynamic resolution, mechanistic studies identified a third reaction

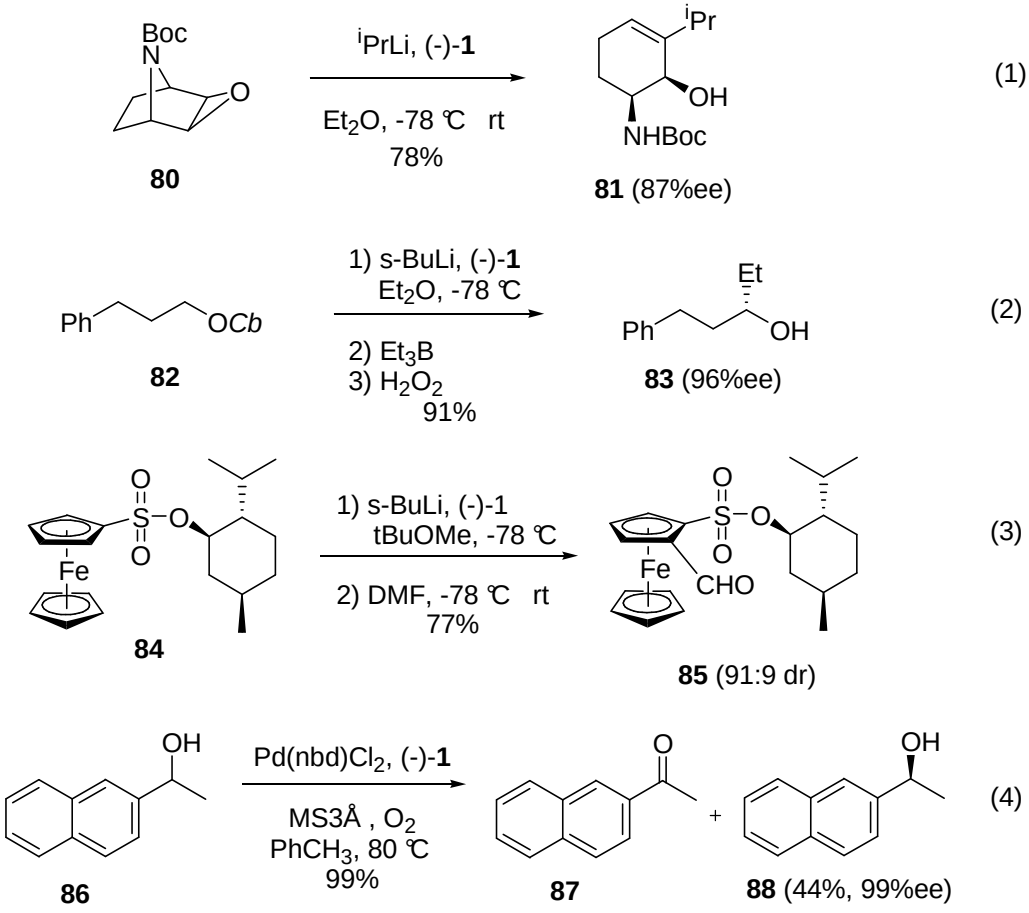
pathway – that of dynamic kinetic resolution. In this case a rapid equilibration of diastereomeric (-)-sparteine-lithium complexes occurs, but stereoselectivity arises from the differences in transition state energies of electrophilic substitution. An illustration of this pathway is the reaction of *o*-ethyl(diisopropyl)benzamide (**77**) with *s*-BuLi/(-)-sparteine at -78 °C followed by allyllation of the resulting **78•(-)-1** complex (Scheme 16, equation 2).[89, 90] A Hoffmann test[91] of configurational stability ruled out the possibility of an asymmetric deprotonation and disfavored (but not necessarily excluded) a dynamic thermodynamic resolution. The fact that the selectivity is reversed with a tosylate as the nucleofuge also supports this hypothesis.




Scheme 16: (-)-Sparteine-mediated asymmetric deprotonation (equation 1) and dynamic kinetic resolution (equation 2)

Recent implementation of (-)-sparteine in asymmetric synthesis includes alkylative desymmetrization of azanorbornene epoxides (Scheme 17, equation 1),[92] amine substitution through borate rearrangements (equation 2),[93, 94] chiral

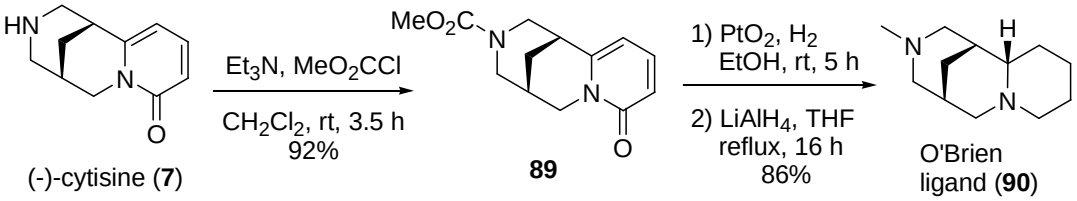
functionalization of ferrocenes (equation 3),[95, 96, 97] and stereoablative oxidative resolution of secondary alcohols (equation 4)[98, 99]. Other applications include asymmetric ring-opening of cyclic meso anhydrides with Grignard reagents,[100] and a non-stereodirecting role in the Crimmins variant of the Ti-mediated Evans aldol reaction.[101]




Scheme 17: Recent applications of (-)-sparteine in asymmetric synthesis

Stereoinduction in the opposite sense has been restricted due to limited natural availability and lack of a practical synthetic route to (+)-sparteine (*d*-**1**).

O'Brien's recently introduced ligand (**90**) has offered a practical solution to a number of these transformations.[102] Prepared in 3 simple steps from natural (-)-cytisine (**7**) (Scheme 18),[103, 104] O'Brien's ligand mimics the A-B-C ring system of (+)-sparteine (*d*-**1**) and has been demonstrated to give similar but opposing stereoselectivity to (-)-sparteine (*l*-**1**) in a number of the above-described reactions - suggesting that the D-ring of sparteine plays a relatively minor role in stereoinduction .[105, 106] Recent studies have also demonstrated the importance of an intact A-ring, and the inferior stereoselectivity of a B-C-D ring analog of sparteine.[107, 108]




Scheme 18: Synthesis of O'Brien's (+)-sparteine surrogate

## 1.3 α- and β-Isosparteine

As early as 1927, Wolffenstein and Reitmann reported a "pseudosparteine", not well-characterized, which was prepared by dehydrogenation of (-)-sparteine (*l*-**1**) with sodium hypobromite, followed by catalytic hydrogenation of the dehydrosparteine.[109] However, (-)-α-isosparteine (*l*-**2**) was obtained unambiguously only after Winterfeld synthesized it from (-)-sparteine (*l*-**1**) in 1934 (Scheme 3).[21] In 1951 it was found to be a naturally

occurring alkaloid – isolated as "genisteine" from *Lupinus caudatus*.[110] (+)-α-isosparteine (*d*-**2**) has yet to be isolated from natural sources.

α-Isosparteine has rarely been a synthetic target in itself,[111, 112, 113] but has been identified as a by-product in a number of lupin alkaloid syntheses, including Leonard & Beyler's seminal total synthesis of sparteine (Scheme 2).[16] However, in 1983 Kakisawa & coworkers reported a remarkable stereoselective synthesis of (±)-α-isosparteine (*dl*-**2**) from 2,3,4,5-tetrahydropyridine 1-oxide and 4H-pyran.[114, 115] More recently, Gallagher and Gray's synthesis of (±)-anagyrine (*dl*-**14**) and (±)-thermopsine (utilizing a Mannich approach) constitute formal syntheses of (±)-sparteine (*dl*-**1**), (±)-α-isosparteine (*dl*-**2**), and (±)-β-isosparteine (*dl*-**3**).[116]

The more sterically encumbered binding pocket in (-)-α-isosparteine (*l*-**2**) produces a less exothermic precomplexation with its organometallics, generally resulting in lower stereoselectivity than (-)-sparteine (*l*-**1**) under comparable conditions.[117] Nevertheless, (-)-α-isosparteine (*l*-**2**) has been demonstrated to be a superior ligand in enantioselective transannular desymmetrization of cyclooctene oxides to bicyclo[3.3.0]octanes.[118]

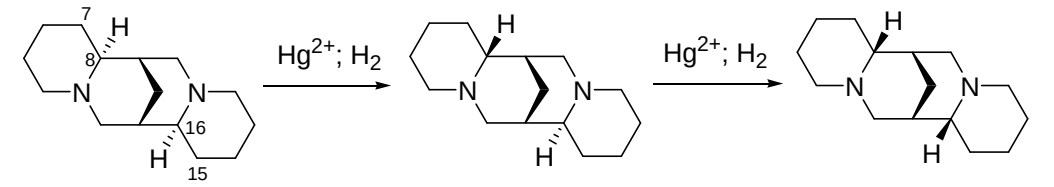
(-)-β-isosparteine (*l*-**3**) was originally isolated in 1948 by Marion & Fenton from *Lupinus pusillus* and designated "pusilline", but mischaracterized as having two more H atoms ($C_{15}H_{28}N_2$) than sparteine.[119] In 1955, a $C_{15}H_{26}N_2$ alkaloid was isolated from specimens of *Lupinus sericeus* and designated "*l*-spartalupine".[120] Through isomerization to (+)-sparteine (*d*-**1**) by the methods of

Winterfeld and Rauch (Scheme 3),[21] this alkaloid was identified as the third remaining enantiomorph of the sparteine series. The following year, Marion & coworkers established the equivalence of their previously isolated "pusilline" with "*l*-spartalupine".[121] (+)-β-isosparteine (*d*-**3**) has only recently been detected in various *Lupinus* species.[122]

Likewise, β-isosparteine has not been a primary synthetic target. It is, however, a product of the Sorm & Keil[24] (Scheme 6) and Wanner & Koomen[43] "sparteine" syntheses (Scheme 10), as well as a formal product of Gallagher & Gray's (±)-thermopsine synthesis.[116] Furthermore, neither enantiomer of β-isosparteine is reported to have been investigated in asymmetric synthesis. However, the lack of an "A-ring", identical to that in (-)-sparteine (with its *exo* H atom), suggests an inferior capacity for enantioselectivity.[108]

## 1.4 Interconversion of sparteine isomers

As previously described (Scheme 3), some interconversion of the sparteine isomers within an enantiomeric series is possible.[21, 123] Beginning with (+)-β-isosparteine (d-**3**), subsequent mercuric ion-mediated oxidation at $\Delta^{7,8}$ and $\Delta^{15,16}$, followed by reductive hydride delivery to the exposed *exo* faces, leads to (-)-sparteine (*l*-**1**) and (-)-α-isosparteine (*l*-**2**) (Scheme 19). Thus, synthesis of β-isosparteine can be considered a formal synthesis of the entire sparteine subgroup. (-)-Sparteine (*l*-**1**) has also been shown to give a mixture of (-)-α- and (+)-β-isosparteine (major:minor) upon heating in $AlCl_3$.[124, 125]

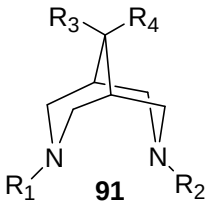



(+)-β-isosparteine (*d*-**3**) (-)-sparteine (*l*-**1**) (-)-α-isosparteine (*l*-**2**)

Scheme 19: Oxidative/reductive interconversion of sparteine isomers

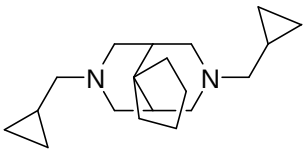
## 1.5 Bispidines

The 3,7-diazabicyclo[3.3.1]nonane (bispidine, **5**) skeleton constitutes the B-C ring system of the sparteine alkaloids. With discovery of the antiarrhythmic properties of sparteine in the 60's and 70's,[56, 57, 58, 59] compounds belonging to the ring system of bispidines became the subject of consideral interest.[126, 127] Solvay Pharmaceuticals of Germany synthesized a large array of 3,7-diazabicyclo[3.3.1]nonane derivatives via Guareschi condensation (Clemens variant), focusing on 3,7,9,9-tetraalkylbispidine derivatives (**91**) (Figure 5).[128] Pharmacological characterization and quantitative structure-activity relationships were examined, leading to tedisamil (KC8857, planned trade name Pulzium) (**92**) as the most promising agent selected for clinical development.[129] In December of 2007, the Cardio-Renal Advisory Committee of the FDA voted against the approval of tedisamil, requesting further information from Solvay.[130]




**91**

$R_1$, $R_2$ = alkyl, alkyenyl
$R_3$, $R_4$ = alkyl




tedisamil (**92**)

Figure 5: 3,7,9,9-tetraalkyl-3,7-diazabicyclo[3.3.1]nonane derivatives

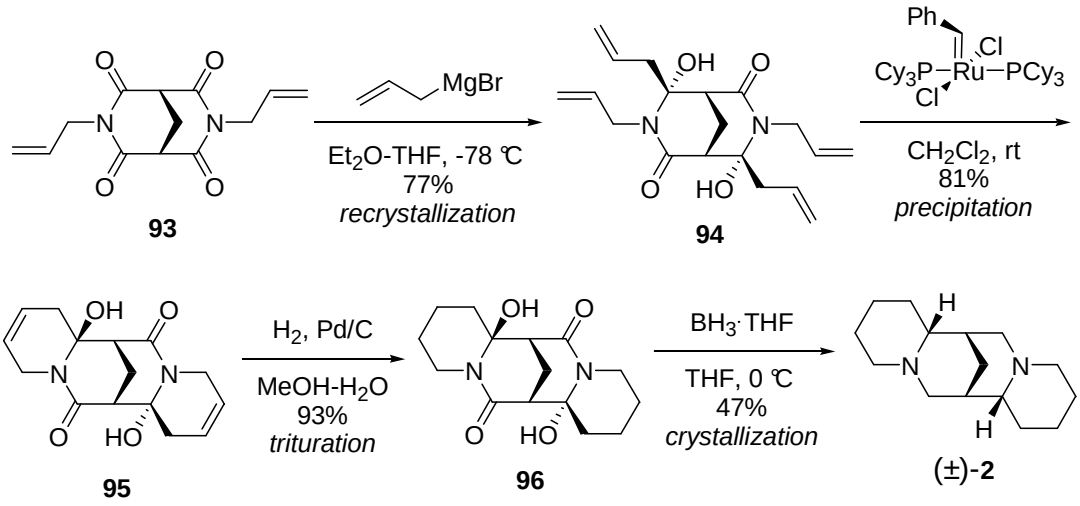
In addition to their potential for the treatment and prophylaxis of anti-arrhythmic events (including the Brugada syndrome),[129] bispidine derivatives also have demonstrated behavior as diuretics.[131] They also show selectivity at kappa-opioid[132] and nicotinic acetylcholine receptors,[133] suggesting promise as analgesics. Recent attention in this area has led to developments in the practical synthesis of chiral bispidines.[134]

# Chapter 2: Results

## 2.1 Synthetic Plan

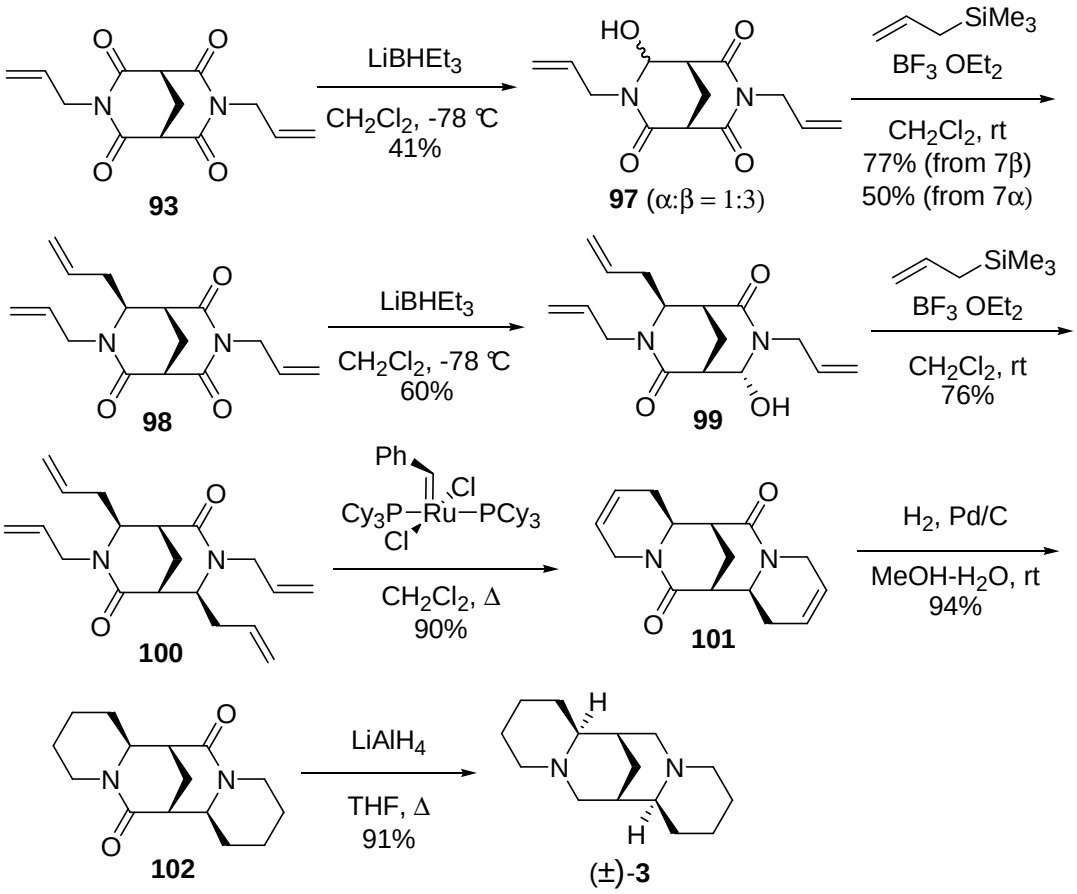
Our group (Blakemore & coworkers) recently reported successful syntheses of both (±)-α- and (±)-β-isosparteine[135, 136] from a common tetraoxobispidine intermediate - diallyltetraoxobispidine **93** (Scheme 20 & 21). The primary purpose of this thesis was to complete a synthesis of the third isomer, the eponymous (±)-sparteine alkaloid (*dl*-**1**) itself, as well as attempt to render these syntheses enantioselective.

In the syntheses of (±)-α- and (±)-β-isosparteine, the required diallyl tetraoxobispidine (**93**) is prepared in 3 simple steps from dimethyl malonate and paraformaldehyde. The path to (±)-α-isosparteine (*dl*-**2**) then proceeds through a highly regio- and stereoselective double nucleophilic allylation of **93** to give $C_2$-symmetric tetraene **94**, which undergoes ring-closing metathesis (RCM) to forge tetracycle **95** (Scheme 20). Hydrogenation of the olefinic moieties followed by exhaustive reduction with borane-tetrahydrofuran yields crystalline (±)-α-isosparteine (*dl*-**2**). It is noteworthy that none of the steps in this synthesis requires chromatography.[135]




Scheme 20: Blakemore synthesis of (±)-α-isosparteine

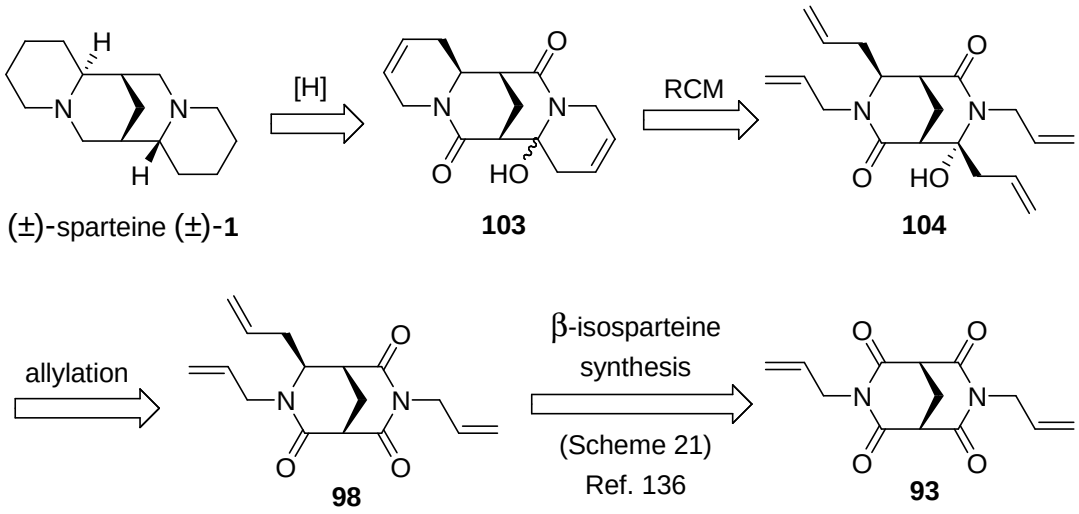
The route to (±)-β-isosparteine (*dl*-**3**) was significantly less concise, requiring a stepwise introduction of allyl groups to diallyl tetraoxobispidine **93** after double reduction attempts proved unsuccessful (Scheme 21). Monoreduction of **93** with lithium triethylborohydride resulted in modest yield of hemiaminal **97**, which was subjected to a Sakurai-type allylation to give triene **98**. Repetition of the same two-step sequence proceeded again in regio- and stereoselective fashion to give the desired $C_2$-symmetric tetraene **100**. Completion of the synthesis through RCM and exhaustive reduction gave (±)-β-isosparteine (*dl*-**3**) as a colorless oil.[136]




Scheme 21: Blakemore 1st generation synthesis of (±)-β-isosparteine

Our plan to access (±)-sparteine (*dl*-**1**) along similar lines would require a strategic reversal of nucleophilic hydride and allyl additions to triene **98**. Thus, the required *endo*-*exo* placement of H atoms at C6 and C11 of (±)-sparteine (*dl*-**1**) would stem from intermediary tetracycle **103**, which upon formal loss of hydroxide should accept exogenous hydride delivery to the generated intermediary acyliminium ion (Scheme 22). Assuming that analogous regio- and

stereoselectivity[135, 136] would result from nucleophilic allylation of triene **98**, tetracycle **103** should readily form on RCM of monohydroxy-tetraene **104**.



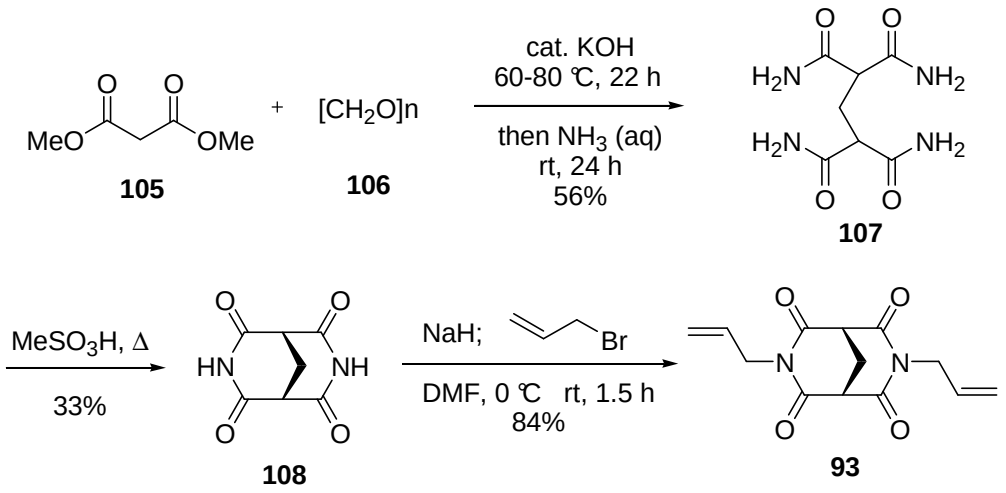

Scheme 22: Retrosynthetic plan for our synthesis of (±)-sparteine (*dl*-**1**)

## 2.2 Synthesis of N,N'-diallyl tetraoxobispidine

Diallyl tetraoxobispidine (**93**) was once again prepared in three steps from dimethyl malonate and paraformaldehyde (Scheme 23).[135] Potassium hydroxide-catalyzed Knoevenagal condensation gave the corresponding tetraester (a known literature procedure),[137] which was treated directly with aqueous ammonia to give a white solid precipitate upon prolonged stirring at rt.[138, 139] Upon filtration and drying, tetraamide **107** was obtained in 56% yield from over 1 mole of paraformaldehyde as the limiting reagent.

Subsequent brief pyrolysis of a manually stirred mixture of finely ground tetraamide **107** in methanesulfonic acid over a gentle Bunsen burner flame resulted in copious gas evolution. Upon cooling, trituration of the resulting thick paste with methanol, followed by washing with water, yielded tetraoxobispidine **108** as a white solid in 33% yield - representing a modest improvement to our previously reported 23%.[135]

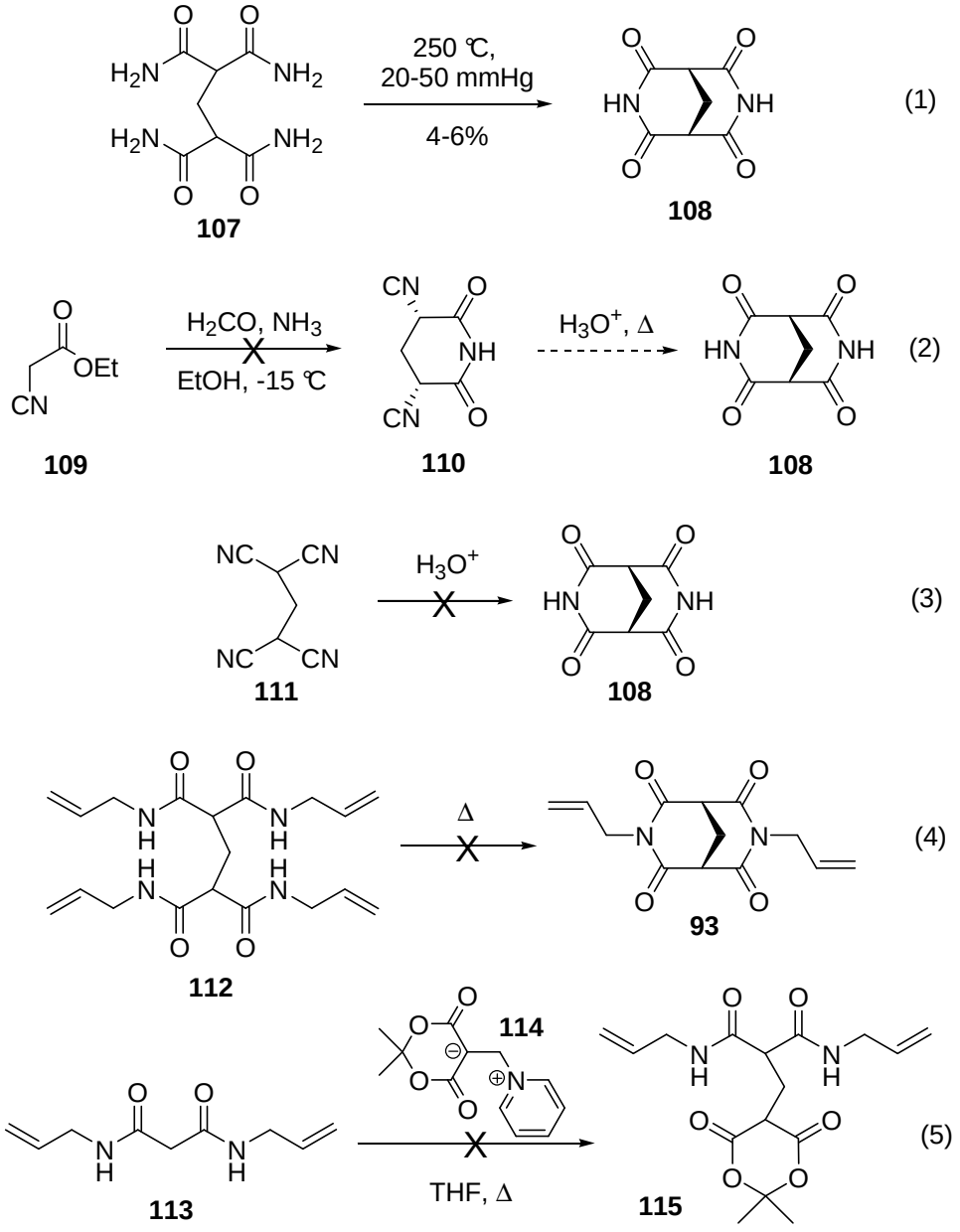
Finally, electrophilic allylation of both nitrogen atoms of **108** proceeded uneventfully with allyl bromide in anhydrous DMF, giving the desired diallyltetraoxobispidine (**93**) in pure form upon trituration with hexanes. The 84% yield for this step was also a marked improvement to our previously reported 73%.




Scheme 23: Synthesis of diallyl tetraoxobispidine **93**

It is worthwhile to mention here the numerous experiments that went into establishing the above sequence of reactions. The Blakemore group[140]

investigated numerous routes to diallyl tetraoxobispidine (**93**), beginning with a century-old process by Guthzeit & Jahn for the cyclization of tetraamide **107** to tetraoxobispidine **108**.[141] Although bispidines substituted at the methylene bridge are well known (Section 1.5, Figure 5),[128] the parent tetraoxobispidine **108** had only been described in this sole 1902 report. Guthzeit's procedure called for pyrolysis at reduced pressure, and thus heating of **107** at 205 °C and 20-50 mmHg permitted only 4-6% yields of **108** to be isolated (Scheme 24, equation 1). Attempts to access **108** via Guareschi condensation[142, 143, 144] of formaldehyde to ethyl cyanoacetate in ethanolic ammonia failed to give the (still unknown) intermediate Guareschi imide **110**,[145] as did the Clemens variant of the Guareschi reaction (equation 2).[146, 147] A direct cyano-group hydrolysis via the malononitrile derived tetracyanide **111** was also investigated,[148] but exposure to numerous acids (including AcOH, HCl, and $H_2SO_4$) at various temperatures gave either no reaction or decomposition (equation 3). Access to **93** directly via cyclization of tetraallyl tetraamide **112**, generated by Knoevenagal condensation of the corresponding diallylamide (**113**), also failed (equation 4), as did attempts to generate mixed tetracarbonyl systems such as **115** with Meldrums's adduct **114** (equation 5).[149] Finally, acidic variants to Guthzeit's original procedure were explored, leading to discovery of the above methanesulfonic acid-mediated cyclization of **107** to **108**. The moderate yield for this step is clearly offset by its simplicity and scaleability, as well as the ease with which the preceding tetraamide **107** is prepared.



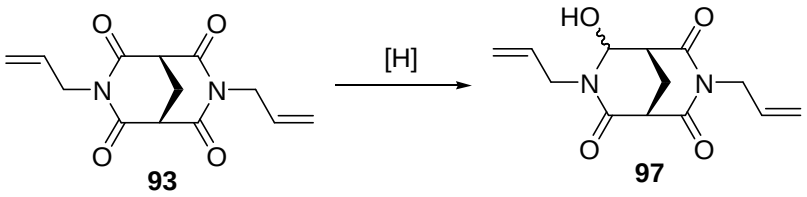

Scheme 24: Previous efforts by
Blakemore & coworkers[140] to access tetraoxobispidines

Electrophilic allylation of N,N'-diallyl tetraoxobispidine (**93**) also underwent extensive prior optimization,[140] finding that $K_2CO_3$ in refluxing

acetone gave poor yields, and the presence of methoxide caused complete decomposition. The identification of a glutarimide by-product indicated the sensitivity of tetraoxobispidines toward ring-opening. A Mitsunobu coupling[150, 151, 152] with allyl alcohol in THF was more successful (61% yield of **93**), but sodium hydride in DMF proved best.

## 2.3 Stereocontrolled mono-allylation of diallyl tetraoxobispidine

We were not satisfied with the $LiBHEt_3$-mediated reduction[153, 154] of **93** according to our reported (±)-β-isosparteine (*dl*-**3**) procedure (Scheme 21),[136] which upon replication proved difficult isolating pure hemiaminal (**97**). An improvement to this procedure was sought, and numerous other conditions and reducing agents were explored (Scheme 25 & Table 1). Increasing the number of equivalents of $LiBHEt_3$ (entry 2) resulted in decomposition, so experiments turned to use of the milder $NaBH_4$.[155] The presence of methoxide once again proved to be deleterious (entries 3-6), so an insoluble suspension of $NaBH_4$ in THF was explored, resulting in moderate improvement with 0.8 equivalents of reductant (entry 7). Lower temperatures (entries 8 & 9) gave no reaction, while excess reductant (entries 10 & 11) led to decomposition. Neither $NaBH(OAc)_3$[156] nor $Na(CN)BH_3$ were strong enough to reduce our substrate (entries 12 & 13), and DIBAL[157] promoted decomposition even at low temperature (entry 14).




Scheme 25: Reduction of diallyl tetraoxobispidine (**93**)

Table 1: Summary of various conditions explored in the reduction of diallyl tetraoxobispidine (**93**) to hemiaminal **97**

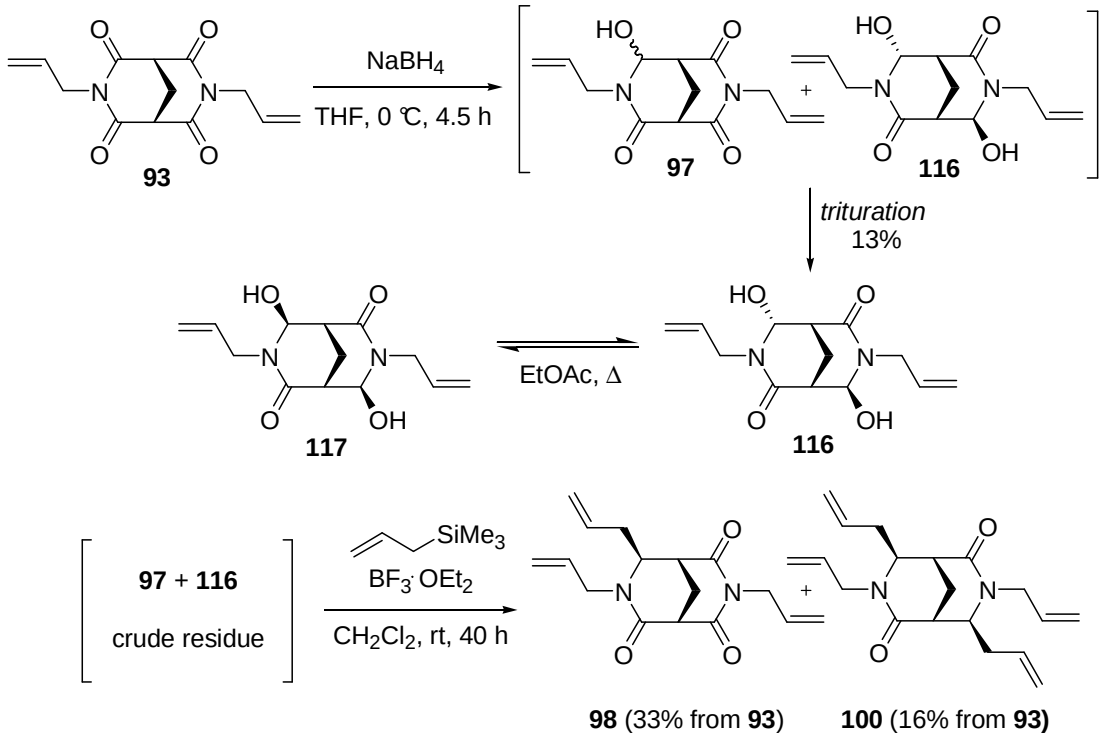
| | *[H]* | *Equiv.* | *Solvent* | *Temp.* | *Time* | *Quench* | *Yield* |
|---|---|---|---|---|---|---|---|
| 1 | $LiBHEt_3$ | **1.1** | **$CH_2Cl_2$** | **-78 ºC** | **2 h** | **$NH_4Cl$** | **23%** |
| 2 | | 4.0 | $CH_2Cl_2$ | -78 °C | 1.1 h | $NH_4Cl$ | decomp. |
| 3 | $NaBH_4$ | 0.3 | MeOH-THF | rt | 50 min | TFA | decomp. |
| 4 | | 0.3 | MeOH-THF | 0 ºC | 3.5 h | MeOH | decomp. |
| 5 | | 0.3 | MeOH-THF | -78 ºC | 2.5 h | MeOH | decomp. |
| 6 | | 0.5 | MeOH-THF | rt | 15 min | TFA | decomp. |
| **7** | | **0.8** | **THF** | **rt** | **30 min** | **$Na_2SO_4$•$H_2O$** | **28%** |
| 8 | | 4.7 | THF | -78 ºC | 8 h | TFA | no rxn |
| 9 | | 5.8 | THF | -78 ºC | 1.6 h | HCl | no rxn |
| 10 | | 10 | THF | rt | 1 h | HCl | decomp. |
| 11 | | 16 | THF | rt | 9 h | $Na_2SO_4$•$H_2O$ | decomp. |
| 12 | $NaBH(OAc)_3$ | 1.1 | THF | rt | 22 h | $NH_4Cl$ | no rxn |
| 13 | $Na(CN)BH_3$ | 1.5 | THF | rt | 24 h | TFA | no rxn |
| 14 | DIBAL | 2 | $CH_2Cl_2$ | -78 ºC | 20 min | $NH_4Cl$ | decomp. |

Information gleaned from these experiments allowed for further optimization of entry 7 and the finding that 0.7 equivalents of $NaBH_4$ added to substrate in THF at 0 °C was most promising. Careful quenching at 0 °C by dropwise addition of 4M HCl generated a crude yellow oil which appeared to contain ($^1$H NMR in $CDCl_3$) a significant portion of hemiaminal **97**, largely as its β-anomer (Scheme 26). Given the experienced difficulty isolating pure hemiaminal (**97**) by chromatography, the crude oil was subjected directly to a Sakurai-type allylation[158] without purification. Prolonged stirring in the presence

of allyl trimethylsilane (2.5 equivalents) and $BF_3$•$OEt_2$[159] gave the desired triene **98** (33%) which, to our surprise, was followed immediately in sequence of elution by tetraene **100** (16%). The unanticipated retrieval of tetraene **100** amounted to a significant improvement in our reported (±)-β-isosparteine (*dl*-**3**) synthesis[136] – shortening the tedious stepwise sequence from **93** to **100** by two steps (Scheme 21). It was possible to isolate a sample of the double-reduced intermediate **116** by trituration with $CH_2Cl_2$. Attempted recrystallization in EtOAc, however, resulted in epimerization to a mixture with its $C_2$-symmetric diastereomer **117**.

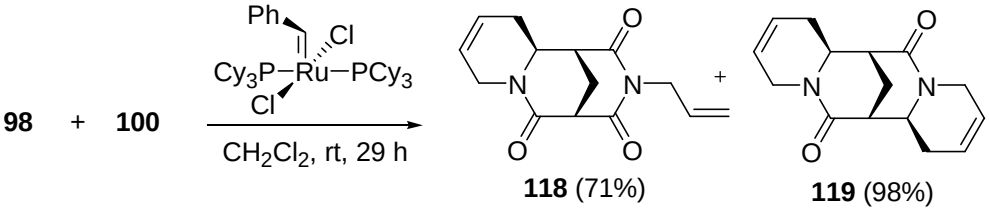
Increasing the quantity of $NaBH_4$ (> 0.7 equivalents) diminished yields significantly (complete decomposition occurred with 2.1 equivalents). Careful monitoring by TLC also suggested the second reduction was taking place regioselectively due to increased electrophilicity (resulting from the first reduction) at the diagonally opposing carbonyl group. A second spot was clearly observed, with higher polarity than the target hemiaminal (**97**), before starting material was fully consumed. Related experiments further explored this phenomenon (see Section 2.8).

Sufficient acidity in the $NaBH_4$ quench (ie. 4 M HCl) appears to be important in maintaining the integrity of hemiaminal **97**. Its direct precursor (**93**) shows similar sensitivity to base: stirring **93** with dilute NaOH (<0.1 M) in MeOH-THF led rapidly to decomposition (see also entries 3-6 of Table 1), while prolonged stirring with AcOH (0.1 to 0.2 M) in MeOH-THF had no effect.




Scheme 26: Optimized allylation of tetraoxobispidine **93**

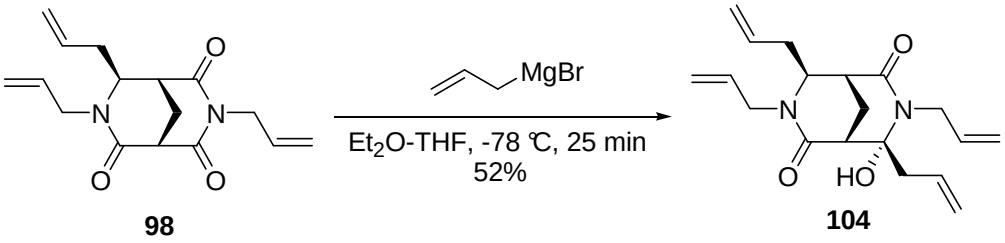
Although the targeted triene (**98**) was isolated in good purity, it proved arduous to liberate tetraene **100** from all traces of triene **93**. However, treatment of the mixture with Grubbs's 1st Generation Ruthenium catalyst[160, 161] generated a readily separable mixture of tricycle **118** and our known β-isosparteine precursor **119** (Scheme 27). Tricycle **118** was later investigated as a potential precursor in an alternate route to (±)-sparteine (*dl*-**1**) and (±)-β-isosparteine (*dl*-**3**) (see section 2.6).




Scheme 27: RCM of the mixture of triene **98** and tetraene **100**

## 2.4 Nucleophilic allylation of triene

With triene **98** in hand, efforts turned toward nucleophilic allylation of the diagonally opposing carbonyl group. Allylmagnesium bromide[162] served this purpose moderately well. With 1.3 equivalents of the Grignard reagent added to substrate in THF at -78 °C, tetraene **104** was obtained in 52% yield as a yellow oil (Scheme 27).



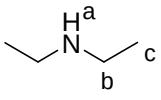

Scheme 28: Allyl Grignard addition to triene **98**

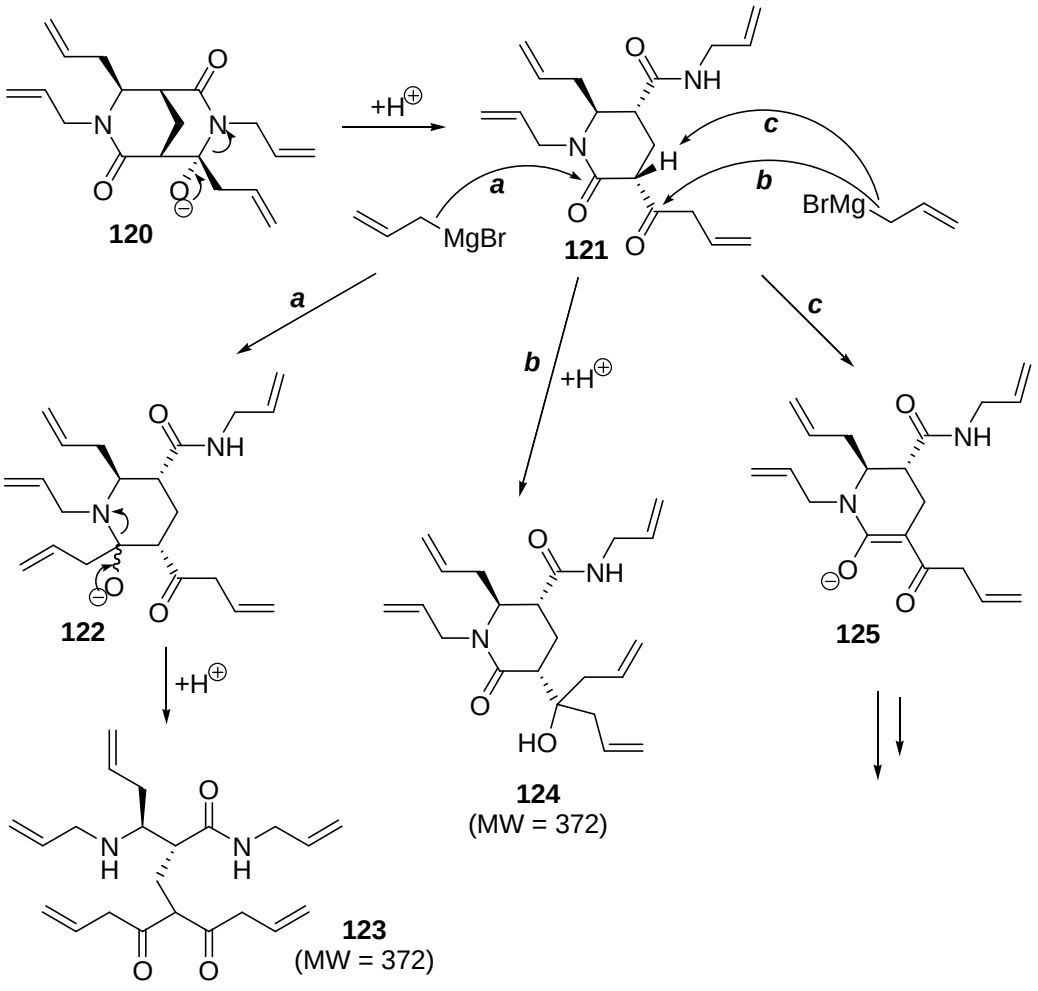
The reaction was also investigated on a mixture of triene **98** and tetraene **100**, given the laborious nature of their separation. Similar yields were obtained with 1.3 equivalents of the allyl Grignard, and unreacted tetraene (**100**) was then easily separated from the product mixture. The reaction was significantly more

sluggish with the addition of $CeCl_3$,[163, 164] or when performed in 100% $Et_2O$, with no improvement in yield.

A second compound, slightly higher in polarity (by TLC) than the desired addition product (**104**), was repeatedly isolated from the product mixture. Its NMR was complex and not indicative of a single compound, but its consistent overall appearance indicated the presence of free N-H bonds (6-9 ppm). Its mass spectrum suggested that a second allyl addition had occurred, giving an $[M+1]^{+\bullet}$ peak at m/z = 373. Furthermore, its IR spectrum could neither confirm nor deny the presence of an -OH group (see Table 2 characterization data below). These data suggest that ring-opening of the initially generated Grignard addition product (**120**) may occur to give lactam **121**, which may itself represent a significant portion of this by-product mixture (Scheme 29). Lactam **121**, however, can react with a second equivalent of the Grignard at several possible locations. The ketone function, being the least hindered and inherently most electrophilic, suggests lactam **124** is the most likely major by-product (path ***b***). Alternatively, attack at the lactam carbonyl (path ***a***) and a second ring-opening may occur, or otherwise enolization of the reactive β-dicarbonyl (path ***c***) and subsequent polymerization may result.

Table 2: Characterization data for the
by-product(s) of the allyl Grignard addition

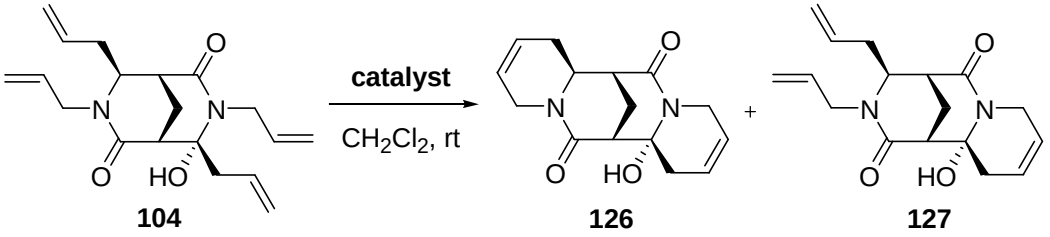
| | | |
|---|---|---|
| $^1$H | $R_2NH_2^+$  | $\delta$ = 7.52 (t), 8.18 (t), 8.67 (t)<br>$\delta_a$ ~ 3.02 (m), $\delta_b$ ~ 2.90 (m) |
| IR | $R_3C$-OH | no prominent sharp band in 1210-1100 $cm^{-1}$ (C-O st) |
| | N-H, O-H | $\nu$ = 3325 (broad), 3080 (sharp), 2916 (multiple) $cm^{-1}$<br>consistent with N-H stretch and/or O-H stretch |
| MS | $(EI^+)$ m/z | 373, 331, 313, 289 (base), 261, 221, 203, 136 |




Scheme 29: Possible by-products of allyl Grignard addition to triene **98**

## 2.5 Completion of the synthesis of (±)-sparteine

With all the required stereochemistry established in (±)-sparteine precursor **104**, it remained only to forge the outer rings (through RCM) and exhaustively reduce the resulting tetracycle. Treatment of tetraene **104** with Grubbs's 1st Generation Ruthenium Alkylidene Complex (up to 30 mol%), however, would not allow for complete conversion to the desired tetracycle (**126**) (Scheme 30). Tricycle **127** was also isolated as a single stereoisomer, presumably with its hydroxyl group maintained in the *endo* orientation. The use of Grubbs's 2nd Generation Catalyst[160, 161] solved this problem unequivocally, giving the desired tetracycle (**126**) in essentially quantitative yield upon filtration. An X-ray crystal structure firmly established the *endo* orientation of the hydroxyl substituent (Figure 6).




**104** **126** **127**

| **catalyst** | isolated yield of **126** | isolated yield of **127** |
|---|---|---|
| Grubbs 1 (4 mol%, 29 h) | 61% | 18% |
| Grubbs 2 (5 mol%, 24 h) | 100% | - |

Scheme 30: RCM of tetraene **104**

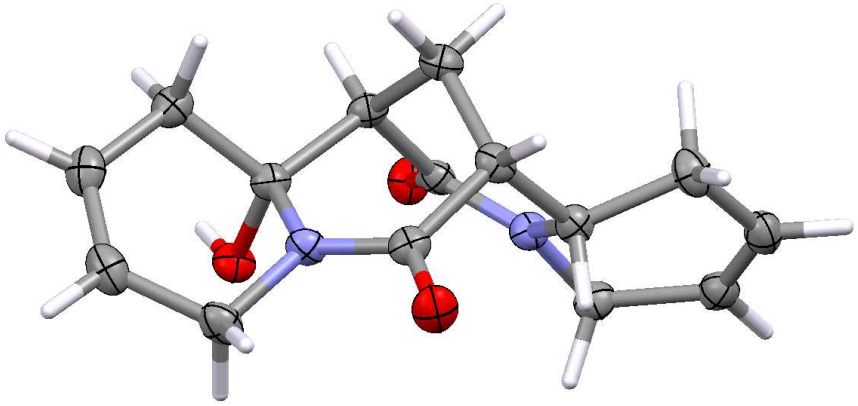
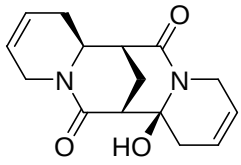


Figure 6: ORTEP diagram of tetracycle **126**, with
50% probability ellipsoids plotted for non-hydrogen atoms

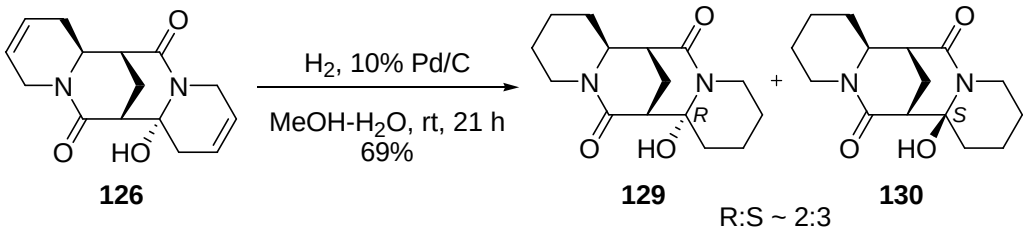
Interestingly, on a single occasion the diastereomeric *exo*-hydroxy tetracycle **128** (Figure 7) was isolated upon submitting a relatively low-grade sample of tetraene **104** to RCM. An incomplete reaction with Grubbs's 2nd Generation Catalyst generated tetracycle **128** in 32% yield, demonstrating again the sensitivity of the hemiaminal function toward configurational equilibration in this strained *oxo*-bispidine system.




**128**

Figure 7: Isolated *exo*-hydroxy tetracycle **128**

Exhaustive reduction proceeded first with saturation of the olefinic moieties. Hydrogenation at atmospheric pressure over palladium on charcoal gave 6-hydroxy-10,17-dioxosparteine as a mixture of the 6*R* (*endo*, **129**) and 6*S* (*exo*, **130**) diastereomers (Scheme 31). An X-ray crystal structure of **129** confirmed the stereochemical assignment (Figure 8). Unfortunately, Grubbs's "one-pot" tandem metathesis/hydrogenation protocol[165] was unsuccessful here.




Scheme 31: Hydrogenation of RCM product **126**

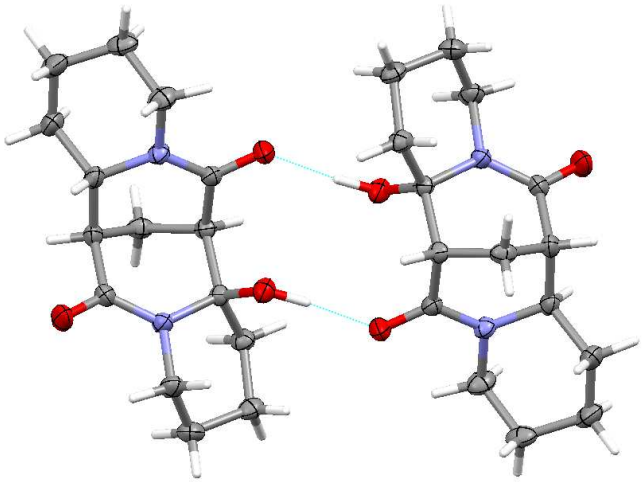
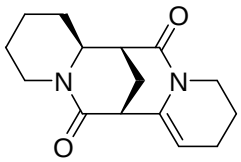


Figure 8: ORTEP diagram of hydrogenation product **129**, showing its hydrogen-bonded enantiomeric dimer; 50% probability ellipsoids are plotted for non-hydrogen atoms

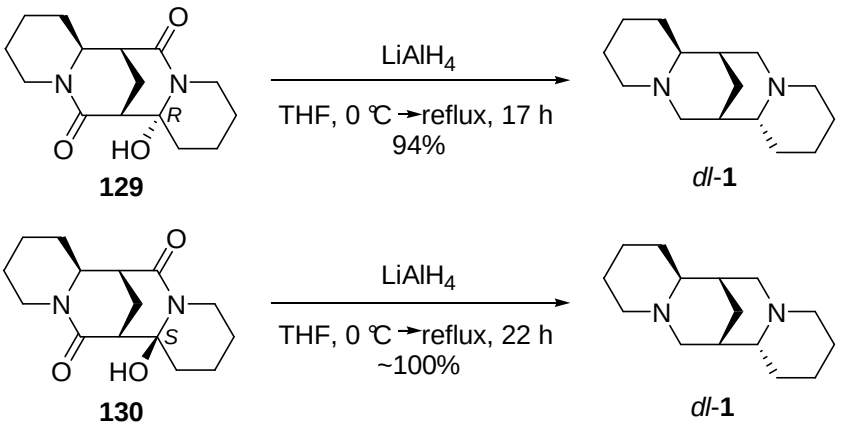
Part of the loss in this step can be attributed to the sensitivity of these compounds to chromatography on silica gel, particularly the *endo*-hydroxy tetracycle (**129**) which can readily eliminate $H_2O$ from its exposed *exo* face. As much as 61% of the dehydration product **131** (Figure 9) was isolated following contact with silica gel.




**131**

Figure 9: Isolated dehydration product
following exposure of **129**/**130** to chromatography on $SiO_2$

Finally, both **129** and **130** were converted to (±)-sparteine (dl-**1**) in high yield through reduction with lithium aluminum hydride (Scheme 32).[55] The final product was indistinguishable by IR and NMR from a commercial (Aldrich) sample of (-)-sparteine (*l*-**1**).




Scheme 32: Reduction to (±)-sparteine (*dl*-**1**)

## 2.6 Alternate routes to (±)-sparteine

In the course of our studies a number of alternate routes to (±)-sparteine (*dl*-**1**) were investigated, beginning with $C_2$-symmetric α-isosparteine precursor **94** and pseudo-$C_2$-symmetric precursor **95** (Scheme 20). It was envisioned that an *endo*-hydroxyl substituent, upon conversion to a hydrido-silane,[166] could anchor delivery of hydride to the bottom face of the diagonally opposing acyliminium ion, generated upon treatment with a Lewis acid (Figure 10).

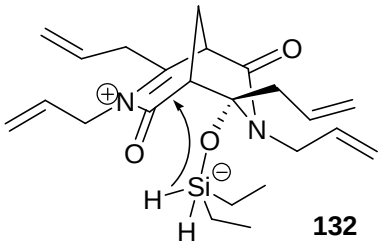
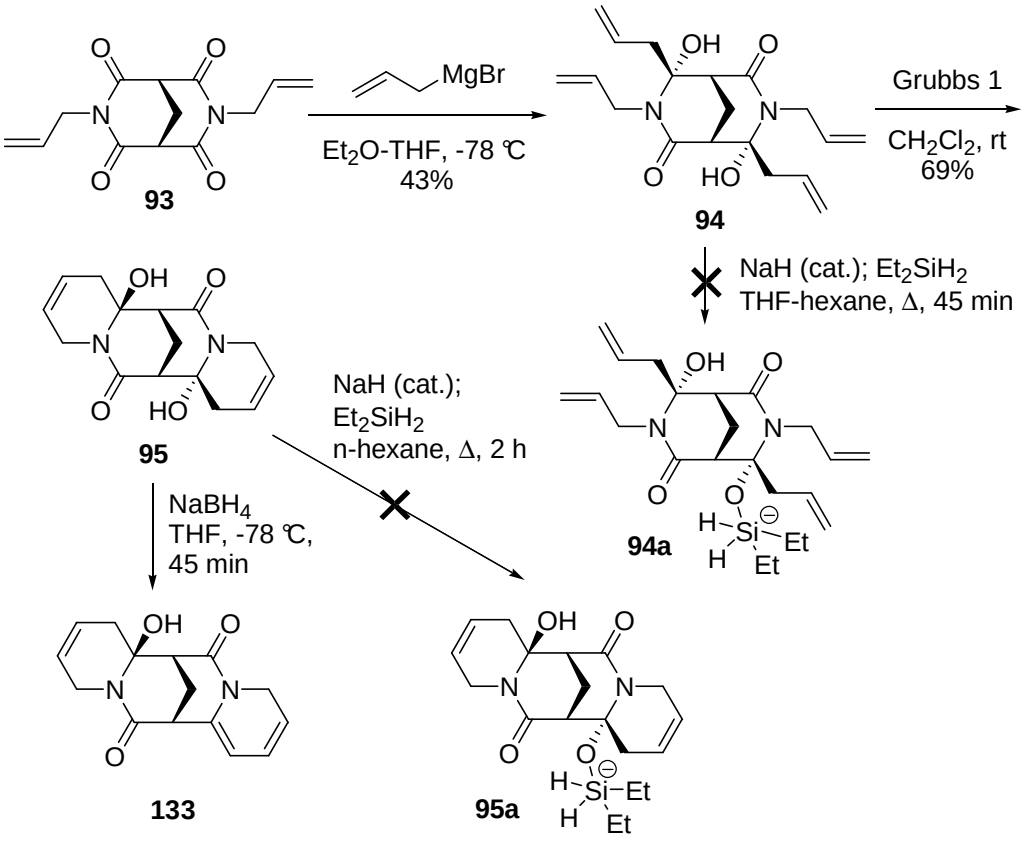



Figure 10: Proposed plan for *endo* hydride delivery

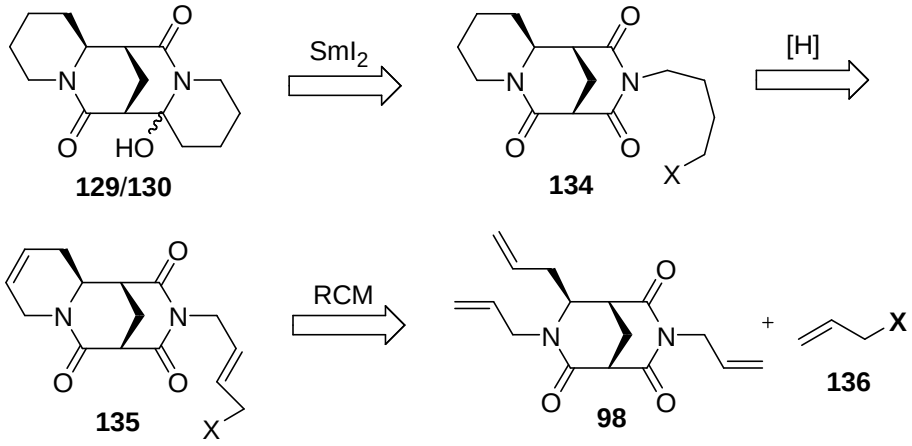
Compounds **94** and **95** were synthesized according to our group's previously published (±)-α-isosparteine synthesis (Scheme 33).[135] Unfortunately, neither of these compounds could successfully be converted to the desired silanes. Similarly, an attempt to convert **95** into the corresponding borate with $NaBH_4$ gave what was identified to be dehydration product **133** in the crude mixture.




Scheme 33: Alternate attempts to convert **94** & **95** to (±)-sparteine (*dl*-**1**)

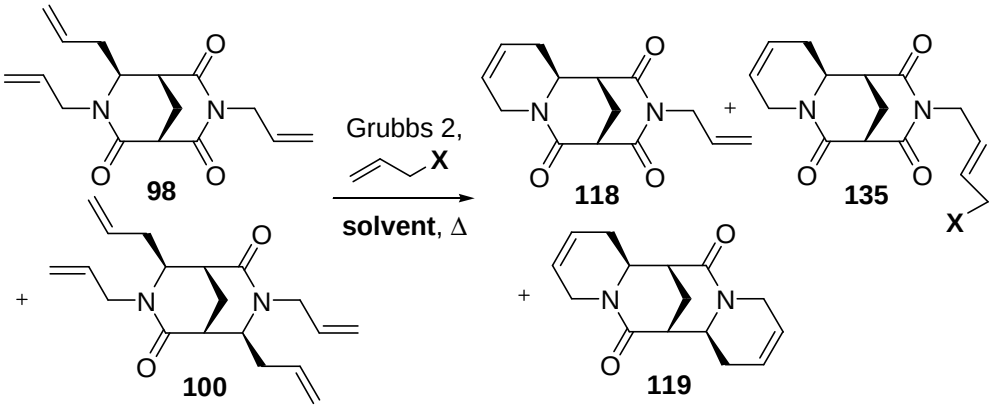
Given the moderate yield for allyl Grignard addition to triene **98**, another strategy was briefly entertained in which the D-ring of sparteine could be forged

through a samarium(II) iodide-mediated Barbier reaction.[167] It was believed that halide precursor **134** could be generated upon hydrogenation of the RCM product of triene **98** with an allyl halide (**136**) (Scheme 34).




Scheme 34: Alternate synthetic strategy to (±)-sparteine (*dl*-**1**) employing a Barbier-type reaction to forge the D-ring

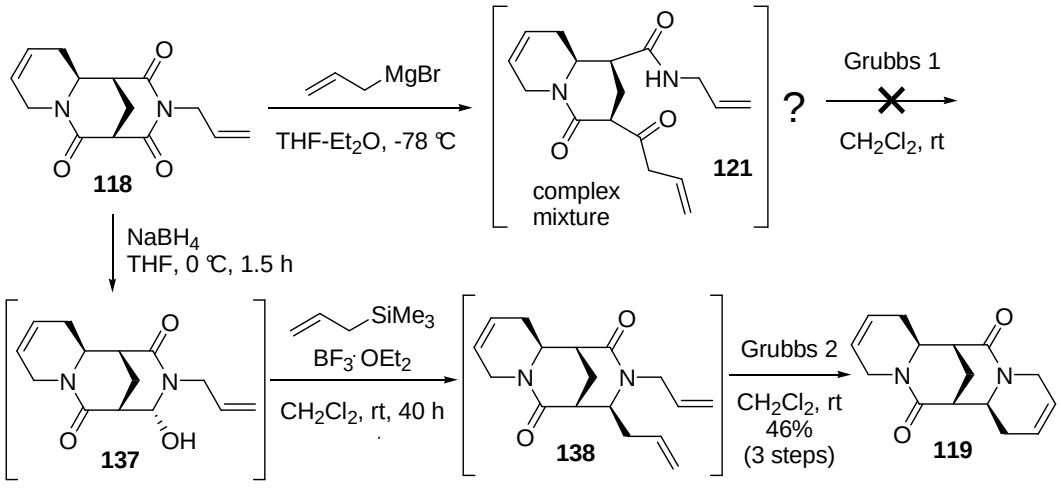
Only a few examples of cross-metathesis involving allyl halides have been reported.[168, 169, 170] Employing the conditions described by Roy *et al.*,[170] however, failed to generate any of the cross-metathesis product (**135**) with allyl bromide. It appears that allyl chloride gave only a trace of the desired product (**135**, X = Cl, 11%) as an intractable mixture with **118** (Scheme 35), and the strategy was abandoned.




| **X**, solvent | Yield of **118** | Yield of **119** | Yield of **135** |
|---|---|---|---|
| Br, $CH_2Cl_2$ | ~100% | ~100% | 0% |
| Br, $(CH_2)_2Cl_2$ | 90% | ~100% | 0% |
| Cl, $CH_2Cl_2$ | 74% | 80% | 11% |

Scheme 35: Attempts to generate Barbier cyclization-precursor **135**

Tricycle **118**, generated by RCM of **98** with **100** (Scheme 27), remained an interesting loose end for further study. As a potential precursor to sparteine, **118** was treated with 1.1 equivalents of allyl Grignard, but resulted in a complex intractable mixture (Scheme 36). Ring-opening of the initially generated addition product is once again the most likely explanation. As a potential β-isosparteine precursor, **118** was treated sequentially with $NaBH_4$, allyl trimethylsilane, and Grubbs 2 without purification of intermediates - successfully generating our known β-isosparteine precursor (**119**) in 46% yield over three steps (**118** to **119**).

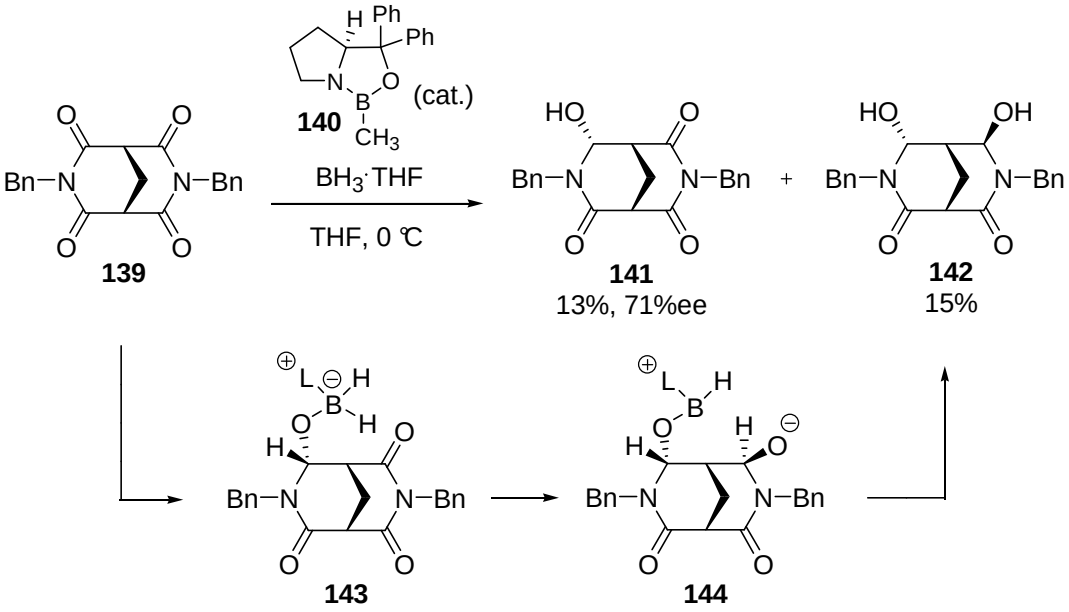



Scheme 36: Attempts to convert tricycle **118** to (±)-sparteine (*dl*-**1**) and (±)-β-isosparteine (*dl*-**3**)

## 2.7 Attempted enantioselective transformations

Enantioselective addition of a single hydride ion equivalent to bisimide **93** would be sufficient to gain access to scalemic samples of both sparteine (**1**) and β-isosparteine (**3**) by the routes already described.[136] Likewise, enantioselective addition of a single allyl anion equivalent would secure α-isosparteine (**2**) in enantioenriched form.[135] Unfortunately, while numerous methods exist for enantioselective allylation of aldehydes and ketones, there is only a single literature precedent involving imides, which involves allyl titanium taddolates.[171, 172] Enantioselective reduction of imides also has little precedent;[173, 174, 175, 176, 177, 178, 179, 180] modest yields but good enantioselectivity has been achieved employing the Corey-Bakshi-Shibata (CBS) catalyst.[181, 182]

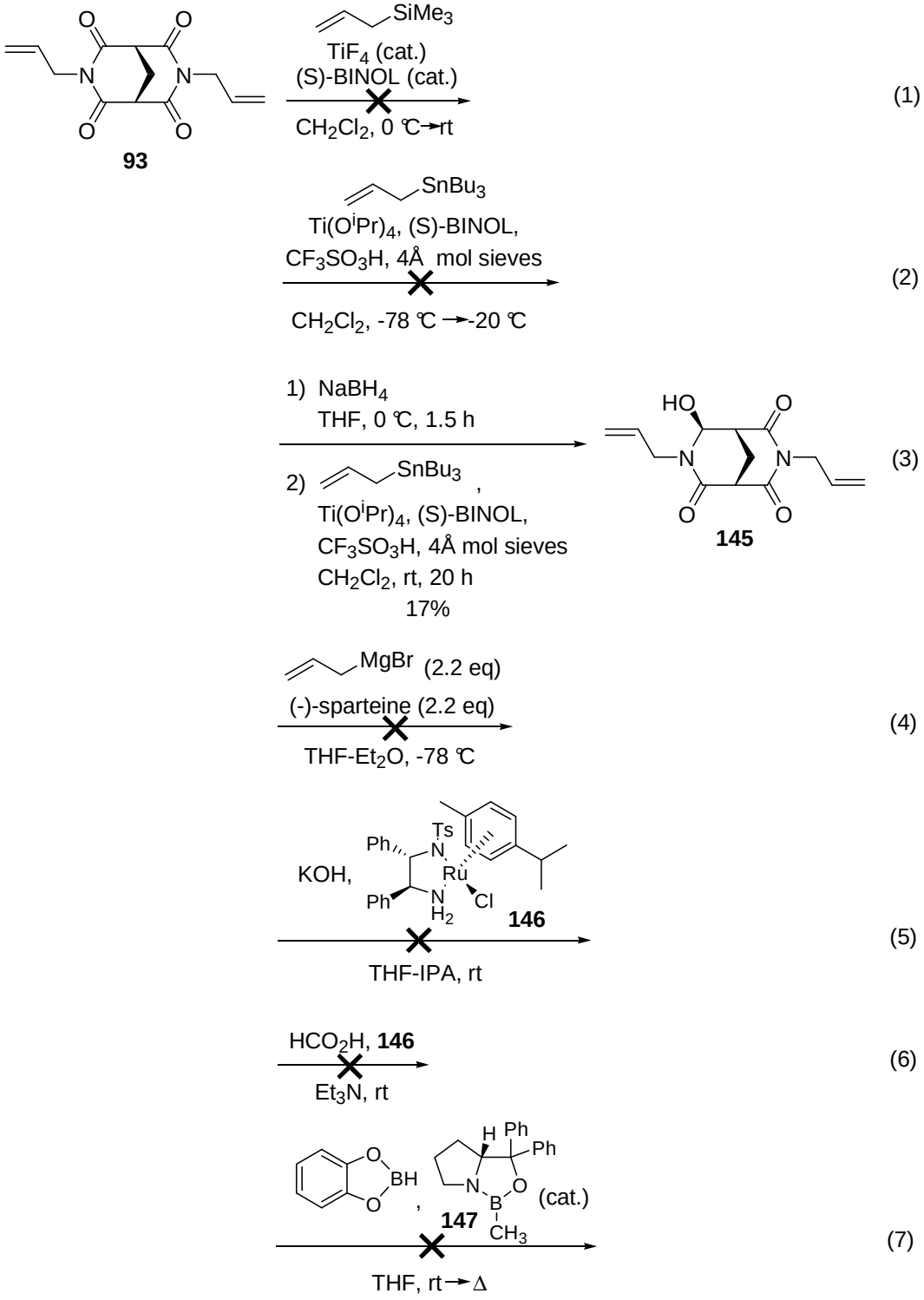
Prior to the work of this thesis, our group investigated numerous enantioselective allyl and hydride additions to various disubstituted tetraoxobispidines, including the crotyl, prenyl, and benzyl analogs of **93**.[140] Enantioselective allylations were attempted with allyl titanium taddolates,[171] Leighton's allyl silacycles,[183] and allyl indium binaphthols,[184] but none of these exhibited sufficient reactivity. Enantioselective reductions, on the other hand, met with some success, albeit minimal. An extensively investigated CBS-catalyzed borane reduction[185] of the dibenzyl analog of **93** gave the corresponding mono-reduced product (**141**) in 71%ee but only 13% yield, due to competing double-reduction to the pseudo-$C_S$-symmetric product (**142**) (Scheme 37). Jones's catalyst[177, 178, 179, 180] gave a similar result, but without any of the double-reduced product (**142**). Furthermore, chiral modifications of $LiAlH_4$ with binapthol (to generate BINAL-H),[186, 187] N-methylephedrine,[188, 189] and ChiralD[190, 191, 192] were employed in the reduction of diallyl tetraoxobispidine (**93**) itself. BINAL-H and N-methylephedrine-complexed $LiAlH_4$ gave modest yields (25-30%) of the mono-reduced product, but did *not* exhibit enantioselectivity. ChiralD-modified $LiAlH_4$ was unreactive.




Scheme 37: Enantioselective reduction of tetraoxobispidine **139** previously observed by Blakemore & coworkers[140]

To expand on these studies, we attempted several still untested asymmetric allylations and reductions of diallyl tetraoxobispidine (**93**) (Scheme 38). A titanium fluoride-BINOL catalyzed asymmetric allylsilylation[193, 194] (with proven efficacy on aldehydes) was unreactive on this substrate (equation 1). A Keck allylation[195, 196, 197, 198] was equally ineffective (equation 2), and an attempt to apply the Keck allylation following reduction with $NaBH_4$ returned only unreacted β-anomer (**145**) (equation 3). A third allylation attempt, with an allyl Grignard in the presence of (-)-sparteine (*l*-**1**) – conditions which exhibit good enantioselectivity on cyclic meso anhydrides,[100] – also failed on our substrate.

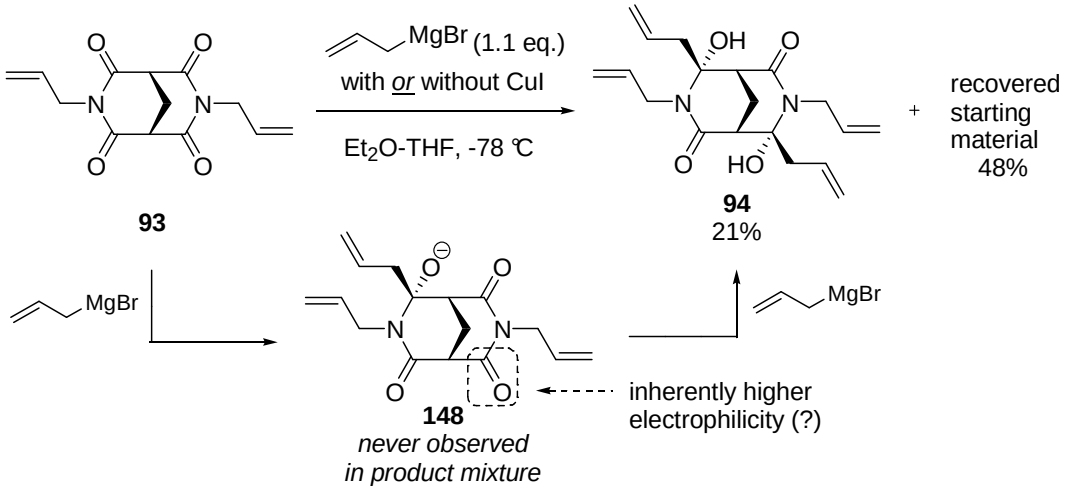
Asymmetric reductions were equally ineffective. Treatment with Noyori's Ruthenium complex **146**,[199, 200, 201] known to give excellent enantioselectivity on aldehydes and ketones, failed on **93** under both basic and acidic conditions (equations 5 & 6). Finally, we revisited the CBS-catalyzed reduction which previously showed some small promise with borane-THF (Scheme 37). With single hydride donor catechol-borane[202] (aiming to avoid a Cs-symmetric by-product analogous to **142** in Scheme 37), however, our substrate remained wholly unreactive (equation 7). Unfortunately, we were unable to make any advancements on this front, and enantioselective transformation of imides remains a significantly undeveloped frontier.




Scheme 38: Failed attempts at asymmetric allyl and hydride addition to diallyl tetraoxobispidines **93**

## 2.8 $C_2$-symmetric regioselectivity

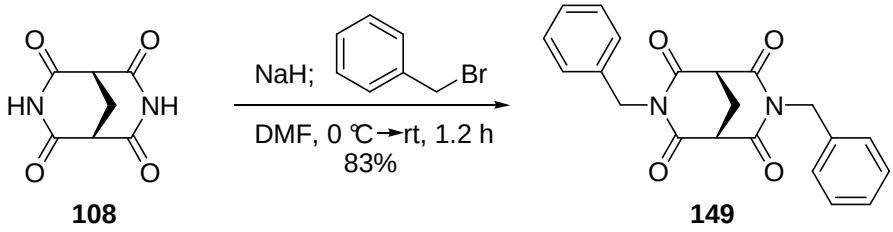
A brief discussion of the inherent regiochemical bias of tetraoxobispidines to accept two sequential nucleophilic additions to generate $C_2$-symmetric products is warranted. It was initially believed that chiral reagent control would be needed to effect the desired $C_2$-symmetry of addition adducts to tetraoxobispidines. However, it became apparent early on that after the first addition occurs, the remaining two imide carbonyl groups are inherently sufficiently differentiated to allow for their regioselective transformation without reagent control. We have tentatively attributed this phenomenon to increased electrophilicity at the diagonally opposing imide carbonyl due to the proximal lactam moiety. This argument is supported by the fact that a mono-addition product of allyl Grignard to disubstituted tetraoxobispidines was never observed. Treatment of diallyl tetraoxobispidine (**93**) with 1.1 equivalent of allyl Grignard (with or without copper(I) iodide)[203] yielded only the $C_2$-symmetric double-addition product **94** and recovered starting material (Scheme 39).




Scheme 39: Regioselective bias observed
in the allyl Grignard addition to tetraoxobispidines **93**

## 2.9 Exhaustive reduction of N,N'-disubstituted tetraoxobispidines

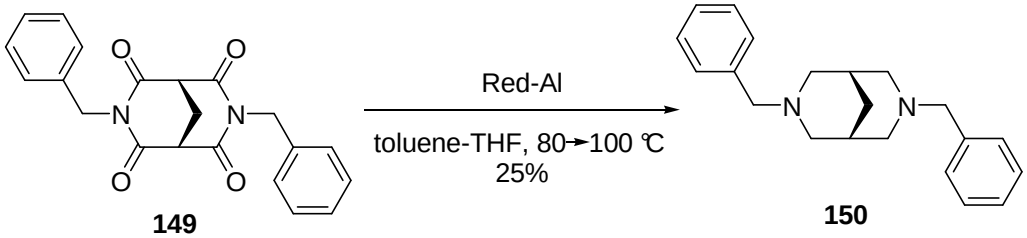
The final efforts of this work were aimed at reducing $C_{2V}$-symmetric N,N'-dialkyl tetraoxobispidines to potentially medicinally useful N,N'-dialkyl bispidines. In addition to N,N'-diallyl tetraoxobispidine (**93**), we synthesized N,N'-dibenzyl tetraoxobispidine (**149**) in 83% yield by the same method (Scheme 40), and subjected both of these analogs to various reductants in excess.




Scheme 40: Synthesis of N,N'-dibenzyl tetraoxobispidine (**149**)

This type of reaction appears only to have recent literature precedent,[128, 129] where it is broadly described that N,N'-disubstituted bispidines substituted at the methylene bridge (Section 1.5, Figure 5) may be prepared through reduction of their corresponding tetraoxo analogs. N,N'-dialkyl tetroxobispidines were reduced with lithium aluminum hydride in THF/toluene. In the case of an unsaturated N-substituted side chain, reduction had to be performed by means of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in order to avoid reduction of double bonds.

Subjection of dibenzyl tetraoxobispidine (**149**) to lithium aluminum hydride in THF resulted in decomposition. We then experimented with borane-tetrahydrofuran as a reductant, which gave a low yielding (10-20%) white solid (not well characterized) presumed to be some type of borate complex. However, all attempts at basic hydrolysis failed to influence its structure. Finally, we tried Red-Al (4 equivalents) in THF/toluene, which gave a 25% yield of dibenzyl tetraoxobispidine (**150**, a known compound)[204, 205] in reasonable purity (Scheme 41). However, attempts to recrystallize this as the HCl salt were not successful.




**149** **150**

Scheme 41: Synthesis of N,N'-dibenzyl bispidine (**150**)

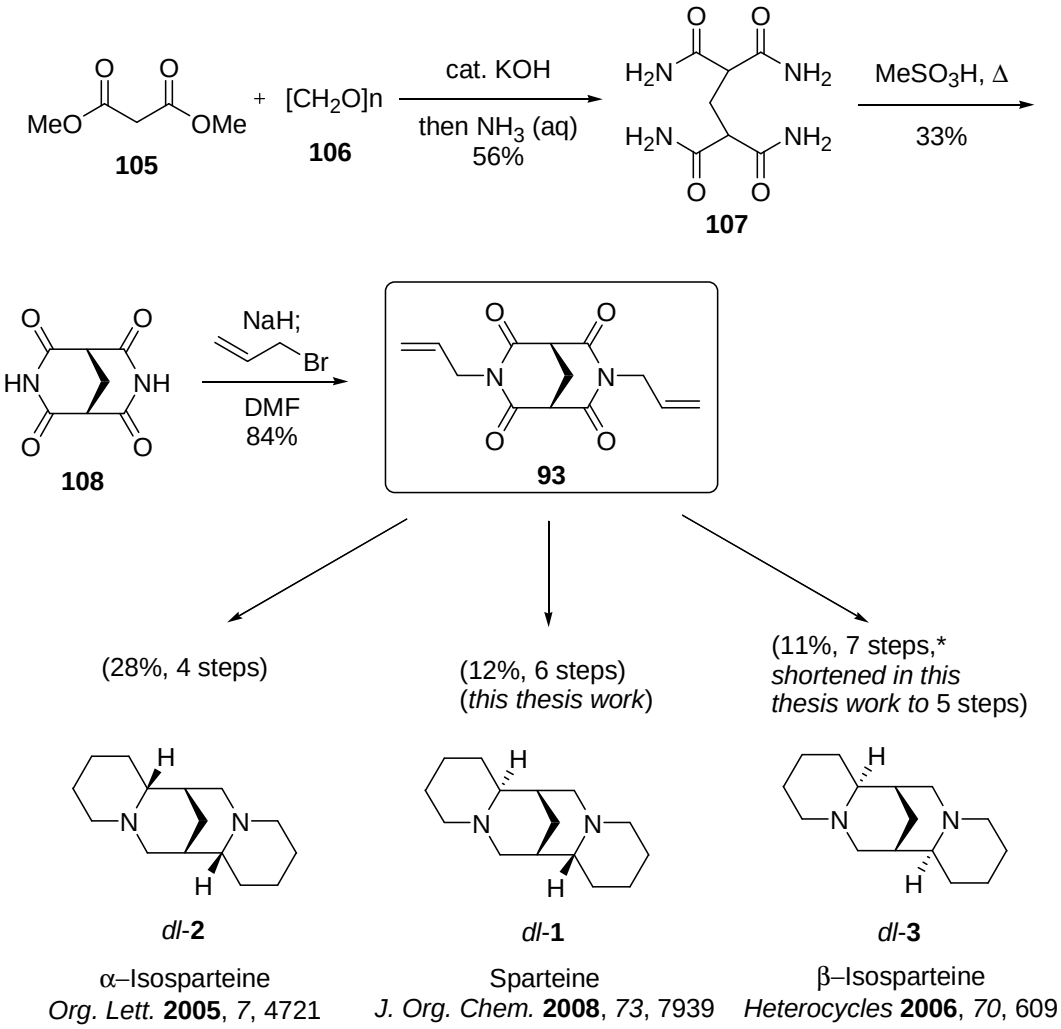
Finally, we subjected our N,N'-diallyl tetraoxobispidine (**93**) to the same conditions. In this case, however, we obtained a complex intractable mixture. We have, nonetheless, succeeded in demonstrating that N,N'-disubstituted bispidines which are *not* substituted at the methylene bridge are accessible with these conditions.

## Chapter 3: Conclusion

In summary, we have successfully synthesized racemic sparteine (*dl*-**1**) in 6 steps and 12% overall yield from diallyl tetraoxobispidine **93**, or in 9 steps and 2% overall yield from dimethyl malonate and formaldehyde (Scheme 41).[206] In the process we have succeeded in shortening our reported β-isosparteine (*dl*-**3**) synthesis[136] by 2 steps (to 5 steps from diallyl tetraoxobispidine **93**). This concludes our research group's synthesis of the complete subgroup of sparteine alkaloids; namely sparteine (*dl*-**1**),[206] α-isosparteine (*dl*-**2**),[135] and β-isosparteine (*dl*-**3**).[136]

Unfortunately, we were unable to satisfactorily render these syntheses enantioselective through an asymmetric allyl or hydride addition to $C_{2V}$-symmetric diallyl tetraoxobispidine (**93**). Our group's previously achieved CBS-catalyzed borane reduction of **93** therefore remains our only effective, albeit poor yielding, method of achieving enantioselectivity.[140, 206] In general, asymmetric transformation of imides remains a significantly undeveloped frontier.

In the course of these studies, $C_{2V}$-symmetric diallyl tetraoxobispidine (**93**) was found to exhibit interesting and predictable reactivity – with a tendency toward $C_2$-type (rather than $C_S$-type) regiomers. We were fortunate from the outset[135] to discover that the diagonally opposing carbonyl groups of tetraoxobispidine **93** were inherently sufficiently differentiated to transfer $C_2$-type regioselectivity without reagent control.



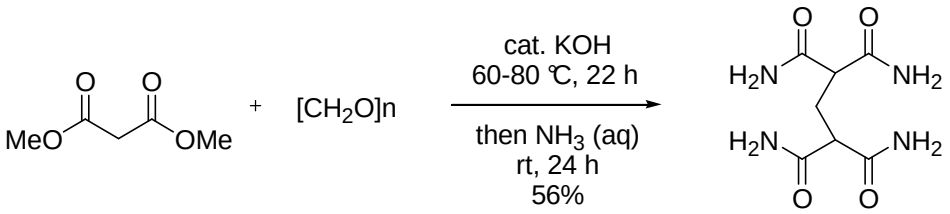

Scheme 42: Summary of our total syntheses
of the complete sparteine subgroup of alkaloids

Our most recent publication[206] summarizes the syntheses of all three sparteine alkaloids, as well as our studies toward rendering these syntheses enantioselective. Finally, we have also succeeded in generating N,N'-dibenzyl bispidine (**150**) through reduction of its corresponding tetraoxo analog. This

demonstrates that N,N’-disubstituted bispidines *not* substituted at the methylene bridge may also be prepared by this method.

# Chapter 4: Experimental

Laboratory notebook reference: jpm77




**105**
$C_5H_8O_4$
(132.11)

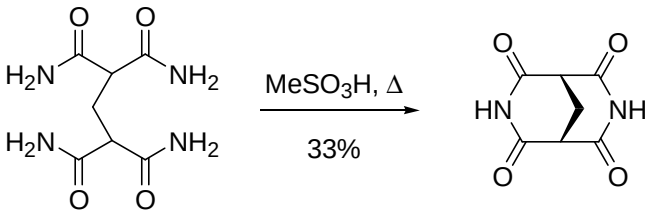
**106**
$CH_2O$
(30.03)

**107**
$C_7H_{12}N_4O_4$
(216.19)

**1,1,3,3-Tetra(aminocarbonyl)propane** (**107**)**:**[135] A stirred mixture of dimethyl malonate (500 mL, d = 1.15, 575 g, 4.36 mol) and paraformaldehyde (32.8 g, 1.09 mol) at 60 °C was treated with 10 wt.% KOH in MeOH (5 mL). The temperature of the reaction mixture was then increased to ca. 80 °C and stirring continued for a further 24 h. After this time, the mixture was allowed to cool to rt and shaken with $H_2O$ (100 mL). The lower organic phase layer was separated and excess dimethyl malonate removed by distillation at reduced pressure (vacuum pump). After cooling, the residue was treated with conc. aq. $NH_3$ (300 mL) and the resulting biphasic mixture stirred vigorously for 40 h. The resulting precipitated product was removed by filtration and washed successively with EtOAc-MeOH (4:1, 250 mL), acetone (100 mL), and dried in an oven (70 °C, overnight) to afford the tetraamide (130.8 g, 0.605 mol, 56%) as a cream-colored powder of sufficient purity for immediate further elaboration: mp 265 °C dec. (MeOH-$H_2O$); IR (KBr) 3385, 3191, 1660, 1424, 1381, 1346, 619 $cm^{-1}$; $^1H$ NMR

(400 MHz, $d_6$-DMSO) δ 7.17 (4H, s), 7.03 (4H, s), 2.95 (2H, t, J = 7.4 Hz), 2.00 (2H, t, J = 7.5 Hz) ppm; $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 170.7 (4C, 0), 50.3 (2C, 1), 28.3 (2) ppm; Characterization data in agreement with cited literature.[135]

Laboratory notebook reference: jpm78



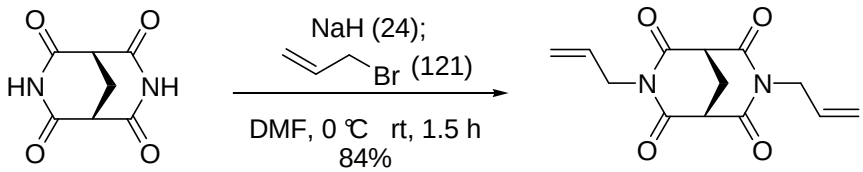

**107**
$C_7H_{12}N_4O_4$
(216.19)

**108**
$C_7H_6N_2O_4$
(182.13)

**2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonane (108):**[135] A mechanically stirred paste of finely powdered tetraamide (65.0 g, 301 mmol) and methanesulfonic acid (60 mL) was carefully heated in a 1 L RB flask with a cool Bunsen burner flame for ca. 30 min. During heating, an initial period of fairly intense effervescence was observed which subsided to leave a gently boiling homogenous yellow solution. The mixture was allowed to cool for 10 min., and then MeOH (120 mL) was added. The resulting thick precipitate was triturated thoroughly and the upper homogenous white solids removed by filtration. Further MeOH (120 mL) was added to the remaining non-homogenized solids, triturated thoroughly and removed by filtration. The filter-cake was transferred to a 500 mL

conical flask and $H_2O$ (120 mL) was added. Subsequent vigorous stirring (10 min.) resulted in dissolution of the majority of the ammonium methanesulfonate by-product and left a fine milky suspension of the desired bisimide. The fine solid matter was removed by filtration, washed with acetone (30 mL) and dried in an oven (70 °C, overnight) to yield tetraoxobispidine (18.0 g, 98.9 mmol, 33%) as a white powder. The material was contaminated with a miniscule quantity of ammonium methanesulfonate but otherwise ready for further elaboration. Recrystallization from $H_2O$ gave colorless needles of pure material: mp 295 °C dec. ($H_2O$); IR (KBr) 3256, 3228, 3106, 2829, 1741, 1710, 1425, 1342, 1275, 1204, 1065, 836, 808 $cm^{-1}$; $^1H$ NMR (400 MHz, $d_6$-DMSO) δ 11.43 (2H, s), 3.64 (2H, t, J = 2.7 Hz), 2.59 (2H, t, J = 2.6 Hz) ppm; $^{13}C$ NMR (75 MHz, $d_6$-DMSO) δ 166.9 (4C, 0), 47.2 (2C, 1), 22.8 (2) ppm; Characterization data in agreement with cited literature.[135]

Laboratory notebook reference: jpm114



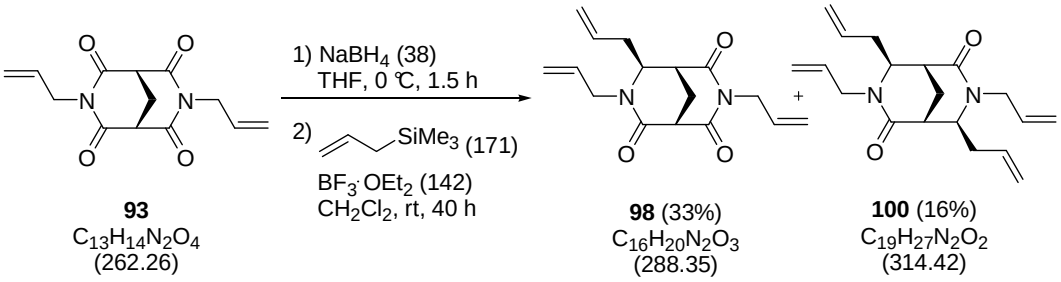

**108**
$C_7H_6N_2O_4$
(182.13)

**93**
$C_{13}H_{14}N_2O_4$
(262.26)

**3,7-Diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (93):**[135] A vigorously stirred suspension of bisimide (17.23 g, 94.7 mmol) in anhydrous DMF (180 mL) at 0 °C under Ar was treated portionwise with sodium hydride (9.11 g, 60 wt.% in oil, 227.8 mmol). The ensuing gas evolution ceased within 1 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, 228.1 mmol). The mixture was warmed to rt and stirred for an additional 1.7 h. After this time, the reaction mixture was quenched with sat. aq. $NH_4Cl$ (50 mL), then partitioned between $H_2O$ (160 mL) and EtOAc (240 mL). The layers were separated and the aqueous phase extracted with EtOAc (2x80 mL). The combined organic extracts were washed successively with $H_2O$ (2x80 mL) and brine (35 mL), 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 (20.85 g, 79.6 mmol, 84%) as a cream-colored powder: mp 128-132 °C (EtOAc); IR (KBr) 3449, 3372, 3005, 2945, 1720, 1425, 1365, 1246, 934, 626, 562 $cm^{-1}$;

$^{1}$H NMR (400 MHz, $d_6$-DMSO) δ 5.67 (2H, ddt, J = 17.1, 10.3, 5.8 Hz), 5.07 (2H, dq, J = 8.6. 1.1 Hz), 5.04 (2H, dq, J = 17.0. 1.2 Hz), 4.29 (4H, dt, J = 5.8, 1.1 Hz), 4.03 (2H, t, J = 2.8 Hz), 2.57 (2H, t, J = 2.9 Hz) ppm; $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 164.9 (4C, 0), 130.7 (2C, 1), 118.4 (2C, 2), 48.3 (2C, 1), 42.2 (2C, 2), 22.3 (2) ppm; Characterization data in agreement with cited literature.[135]

Laboratory notebook reference: jpm143




**(±)-(6R)-3,6,7-Triallyl-2,4,8-trioxo-3,7-diazabicyclo[3.3.1]nonane** (**98**)**:** A well-stirred solution of bisimide (2.70 g, 10.3 mmol) in anhydrous THF (45 mL) at 0 °C was treated with $NaBH_4$ (274 mg, 7.2 mmol). The reaction was stirred for 4.5 h before quenching by dropwise addition of 4 M HCl (8 mL). Stirring continued at 0 °C until the evolution of $H_2$ bubbles ceased (ca. 5 min), then the mixture was brought to rt with continued stirring. The mixture was partitioned between EtOAc (40 mL) and $H_2O$ (20 mL), and the layers shaken and separated.

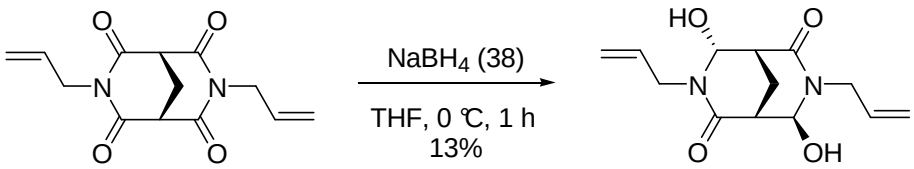
The aqueous phase was reextracted with EtOAc (2x40 mL), and the combined organic phases washed with sat. aq. $NaHCO_3$ (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give 2.30 g crude residue as a pale yellow oil.

A stirred solution of the crude residue (2.30 g) in anhydrous $CH_2Cl_2$ (25 mL) at rt under Ar was treated with silane (4.16 mL, 26.2 mmol), followed by dropwise addition of $BF_3 \bullet OEt_2$ (1.64 mL, 13.1 mmol). The mixture was stirred for 40 h, then diluted with $CH_2Cl_2$ (30 mL), washed with $H_2O$ (2x20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give 2.55 g crude residue as a yellow oil. This was further purified by column chromatography ($SiO_2$, eluting with 100% $CH_2Cl_2$) to give 829 mg (2.9 mmol, 28%) of the pure triallylated product as a yellow oil. Further elution (1% to 2% MeOH in $CH_2Cl_2$) yielded a mixture of mostly tetraallylated product (506 mg, 1.6 mmol, 16%) contaminated with residual triallyl material (134 mg, 0.5 mmol, 5% additional). The authenticity of the tetraallyl material was confirmed through comparison with the known compound.[136]

**(±)-(6R)-3,6,7-Triallyl-2,4,8-trioxo-3,7-diazabicyclo[3.3.1]nonane (98):** IR (KBr) 3082, 2949, 1739, 1684, 1455, 1357, 1194, 995, 922, 758, 630 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.78-5.55 (3H, m), 5.24-5.06 (6H, m), 4.51 (1H, dm, J = 15.2 Hz), 4.37-4.25 (2H, m), 3.70 (1H, d, J = 10.5 Hz), 3.66 (1H, m), 3.49 (1H, dd, J = 15.3 Hz, 7.3 Hz), 3.11 (1H, m), 2.71 (1H, dm, J = 14.6 Hz), 2.40-2.34 (1H, m), 2.29-2.19 (2H, m) ppm; $^{13}C$ NMR (75 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 (0), 58.7 (1),

48.3 (1), 47.8 (2), 42.1 (2), 39.9 (1), 36.7 (2), 19.8 (2) ppm; Characterization data in agreement with cited literature.[136]

Laboratory notebook reference: jpm141



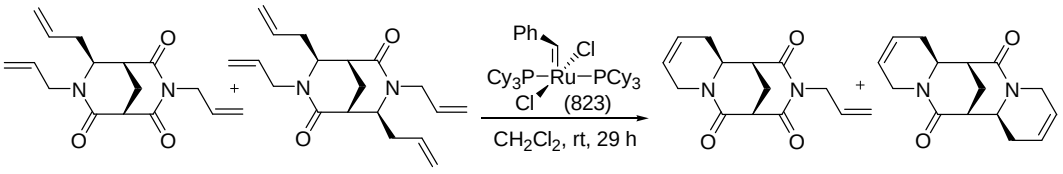

**93**
$C_{13}H_{14}N_2O_4$
(262.26)

**116**
$C_{13}H_{18}N_2O_4$
(266.16)

**(±)-(4R,8S)-4,8-Hydroxy-2,6-dioxo-3,7-diazabicyclo[3.3.1]nonane (116):** A well-stirred solution of bisimide (2.06 g, 7.9 mmol) in anhydrous THF (34 mL) at 0 °C was treated with $NaBH_4$ (209 mg, 5.5 mmol). The reaction was stirred for 1 h before quenching by dropwise addition of 4 M HCl (6 mL). The mixture was partitioned between EtOAc (40 mL) and $H_2O$ (20 mL), and the layers shaken and separated. The aqueous phase was reextracted with EtOAc (2x40 mL), and the combined organic phases washed with sat. aq. $NaHCO_3$ (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give 1.63 g crude residue as an opaque white oil. This was triturated with $CH_2Cl_2$, then the solids removed by filtration and washed well with $CH_2Cl_2$ to give 275 mg (1.03 mmol, 13%) white solid. An attempt to recrystallize in EtOAc resulted in an increased proportion of the C2-symmetric *exo*-hydroxyl epimer: mp 150-160 °C (EtOAc), softens @ 144 °C; IR (KBr) 3314

(br), 2943, 2731, 1631, 1478, 1418, 1266, 1217, 1064, 934, 738, 563 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 5.83-5.63 (2H, m), 5.21-5.09 (4H, m), 5.08-5.01 (2H, m), 4.70 (1H, d, J = 9.8), 4.41 (1H, ddt, J = 15.5, 4.6, 1.7 Hz), 4.18 (1H, ddt, J = 14.9, 5.0, 1.4 Hz), 4.03 (1H, ddm, J = 14.8, 7.0 Hz), 3.77 (1H, ddm, J = 15.5, 6.8 Hz), 3.05-3.00 (1H, m), 2.90-2.85 (1H, m), 2.61 (1H, ddd, J = 13.6, 4.7, 1.9 Hz), 1.90 (1H, d, J = 9.3), 1.90 (1H, dm, J = 13.6 Hz) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.4 (0), 168.4 (0), 132.7 (1), 132.1 (1), 118.4 (2), 118.0 (2), 80.6 (1), 79.4 (1), 46.76 (2), 45.2 (1), 43.8 (2), 41.9 (1), 18.6 (2) ppm; MS (EI+) m/z 266 (M+•), 136 (base); HRMS (EI+) m/z 266.12661 (calculated for $C_{13}H_{18}N_2O_4$: 266.12666).

Laboratory notebook reference: jpm100




**98** (33%)
$C_{16}H_{20}N_2O_3$
(288.35)

**100** (16%)
$C_{19}H_{27}N_2O_2$
(314.42)

**118** (71%)
$C_{14}H_{16}N_2O_3$
(260.29)

**119** (71%)
$C_{15}H_{18}N_2O_2$
(258.32)

**Ring-Closing Metathesis:** A stirred solution of the 71:29 triallyl:tetraallyl mixture (607 mg total: 431 mg, 1.50 mmol triallyl : 176 mg, 0.56 mmol tetraallyl) in anhydrous $CH_2Cl_2$ (14 mL) at rt under Ar was treated with Grubbs's 1st Generation Ruthenium alkylidene complex (30 mg). The reaction mixture was

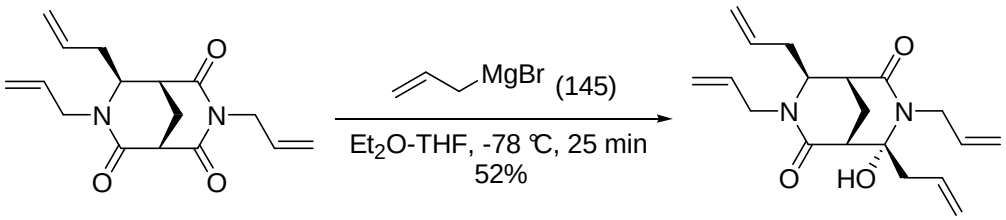
stirred for 29 h, during which time additional portions of Grubbs's catalyst (4 mg, 6 mg: 40 mg overall, 2 mol%) were added. The mixture was then diluted with $CH_2Cl_2$ (10 mL), washed with $H_2O$ (2 x 10 mL), brine (10 mL), dried ($Na_2SO_4$) and concentrated in vacuo to give 600 mg oil, discolored brown with catalyst. This was further purified by column chromatography ($SiO_2$, eluting with EtOAc) to yield 278 mg (1.07 mmol, 71%) of the tricyclic product (RF = .36) as a crystalline solid, followed by 143 mg (0.55 mmol, 98%) of the tetracyclic product (RF = .08) as a crystalline solid.

**(±)-3-Allyl-$\Delta^{9}$-dehydro-2,4,6-trioxo-3,7-diazatricyclo-[7.3.1.0$^{7,12}$]dodecane (118):** mp 152-158 °C (EtOAc); IR (KBr) 2968, 1742, 1686, 1639, 1454, 1333, 1204, 985, 705, 551 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 5.81-5.62 (3H, m), 5.10-4.99 (2H, m), 4.83 (1H, dm, J = 18.5 Hz), 4.31 (2H, m), 3.82 (1H, dd, J = 11.2, 3.7 Hz), 3.67 (1H, q, J = 2.6), 3.38 (1H, dm, J = 18.5 Hz), 2.97 (1H, m), 2.48-2.34 (1H, m), 2.32 (2H, t, J = 2.9 Hz), 2.26-2.15 (1H, m) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 172.6 (0), 167.6 (0), 161.7 (0), 131.5 (1), 124.2 (1), 124.0 (1), 117.4 (2), 55.5 (1), 48.0 (1), 42.8 (2), 41.8 (2), 41.7 (1), 31.8 (2), 19.9 (2) ppm; MS (EI) m/z 260 $M^{+\bullet}$, 43 (base); HRMS (EI) m/z 260.1162 (calcd. for $C_{14}H_{16}N_2O_3$: 260.1161)

**(±)-$\Delta^{3,13}$-Didehydro-10,17-dioxo-β-isosparteine (119):**[136] mp 196-197 °C (EtOAc-hexanes); IR (KBr) 3514, 3333, 3243, 2852, 2142, 1656, 1437, 1355, 959, 705 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 5.80-5.71 (2H, m), 5.67-5.60 (2H, m), 4.75 (2H, dm, J = 17.0 Hz), 3.77 (2H, dd, J = 11.3, 3.9 Hz), 3.40 (2H, dm, J =

18.5 Hz), 2.65 (2H, t, J = 3.0 Hz), 2.42-2.27 (2H, m), 2.13 (2H, dm, J = 16.9 Hz), 2.07 (2H, t, J = 3.1 Hz) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.5 (2C, 0), 124.5 (2C, 1), 124.1 (2C, 1), 56.2 (2C, 1), 42.8 (2C, 2), 41.4 (2C, 1), 31.5 (2C, 2), 17.3 (2) ppm; Characterization data in agreement with cited literature.[136]

Laboratory notebook reference: jpm146




**98**
$C_{16}H_{20}N_2O_3$
(288.35)

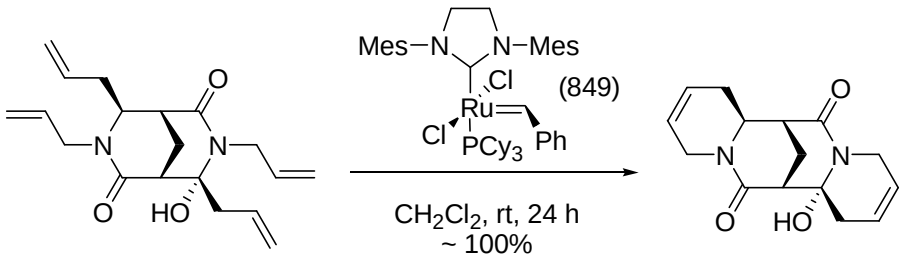
**104**
$C_{19}H_{26}N_2O_3$
(330.43)

**(±)-4-Hydroxy-2,6-dioxo-3,4,7,8-tetraallyl-3,7-diazabicyclo[3.3.1]nonane (104):** Grignard solution titration: an oven-dried flask was charged with ca. 2 mg 9,10-phenanthroline, then treated with 1.0 mL commercial allyl-Magnesium Grignard solution in $Et_2O$. Benzyl alcohol (1.0 M in THF) was added dropwise to the rapidly stirred mixture under Ar until the dark red color dissipated to bright yellow (0.74 mL benzyl alcohol required). Grignard concentration: 0.74 M.

A rapidly stirred solution of the triallyl (405 mg, 1.41 mmol) in anhydrous THF (11 mL) at -78 °C under Ar was treated dropwise with Grignard solution (2.47 mL, 0.74 M in $Et_2O$, 1.83 mmol). The mixture was stirred for 25 min

before quenching with sat. aq. $NH_4Cl$ (5 mL), then stirred for 5 min at -78 °C before bringing to rt. The mixture was partitioned between EtOAc (20 mL) and $H_2O$ (20 mL), the layers shaken and separated. The aqueous phase was reextracted with EtOAc (2x20 mL), and the combined organic phases washed with brine (10 mL), dried ($Na_2SO_4$), and concentrated *in vacuo* to yield 504 mg crude residue as an orange oil. This was further purified by column chromatography ($SiO_2$, 0% to 50% EtOAc in hexanes) to yield the addition product (240 mg, 0.73 mmol, 52%) as a yellow oil: IR (KBr) 3329, 3071, 2972, 2925, 1643, 1613, 1432, 1157, 916 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.8-5.4 (4H, m), 5.32 (1H, d, J = 1.9 Hz), 5.07-4.89 (8H, m), 4.30-4.21 (1H, ddt, J = 15.2, 4.8, 1.4 Hz), 4.05-3.96 (1H, ddm, J = 14.9, 6.6 Hz), 3.76 (1H, ddm, J = 14.9, 5.0 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), 87.1 (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 330.0 $M^{+\cdot}$, 289 base, 206(20%), 136(16%), 96(16%); HRMS (EI) m/z 330.1946 (calculated for $C_{19}H_{26}N_2O_3$: 330.1944)

Laboratory notebook reference: jpm151



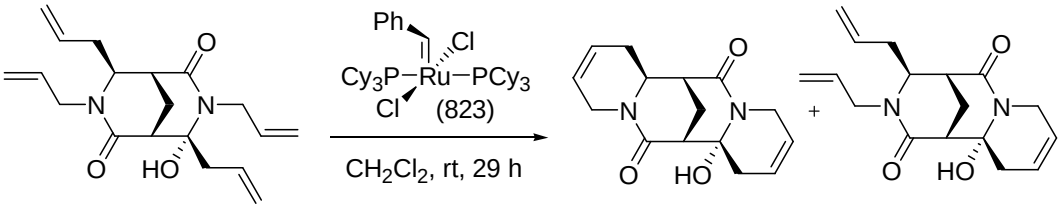

**104**
$C_{19}H_{26}N_2O_3$
(330.43)

**126**
$C_{15}H_{18}N_2O_3$
(274.32)

**(±)-$\Delta^{3,13}$-Didehydro-6-hydroxy-10,17-dioxosparteine** (**126**)**:** A solution of the tetraallyl (116 mg, 0.35 mmol) and Grubbs's 2nd Generation Ruthenium Alkylidene complex (15 mg, 0.018 mmol, 5 mol%) in anhydrous $CH_2Cl_2$ (3.5 mL) at rt under Ar was stirred for 24 h. The solvent was then removed under vacuum to give the crude residue as a solid, discolored brown with catalyst. This was triturated with $Et_2O$ (10 mL), and the solids removed by filtration to give 97 mg (0.35 mmol, ~100%) of the tetracycle as a light-brown-discolored solid, but of good purity by $^1$H NMR. A small sample was recrystallized from MeOH for characterization purposes: mp – softens and takes on a reddish tint @ 108 °C, then melts @ 224-227 °C; IR (KBr) 3270, 3036, 2916, 1620, 1429, 1255, 1201, 1184, 988, 896, 672 $cm^{-1}$; $^1$H NMR (300 MHz, $d_6$-DMSO) δ 5.83-5.58 (4H, m), 5.54 (1H, s), 4.75 (1H, dm, J = 18.7 Hz), 4.53 (1H, dm, J = 18.0 Hz), 3.56 (1H, dd, J = 11.2, 3.8), 3.48-3.27 (2H, m), 2.72-2.53 (3H, m), 2.42-2.27 (1H, m), 2.20-1.99 (4H, m) ppm; $^{13}$C NMR (100 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 256 $(M\text{-}H_2O)^+$; HRMS (EI+) m/z 274.13112 (calculated for $C_{15}H_{18}N_2O_3$: 274.13175).

Laboratory notebook reference: jpm99




**104**
$C_{19}H_{26}N_2O_3$
(330.43)

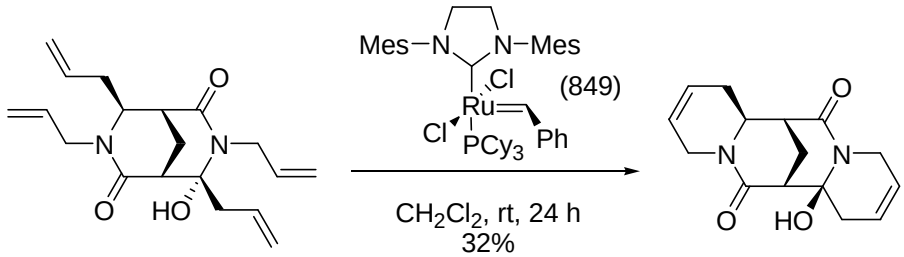
**126** (61%)
$C_{15}H_{18}N_2O_3$
(274.32)

**127** (18%)
$C_{17}H_{22}N_2O_3$
(302.37)

**(±)-3,4-Diallyl-$\Delta^9$-dehydro-2,6-dioxo-3,7-diazatricyclo-[7.3.1.0$^{7,12}$]dodecane** (**127**)**:** A stirred solution of the tetraallyl (269 mg, 0.82 mmol) in anhydrous $CH_2Cl_2$ a rt under Ar was treated with Grubbs's 1$^{st}$ Generation Ruthenium Alkylidene Complex (14 mg, 0.02 mmol). The reaction was stirred for 29 h, during which time additional portions of Grubbs's catalyst were added (4 mg, 6 mg; 24 mg overall, 0.03 mmol, 4 mol%). The mixture was then diluted with $CH_2Cl_2$ (15 mL), washed with $H_2O$ (2 x 10 mL), brine (10 mL), dried ($Na_2SO_4$), and concentrated *in vacuo* to yield 190 mg crude residue as a pale white oil covered with spots of the brown catalyst. This was further purified by column chromatography ($SiO_2$, eluting with 70/30 EtOAc/hexanes) to give 44 mg (0.15 mmol, 18%) of the undesired tricycle (RF = 0.28), followed by 137 mg (0.50

mmol, 61%) of the desired tetracycle (RF = .08). Tricycle (**127**) characterization data: mp 150-154 °C (EtOAc-hexanes); IR (KBr) 3359, 2920, 1622, 1432, 1415, 903 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 5.83-5.61 (4H, m), 5.23-5.12 (4H, m), 5.07 (1H, dq, J = 17.2, 1.3 Hz) 4.75 (1H, dm, J = 18.1 Hz), 4.42-4.33 (1H, ddt, J = 15.7, 4.7, 1.7 Hz), 3.75-3.61 (3H, m), 2.85-2.62 (4H, m), 2.31-2.17 (3H, m), 2.12-2.03 (1H, ddm, J = 14.3, 4.5 Hz) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.8 (0), 168.6 (0), 133.1 (1), 131.5 (1), 124.2 (1), 121.9 (1), 119.3 (2), 117.5 (2), 82.8 (0), 58.7 (1), 47.9 (2), 45.4 (1), 39.3 (1), 39.1 (2), 37.7 (2), 36.5 (2), 18.1 (2) ppm; MS (EI) m/z 302 (M+•), 261 (base); HRMS (EI) m/z 302.1626 (calcd. For $C_{17}H_{22}N_2O_3$: 302.1631).

Laboratory notebook reference: jpm152



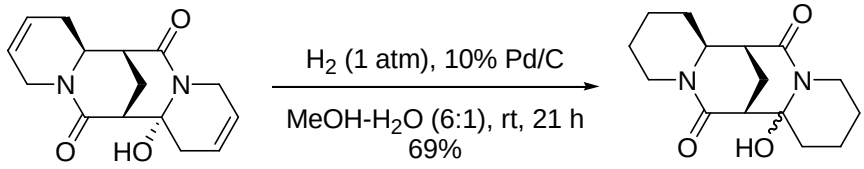

**104**
$C_{19}H_{26}N_2O_3$
(330.43)

**128**
$C_{15}H_{18}N_2O_3$
(274.32)

**(±)-$\Delta^{3,13}$-didehydro-6S-hydroxy-10,17-dioxosparteine** (**128**)**:** A solution of the tetraallyl (307 mg, 0.93 mmol) and Grubbs's 2nd Generation Ruthenium Alkylidene complex (40 mg, 0.047 mmol, 5 mol%) in anhydrous $CH_2Cl_2$ (9 mL)

at rt under Ar was stirred for 24 h. The solvent was then removed under vacuum to give the crude residue as a brown oily solid. This was triturated with $Et_2O$ (20 mL) and the solids removed by filtration to give 125 mg brown solid. This was further purified by column chromatography ($SiO_2$, 0-2% MeOH in $CH_2Cl_2$) to give 82 mg (0.30 mmol, 32%) of the exo-hydroxyl product as a light-brown solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.90-5.62 (4H, m), 5.11 (1H, s), 4.75 (2H, dm, J = 18.0 Hz), 3.78 (1H, dd, J = 11.3, 3.8 Hz), 3.66 (1H, dm, J = 18.0 Hz), 3.50 (1H, dm, J = 18.2 Hz), 2.84 (1H, m), 2.70 (1H, d, J = 17.1 Hz), 2.67 (1H, s), 2.44-2.10 (5H, m) ppm.

Laboratory notebook reference: jpm149




**126**
$C_{15}H_{18}N_2O_3$
(274.32)

R(**129**):S(**130**) ~ 2:3
$C_{15}H_{22}N_2O_3$
(278.35)

A solution of the diene (92 mg, 0.34 mmol) and 10 wt% Palladium on Carbon (30 mg) in methanol-$H_2O$ (6:1, 18 mL) was vigorously stirred under an atmosphere of $H_2$ gas (1 atm balloon) for 21 h. The active gas was then purged with Ar and the mixture filtered through a Celite pad. The pad was washed well with MeOH and the filtrate/washings concentrated *in vacuo* to give 115 mg crude residue as a

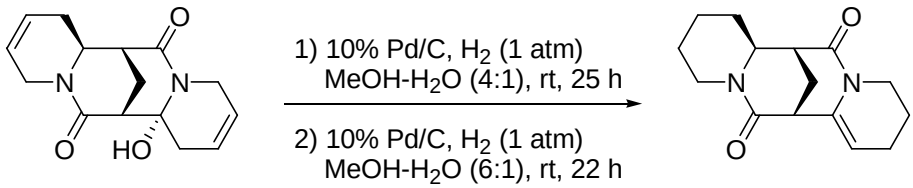
brown oil. This was further purified by column chromatography ($SiO_2$, eluting with 5% MeOH in $CH_2Cl_2$) to yield the R-hydroxyl diastereomer as a crystalline solid (26 mg, 0.09 mmol, 28%), a small sample of which was recrystallized from $Et_3N$ for characterization purposes. This was followed by the S-hydroxyl diastereomer as a clear oil (39 mg, 0.14 mmol, 41%).

**(±)-6R-hydroxy-10,17-dioxosparteine** (**129**)**:** mp 198-200 °C ($Et_3N$), softens @ 170 °C; IR (KBr) 3183, 2943, 1642, 1473, 1429, 1271, 1190, 1005, 966, 634, 503 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.71 (1H, dm, J = 13.1 Hz), 4.70 (1H, d, J = 1.0 Hz), 4.40 (1H, dm, J = 12.8 Hz), 3.50 (1H, dm, J = 11.3 Hz), 3.17 (1H, td, J = 13.1, 3.0 Hz), 2.73 (1H, dt, J = 3.4, 2.6 Hz), 2.60 (1H, dm, J = 2.4 Hz), 2.52 (1H, td, J = 13.0, 2.8 Hz), 2.23-2.05 (3H, m), 2.02-1.92 (1H, m), 1.90-1.50 (8H, m), 1.49-1.29 (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 260 $(M\text{-}H_2O)^+$; HRMS (EI+) m/z 278.16351 (calculated for $C_{15}H_{22}N_2O_3$: 278.16305).

**(±)-6S-hydroxy-10,17-dioxosparteine** (**130**)**:** IR (KBr) 3455(br), 2856, 1653, 1473, 1141, 1032, 966, 896, 863, 738 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, dm, J = 13.0 Hz), 4.42 (1H, dm, J = 13.0 Hz), 4.07 (1H, s), 3.48 (1H, dm, J = 11.2 Hz), 2.85 (1H, td, J = 13.4, 3.2 Hz), 2.72 (1H, m), 2.55 (1H, s), 2.50 (1H, dm, J = 13.3 Hz), 2.42 (1H, td, J = 12.9, 2.6 Hz), 2.02-1.89 (3H, m), 1.85-1.47

(8H, m), 1.43-1.28 (2H, m) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.0 (0), 166.6 (0), 83.9 (0), 60.2 (1), 49.9 (1), 43.7 (2), 43.1 (1), 37.9 (2), 36.3 (2), 32.5 (2), 25.3 (2), 25.0 (2), 24.9 (2), 19.4 (2), 18.1 (2) ppm; MS (EI+) m/z 294, 276, 260 (M-$H_2O$)$^+$; HRMS (EI+) m/z 260.15270 (100.0% base, calculated for $C_{15}H_{20}N_2O_2$: 260.15248), 274.13028 (57.1% base, calculated for $C_{15}H_{18}N_2O_3$: 274.13175), 276.14679 (63.1% base, calculated for $C_{15}H_{20}N_2O_3$: 276.14740).

Laboratory notebook reference: jpm153



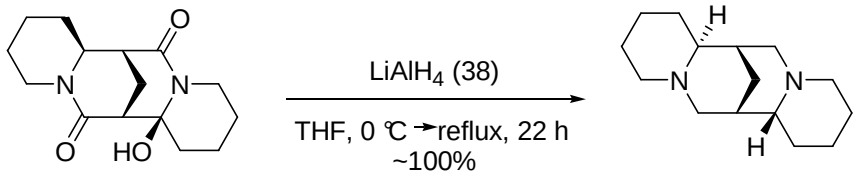

**126**
$C_{15}H_{18}N_2O_3$
(274.32)

**131**
$C_{15}H_{20}N_2O_2$
(260.34)

**(±)-Δ$^5$-dehydro-10,17-dioxosparteine** (**131**)**:** A solution of the diene (82 mg, 0.30 mmol) and 10% palladium on charcoal (20 mg) in methanol-$H_2O$ (5:1, 12 mL) was vigorously stirred under an atmosphere of $H_2$ gas (1 atm balloon) for 25 h. The active gas was purged with Ar and the mixture filtered through a pad of Celite. The pad was washed well with MeOH/$CH_2Cl_2$ (1:1, 120 mL) and the combined washings removed under vacuum to give 80 mg crude residue as a brown oil, which still showed significant alkenyl groups by $^1$H NMR. The residue was resubjected to the reaction conditions in methanol-$H_2O$ (6:1, 14 mL)

with 10% Pd/C (34 mg) for 22 h. The active gas was purged with Ar and the mixture filtered through a Celite pad. The pad was washed well with MeOH/$CH_2Cl_2$ (1:1, 100 mL) and the combined washings concentrated *in vacuo* to give 100 mg crude residue as a brown oil. This was further purified by chromatography ($SiO_2$, 2% MeOH in $CH_2Cl_2$) to give 48 mg (0.18 mmol, 61%) of the elimination product as a white solid. mp 144-149 °C; IR (KBr) 2926, 2856, 1649, 1470, 1389, 1272, 1206, 1023, 976, 774 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.09 (1H, t, J = 4.0 Hz), 4.68 (1H, dm, J = 13.0 Hz), 4.05-3.96 (1H, m), 3.58 (1H, dm, J = 11.1 Hz), 3.44 (1H, ddd, J = 13.1, 9.2, 3.9 Hz), 3.28 (1H, dt, J = 3.2, 2.5 Hz), 2.71 (1H, dm, J = 2.1 Hz), 2.43 (1H, td, J = 12.8, 2.8 Hz), 2.24-1.99 (4H, m), 1.99-1.90 (1H, m), 1.90-1.65 (4H, m), 1.70-1.52 (2H, m), 1.47-1.32 (1H, m) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.2 (0), 167.0 (0), 133.8 (0), 107.2 (1), 61.0 (1), 44.1 (1), 43.8 (2), 43.1 (1), 40.7 (2), 32.5 (2), 25.4 (2), 25.1 (2), 22.5 (2), 21.9 (2), 21.3 (2) ppm; MS (EI+) m/z 260 ($M^{+\bullet}$, base), 149; HRMS (EI+) m/z 260.15165 (calculated for $C_{15}H_{20}N_2O_2$: 260.15248).

Laboratory notebook reference: jpm103



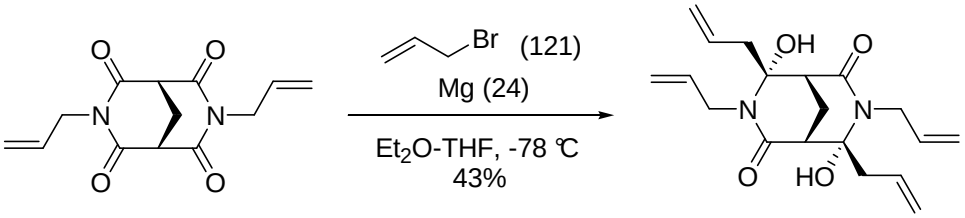

**130**
$C_{15}H_{22}N_2O_3$
(278.35)

*dl*-**1**
$C_{15}H_{26}N_2$
(234.39)

**(±)-Sparteine** (*dl*-**1**)**:**[207] A stirred solution of the oxo-tetracycle (50 mg, 0.18 mmol) in anhydrous THF (1 mL) at 0°C under Ar was treated with LAH (90 mg), and the resulting suspension heated at reflux for 22 h. The mixture was brought to rt and diluted with $Et_2O$ (10 mL), then quenched by careful portionwise addition of moist $Na_2SO_4$ and stirred for a further 10 min until the evolution of $H_2$ bubbles ceased. It was then filtered through a Celite pad and washed well with 10% MeOH in $CH_2Cl_2$ (50 mL). The filtrate/washings were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford 46 mg sparteine (0.20 mmol, ~100%) as a colorless oil, of good purity by $^1$H and $^{13}$C NMR in comparison with a commercial (Aldrich) sample of (-)-sparteine; IR (neat) 3395(br), 2927, 2856, 2758, 1647, 1446, 1353, 1288, 1113 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.76 (1H, dm, J = 11.0 Hz), 2.68 (1H, t, J = 11.0 Hz), 2.66 (1H, dm, J = 11.0 Hz), 2.51 (1H, dm, J = 10.9 Hz), 2.32 (1H, dd, J = 11.2, 3.5 Hz), 2.09-1.86 (5H, m), 1.86-1.77 (1H, m), 1.75-1.62 (3H, m), 1.60-1.41 (6H, m), 1.41-1.10 (5H, 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), 35.0 (2), 33.2 (1), 29.5 (2), 27.8 (2), 26.0 (2), 25.8 (2), 24.9 (2), 24.8 (2) ppm; Characterization data in agreement with cited literature[207] and Aldrich sample of (-)-sparteine (*l*-**1**).

Laboratory notebook reference: jpm14



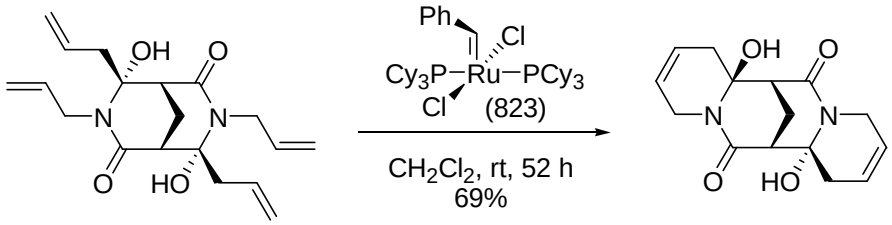

**93**
$C_{13}H_{14}N_2O_4$
(262.26)

**94**
$C_{19}H_{26}N_2O_4$
(346.42)

**4,8-Dihydroxy-2,6-dioxo-3,4,7,8-tetraallyl-3,7-diazabicyclo[3.3.1]nonane (94):**[135] A stirred suspension of mechanically-activated magnesium (1.09 g, 45.4 mmol) in anhydrous $Et_2O$ (15 mL) at rt under Ar was treated with several grains of iodine, then dropwise with allyl bromide (1.30 mL, d = 1.43, 1.86 g, 15.4 mmol) in anhydrous $Et_2O$ (15 mL) over 25 min such that a gentle reflux was maintained. After stirring for an additional 2.2 h, the resulting dark grey solution of alllmagnesium bromide was added rapidly via syringe to a cooled solution of bisimide (1.00 g, 3.8 mmol) in anhydrous THF (30 mL) at -78 °C under Ar. A thick white precipitate formed immediately upon addition, and the resulting

suspension was stirred vigorously for 50 min before being quenched with sat. aq. $NH_4Cl$ (10 mL). The mixture was warmed to rt, partitioned between EtOAc (20 mL) and $H_2O$ (20 mL), and the layers well shaken and separated. The aqueous phase was extracted with EtOAc (10 mL), and the combined organic phases washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated in vacuo. The resulting solid residue was triturated with refluxing hexanes (3x5 mL) and the supernatant liquor decanted off from an insoluble yellow oil which was discarded. The hexanes triturate was slowly cooled to induce crystallization of the desired product (.57 g, 1.65 mmol, 43 %) which was isolated as large colorless needles by filtration: mp 86-87 °C (hexanes); IR (KBr) 3329, 3088, 2989, 2942, 1609, 1432, 1075, 998, 929, 753, 615 $cm^{-1}$; $^1H$ NMR (400 MHz, $d_6$-DMSO) δ 5.88-5.67 (4H, m), 5.56 (2H, d, J = 2.0 Hz), 5.17-5.02 (8H, m), 4.12 (2H, ddt, J = 15.2, 6.3, 1.2 Hz), 3.94 (2H, ddt, J = 15.2, 5.2, 1.4 Hz), 2.83 (2H, t, J = 3.2 Hz), 2.81 (2H, ddt, J = 14.8, 4.6, 1.7 Hz), 2.34 (2H, ddd, J = 14.4, 9.7, 2.0 Hz), 2.13 (2H, t, 3.2 Hz) ppm; $^{13}C$ NMR (75 MHz, $d_6$-DMSO) δ 169.0 (2C, 0), 134.0 (2C, 1), 132.3 (2C, 1), 119.3 (2C, 2), 116.9 (2C, 2), 87.1 (2C, 0), 43.2 (4C, 2), 42.7 (2C, 1), 17.9 (2) ppm; Characterization data in agreement with cited literature.[135]

Laboratory notebook reference: jpm41



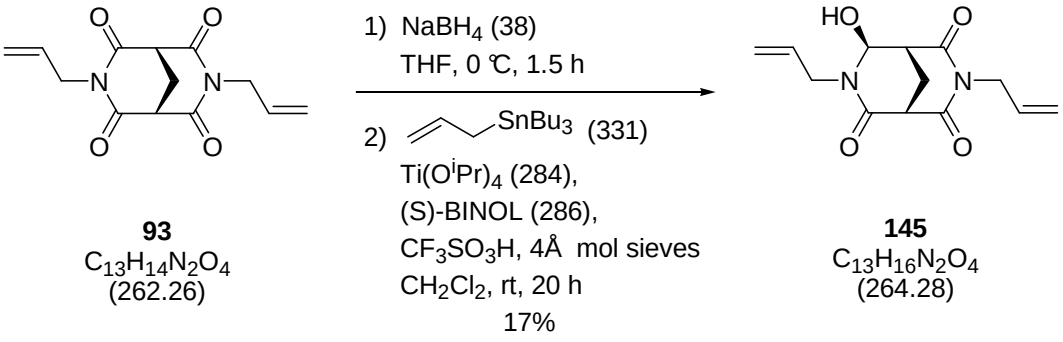

**94**
$C_{19}H_{26}N_2O_4$
(346.42)

**95**
$C_{15}H_{18}N_2O_4$
(290.32)

**(±)-$\Delta^{3,13}$-Didehydro-6,11-dihydroxy-10,17-dioxosparteine** (**95**)**:**[135] A solution of the tetraene (605 mg, 1.75 mmol) in anhydrous $CH_2Cl_2$ (17 mL) at rt under Ar was treated with Grubbs's 1st generation ruthenium alkylidene complex (36 mg, 0.04 mmol). The resulting mixture was stirred for 52 h and at regular intervals within this time frame, additional portions of Grubbs's catalyst were added (5x11 mg, 5x0.01 mmol; 1x20 mg, 1x0.02 mmol: overall 111 mg, 0.13 mmol, 8 mol%). After this time, the by then heavy precipitate was removed by filtration and the solid washed with $CH_2Cl_2$ (5 mL) to afford the ring-closed product (350 mg, 1.21 mmol, 69%) as a colorless powder: mp 268 °C (EtOH-$H_2O$); IR (KBr) 3548, 3510, 3174 (br), 1669, 1617, 1437, 1200, 1019, 895, 748, 662, 606 $cm^{-1}$; $^1H$ NMR (300 MHz, $d_6$-DMSO) δ 5.69 (2H, dm, J = 10.2 Hz), 5.60 (2H, dm, J = 10.2 Hz), 5.52 (2H, s, OH), 4.69 (2H, dm, J = 17.7 Hz), 3.39 (2H, dm, J = 18.2 Hz), 2.68 (2H, t, J = 2.9 Hz), 2.59 (2H, dm, J = 17.8), 2.13 (2H, dm, J = 17.8 Hz), 2.08 (2H, t, J = 2.9 Hz) ppm; $^{13}C$ NMR (75 MHz, $d_6$-DMSO) δ 165.7 (2C, 0), 123.7 (2C, 1),

122.5 (2C, 1), 82.3 (2C, 0), 47.4 (2C, 1), 37.6 (2C, 2), 37.4 (2C, 2), 20.4 (2) ppm; Characterization data in agreement with cited literature.[135]

Laboratory notebook reference: jpm192




**93**
$C_{13}H_{14}N_2O_4$
(262.26)

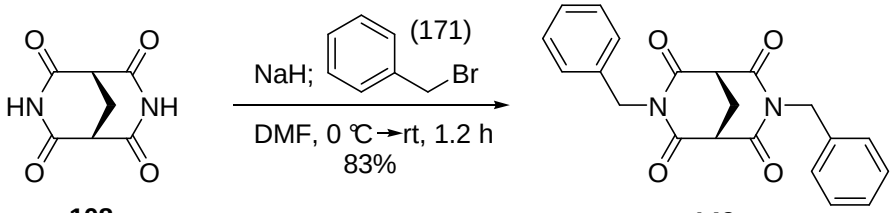
**145**
$C_{13}H_{16}N_2O_4$
(264.28)

**(±)-(6R)-3,7-Diallyl-6-hydroxy-2,4,8-trioxo-3,7-diazabicyclo[3.3.1]nonane (145):**[136] A stirred solution of the bisimide (200 mg) in anhydrous THF (2.5 mL) at 0 °C was treated with $NaBH_4$ (20 mg). The mixture was stirred for 1.5 h before quenching with 4 M HCl (0.5 mL), then stirred for a further 10 min at 0 °C until evolution of $H_2$ ceased. Brine (10 mL) and EtOAc (40 mL) were added, and the layers shaken and separated. The organic phase was washed with sat. aq. $NaHCO_3$, dried ($Na_2SO_4$) and concentrated to give 175 mg crude as a pale white oil.

A mixture of 4 angstrom molecular sieves (325 mg), $Ti(O^iPr)_4$ (22 mg, 20 mol%), (S)-BINOL (43 mg, 10 mol%), and TfOH (0.8 mL of a saturated $CH_2Cl_2$ solution) in anhydrous $CH_2Cl_2$ (3 mL) was refluxed under Ar for 1.5 h. The

reddish-brown mixture was cooled to rt and the crude product from above (in 1.5 mL anhydrous $CH_2Cl_2$) was added. The mixture was stirred for 1.5 h at rt, then treated with the allylstannane (440 mg, 1.33 mmol, 0.41 mL) and stirred for an additional 20 h. Sat. aq. $NaHCO_3$ (2 mL) was added, then the mixture partitioned with brine (30 mL) and $CH_2Cl_2$ (60 mL), the layers shaken and separated. The organic layer was washed with brine (30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give 544 mg crude residue. This was further purified by chromatography ($SiO_2$, 0 to 6% MeOH in $CH_2Cl_2$) to yield only the unreacted ß-anomer (35 mg, 17%) as a clear oil, impure by $^1$H NMR with approximately 5% α-anomer. ß-anomer: IR (neat) 3390 (br), 3085, 2949, 1740, 1691, 1473, 1206, 1064, 934, 765, 558 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 5.83-5.64 (2H, m), 5.22-5.07 (5H, m), 4.40-4.25 (3H, m), 4.33 (OH, d, J = 0.8 Hz), 3.76 (1H, ddm, J = 15.3, 7.1 Hz), 3.71 (1H, dt, J = 3.1, 2.4 Hz), 3.26 (1H, ddd, J = 4.1, 2.2, 2.2 Hz), 2.77 (1H, ddd, J = 13.7, 3.4, 2.1 Hz), 2.30 (1H, dddd, J = 13.6, 3.7, 2.3, 1.1 Hz) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.6 (0), 167.7 (0), 163.8 (0), 132.3 (1), 131.2 (1), 118.9 (2), 118.2 (2), 80.0 (1), 48.8 (1), 47.1 (2), 45.2 (1), 42.0 (2), 19.6 (2) ppm; Characterization data in agreement with cited literature.[136]

Laboratory notebook reference: jpm31



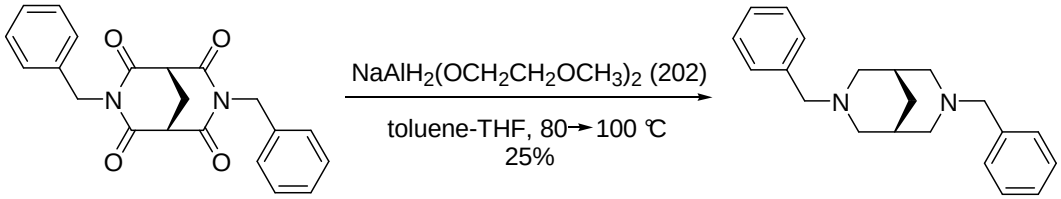

**108**
$C_7H_6N_2O_4$
(182.13)

**149**
$C_{21}H_{18}N_2O_4$
(362.38)

**3,7-Diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane** (**149**)**:** A stirred suspension of bisimide (1.98 g, 10.9 mmol) in anhydrous DMF (30 mL) at 0 °C under Ar was treated portionwise with sodium hydride (1.06 g, 60 wt.% in oil, 26.4 mmol) over ca. 5 minutes. The mixture was then treated dropwise with benzyl bromide (2.24 mL, d = 1.44, 3.2 g, 26.4 mmol). The mixture was allowed to warm to rt while stirring for 1.2 h. After this time, it was quenched with sat. aq. $NH_4Cl$ (6 mL), then partitioned between $H_2O$ (20 mL) and EtOAc (30 mL). The layers were separated and the aqueous phase extracted with EtOAc (2x10 mL). The combined organic extracts were washed successively with $H_2O$ (2x10 mL) and brine (10 mL), then dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting solid residue was triturated with hexanes (30 mL), filtered-off and dried (70 °C, 4 h) to afford the pure dibenzylated product (3.26 g, 9.0 mmol, 83%) as a white powder: mp 167-168 °C ($Et_2O$); IR (KBr) 3385, 3036, 2965, 1702, 1435, 1364, 1326, 1190, 1064, 1005, 705, 618 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.24 (10H, s), 4.91 (4H, s), 4.08 (2H, t, J = 2.8 Hz), 2.50 (2H, t, J = 2.9 Hz) ppm; $^{13}C$

NMR (100 MHz, $CDCl_3$) δ 165.1 (4C, 0), 135.9 (2C, 0), 128.8 (4C, 1), 128.7 (2C, 1), 128.0 (4C, 1), 48.5 (2C, 1), 43.8 (2C, 2), 22.3 (2) ppm; MS (ES) m/z 363 $(M+H)^+$; HRMS (ES) m/z 363.1356 (calcd. for $C_{21}H_{19}N_2O_4$: 363.1345).

Laboratory notebook reference: jpm197




**149**
$C_{21}H_{18}N_2O_4$
(362.38)

**150**
$C_{21}H_{26}N_2$
(306.45)

**3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane (150):**[204] A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (0.75 mL, 65 wt% in toluene, d = 1.036, 505 mg, 2.5 mmol) in anhydrous toluene (4.25 mL) under Ar at 80 °C oil bath temperature was treated dropwise with a solution of bisimide (228 mg, 0.63 mmol) in anhydrous THF (2.5 mL). The oil bath temperature was then increased to 120 °C and the mixture refluxed overnight. Upon hydrolysis with 15wt% aq. NaOH (20 mL), the mixture was extracted with $CH_2Cl_2$ (3 x 25 mL), and the combined organic phases extracted with 1.5 M HCl (3 x 25 mL). The combined aqueous extractions were made basic with the careful portionwise addition of 15 g

NaOH, then extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic phases were dried and concentrated, then dried *in vacuo* overnight to remove methoxyethanol, giving 50 mg yellow oil. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, m), 7.28 (8H, m), 3.46 (4H, s), 2.80 (4H, dm, J = 11.0 Hz), 2.33 (4H, dm, J = 11.0 Hz), 1.88 (2H, m), 1.55 (2H, m) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 139.9 (2C, 0), 129.0 (4C, 1), 128.2 (4C, 1), 126.7 (2C, 1), 63.5 (2C, 2), 58.1 (4C, 2), 31.1 (2), 30.0 (2C, 1) ppm. Characterization data in agreement with cited literature.[204]

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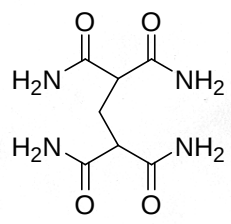
# APPENDIX

$^{1}$H NMR / $^{13}$C NMR

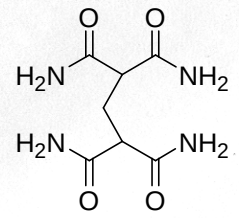
COMPOUND SPECTRA

jpm77rec, 16 scans, DMSO, 400 MHz, 5/25/07




**107**
$C_7H_{12}N_4O_4$
(216.19)

jpm77rec, 13C, DMSO, 75 MHz, 6/1/07

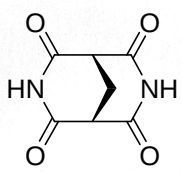


**107**

$C_7H_{12}N_4O_4$

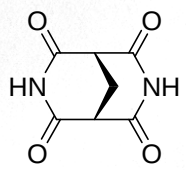
(216.19)

jpm81rec, 32 scans, DMSO, 400 MHz, 5/25/07




**108**
$C_7H_6N_2O_4$
(182.13)

jpm81rec, 13C, DMSO, 75 MHz, 6/1/07

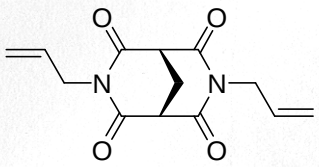



**108**

$C_7H_6N_2O_4$

(182.13)

jpm79rec, 32 scans, CDCl3, 400 MHz, 5/26/07

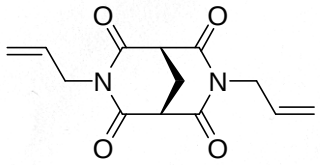


**93**

$C_{13}H_{14}N_2O_4$

(262.26)

jpm79rec, 13C, CDCl3, 75 MHz, 5/26/07

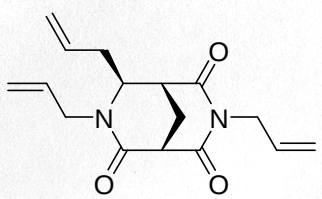


**93**

$C_{13}H_{14}N_2O_4$

(262.26)

jpm143, CDCl3, 400 MHz, 11/19/07

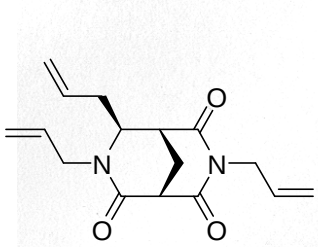



**98**

$C_{16}H_{20}N_2O_3$

(288.35)

jpm139, 13C, CDCl3, 75 MHz, 11/19/07

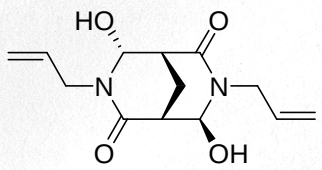


**98**

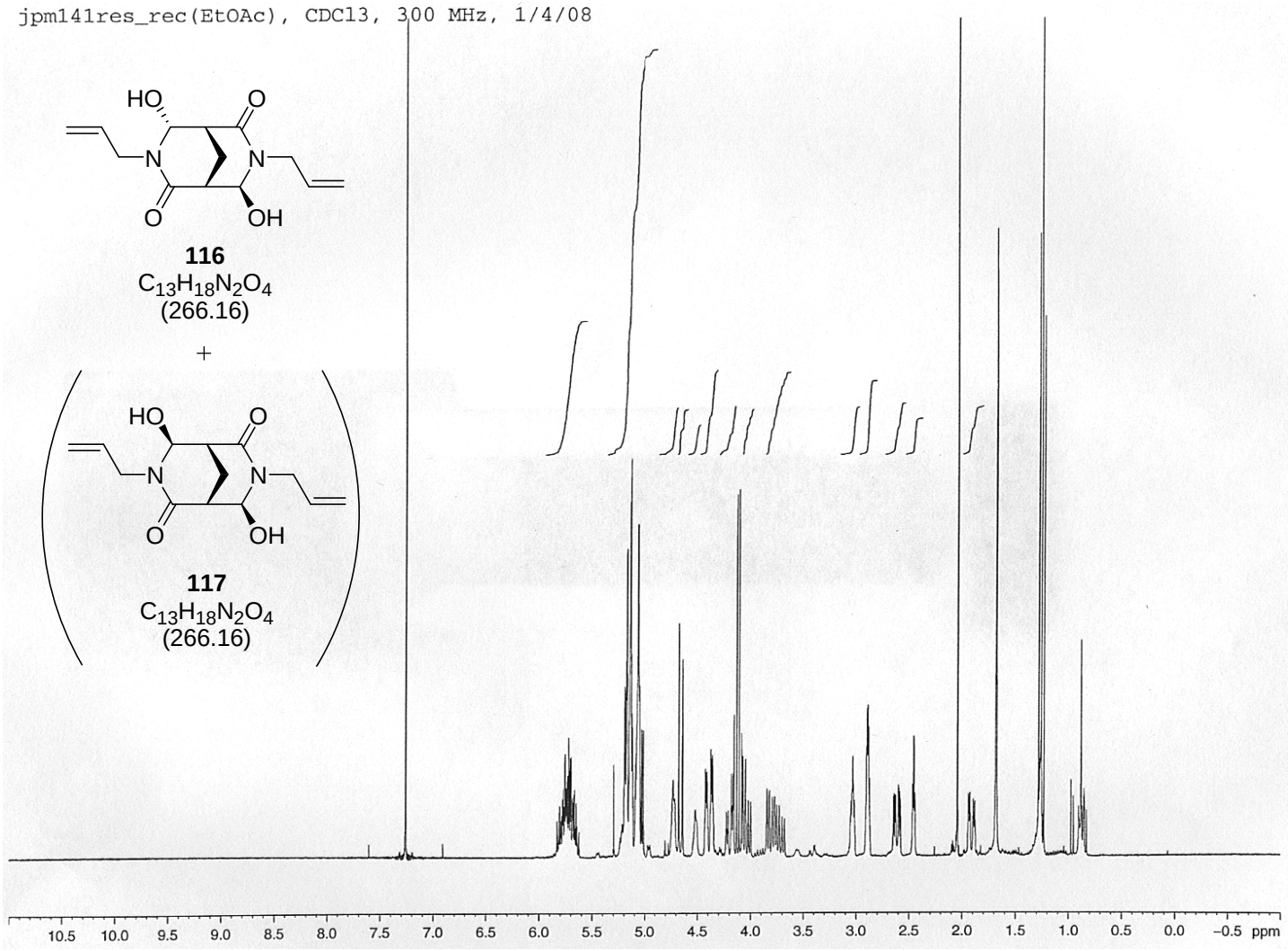
$C_{16}H_{20}N_2O_3$

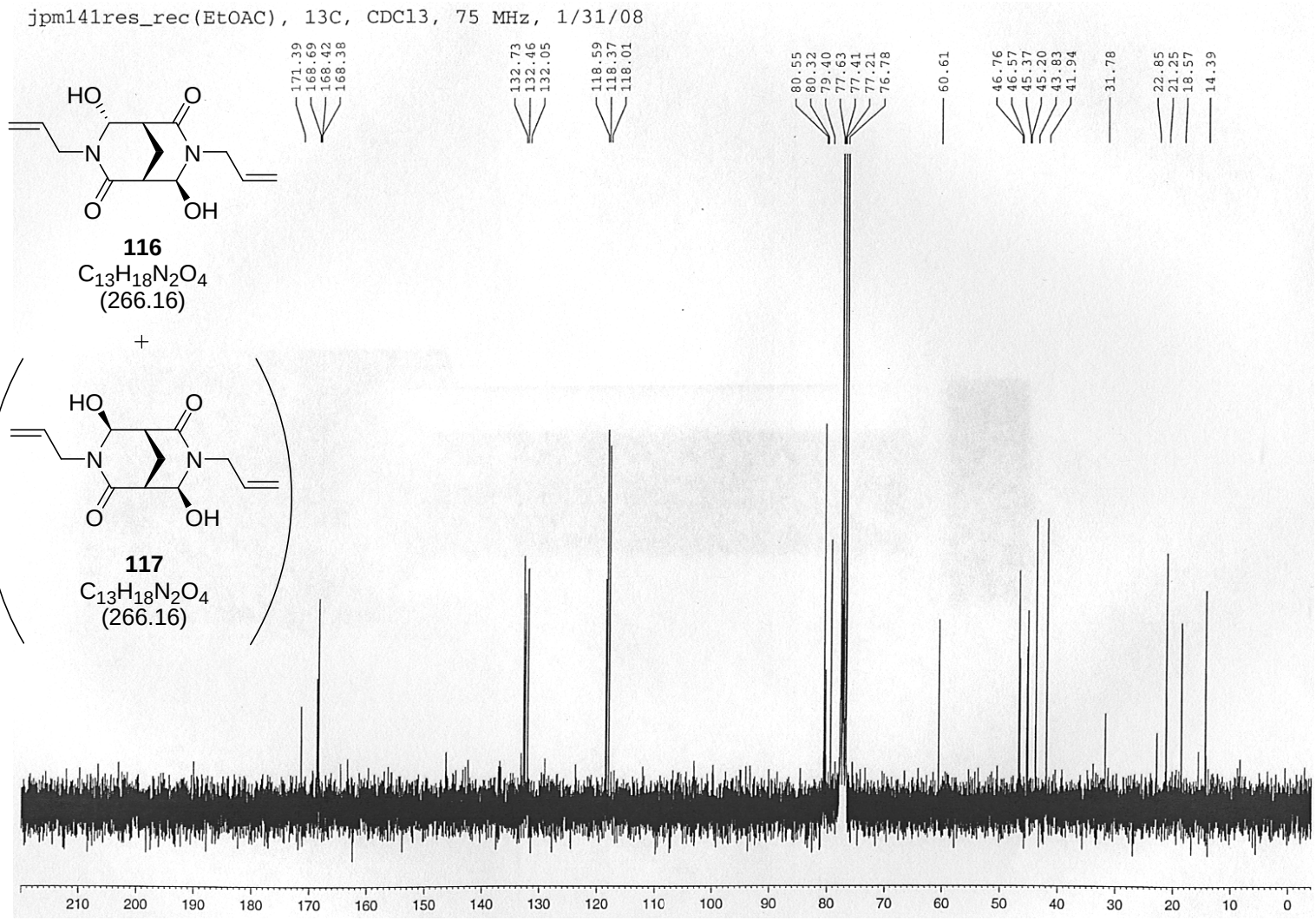
(288.35)

jpm141res, CDCl3, 300 MHz, 10/16/07

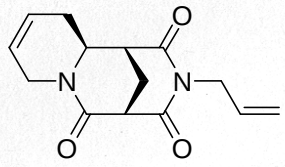



**116**
$C_{13}H_{18}N_2O_4$
(266.16)


jpm141res_rec(EtOAc), CDCl3, 300 MHz, 1/4/08
HO
O
N
N
O
OH
116
C13H18N2O4
(266.16)
+
HO
O
N
N
O
OH
117
C13H18N2O4
(266.16)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 ppm


jpm141res_rec(EtOAC), 13C, CDCl3, 75 MHz, 1/31/08
171.39
168.69
168.42
168.38
132.73
132.46
132.05
118.59
118.37
118.01
80.55
80.32
79.40
77.63
77.41
77.21
76.78
60.61
46.76
46.57
45.37
45.20
43.83
41.94
31.78
22.85
21.25
18.57
14.39
HO
O
N
N
O
OH
116
C13H18N2O4
(266.16)
+
HO
O
N
N
O
OH
117
C13H18N2O4
(266.16)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

jpm100Arec, CDCl3, 300 MHz, 6/29/07

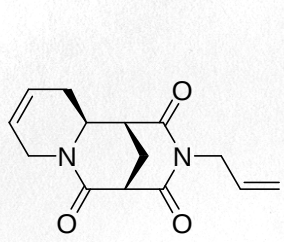



**118**

$C_{14}H_{16}N_2O_3$

(260.29)

jpm100Arec, 13C, CDCl3, 75 MHz, 6/29/07

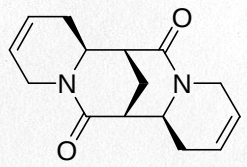


**118**

$C_{14}H_{16}N_2O_3$

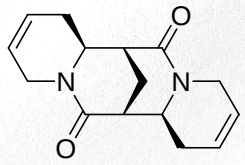
(260.29)

jpm100Brec, CDCl3, 300 MHz, 6/29/07




**119**
$C_{15}H_{18}N_2O_2$
(258.32)

jpm100Brec, 13C, CDCl3, 75 MHz, 6/29/07

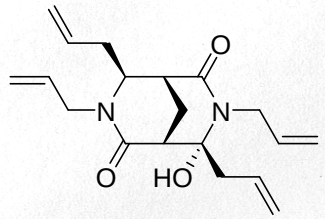



**119**

$C_{15}H_{18}N_2O_2$

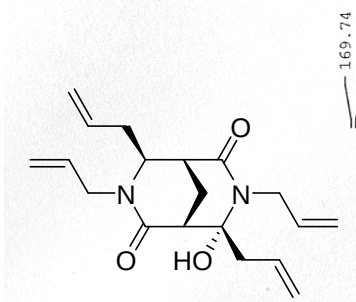
(258.32)

jpm82A, CDCl3, 300 MHz, 6/18/07




**104**
$C_{19}H_{26}N_2O_3$
(330.43)

jpm82A, 13C, CDCl3, 75 MHz, 6/18/07

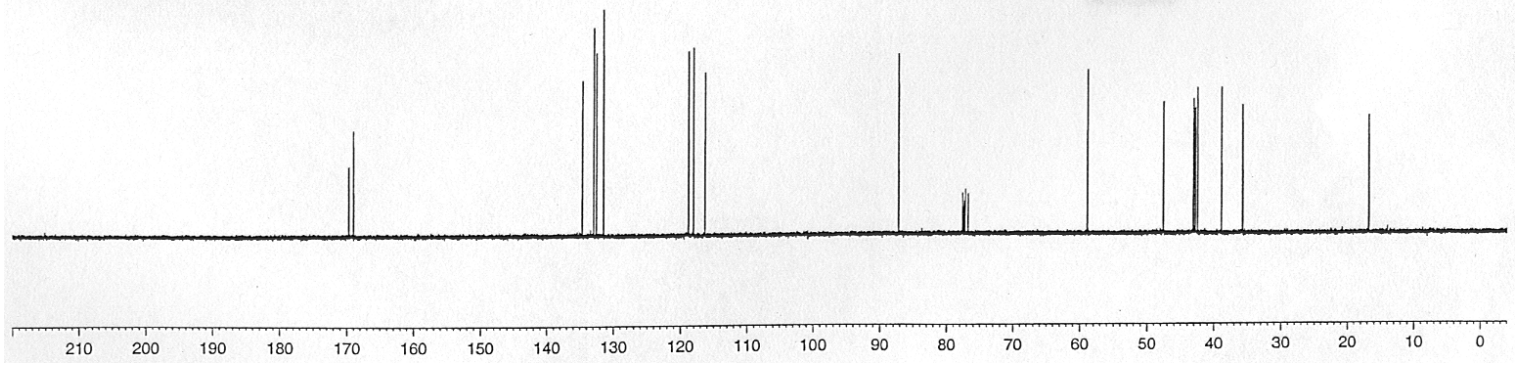



**104**

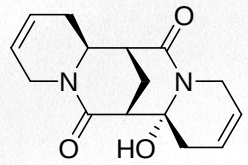
$C_{19}H_{26}N_2O_3$

(330.43)

169.74
169.08
134.65
133.44
132.96
132.57
131.53
118.83
118.81
118.10
116.37
87.19
77.63
77.40
77.20
76.78
58.84
47.61
43.11
42.83
42.52
38.95
35.78
16.83
14.00



jpm147rec, DMSO, 300 MHz, 12/6/07

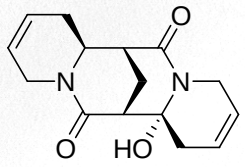



**126**

$C_{15}H_{18}N_2O_3$

(274.32)

jpm147rec, 13C, DMSO, 100 MHz, 12/6/07

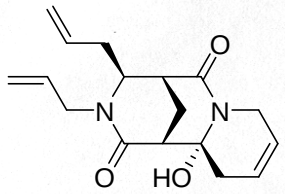



**126**

$C_{15}H_{18}N_2O_3$

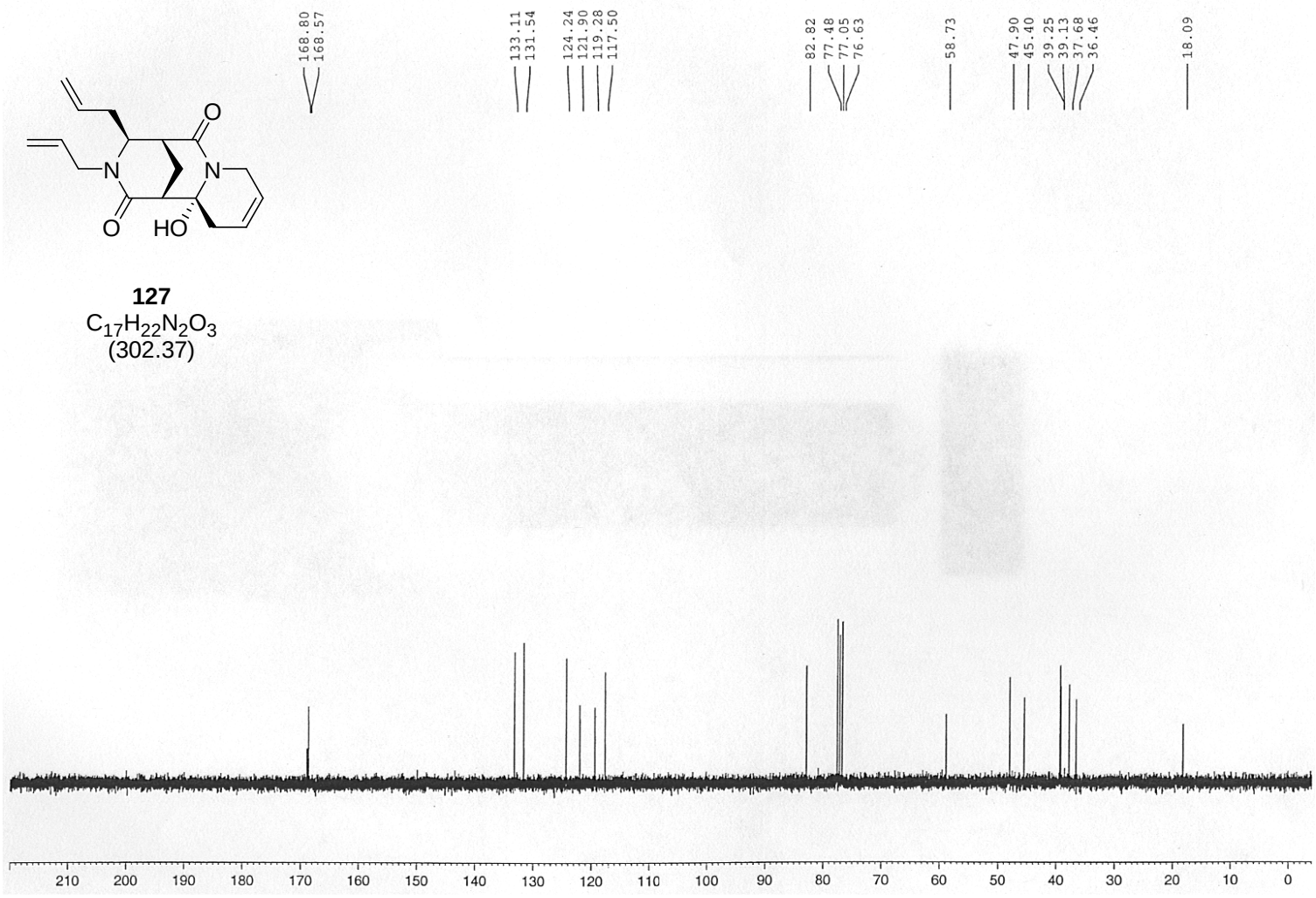
(274.32)

jpm99A, CDCl3, 300 MHz, 6/26/07




**127**
$C_{17}H_{22}N_2O_3$
(302.37)

jpm99A, 13C, CDCl3, 75 MHz, 6/26/07

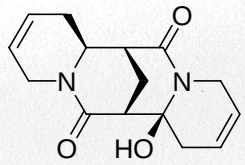



**127**

$C_{17}H_{22}N_2O_3$

(302.37)

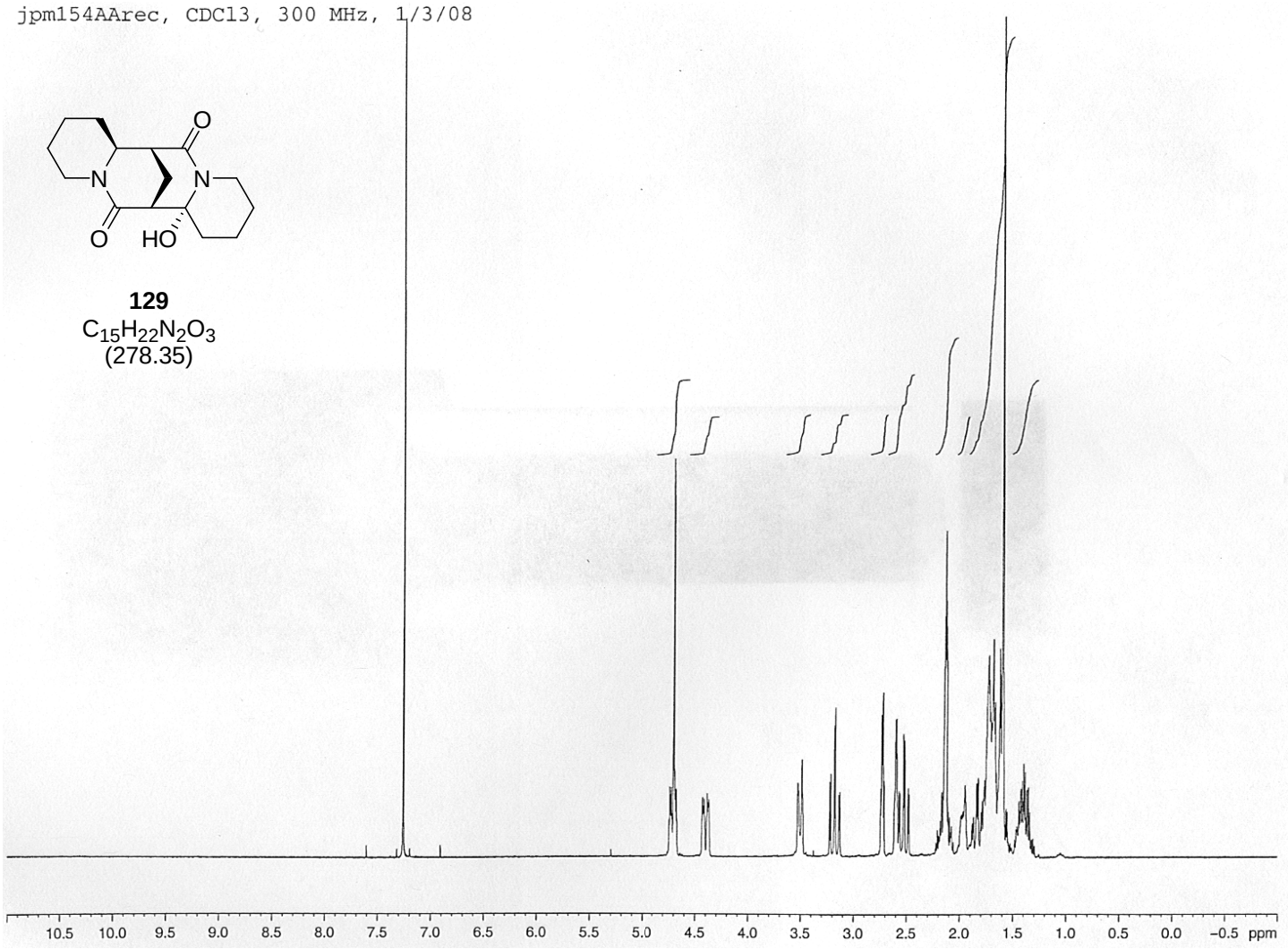
jpm152, CDCl3, 300 MHz, 12/16/07




**128**

$C_{15}H_{18}N_2O_3$

(274.32)

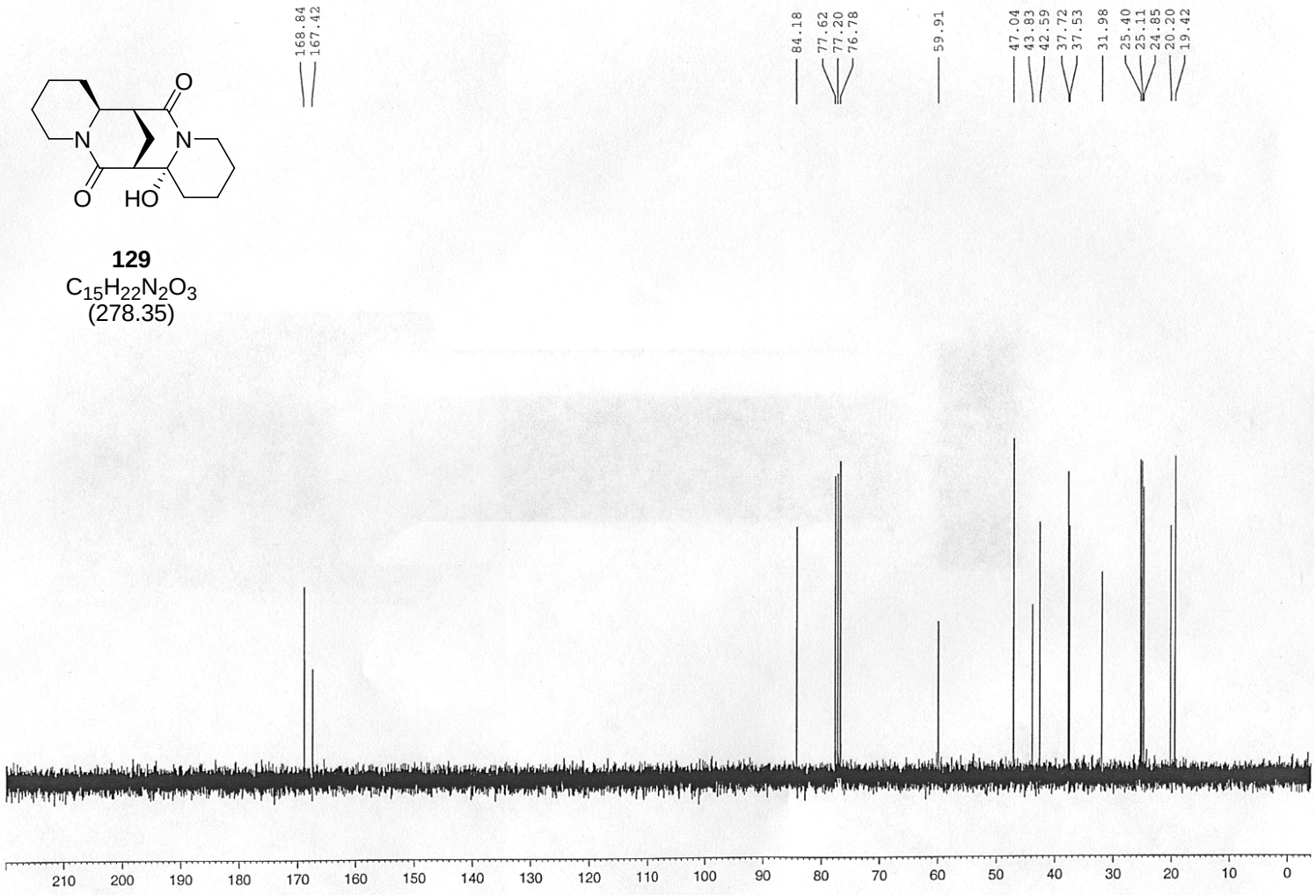



**129**

$C_{15}H_{22}N_2O_3$

(278.35)

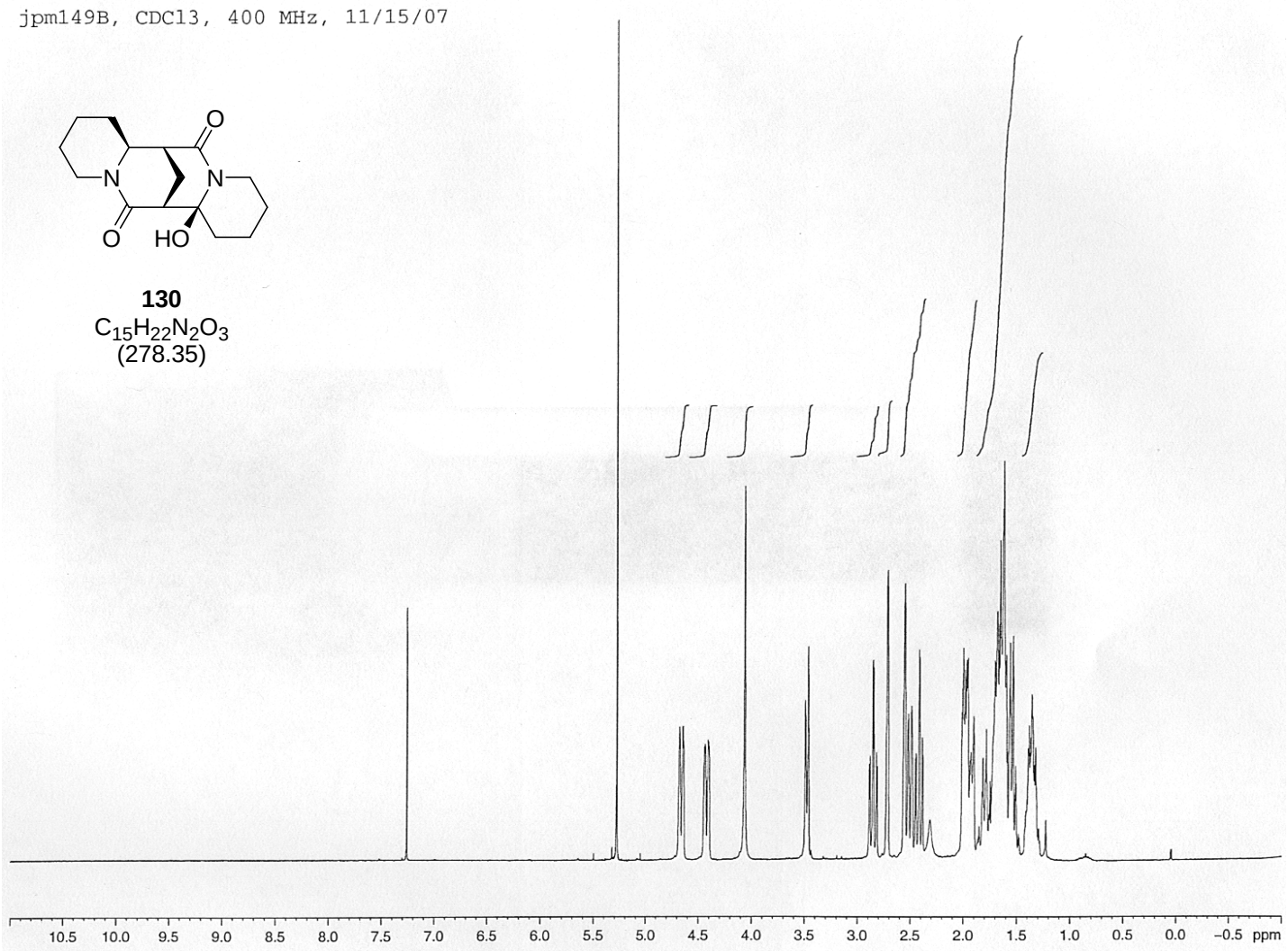
jpm149A, 13C, CDCl3, 75 MHz, 11/15/07




**129**

$C_{15}H_{22}N_2O_3$

(278.35)

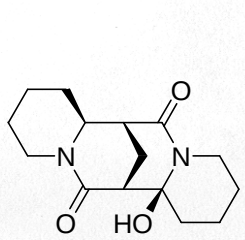



**130**

$C_{15}H_{22}N_2O_3$

(278.35)

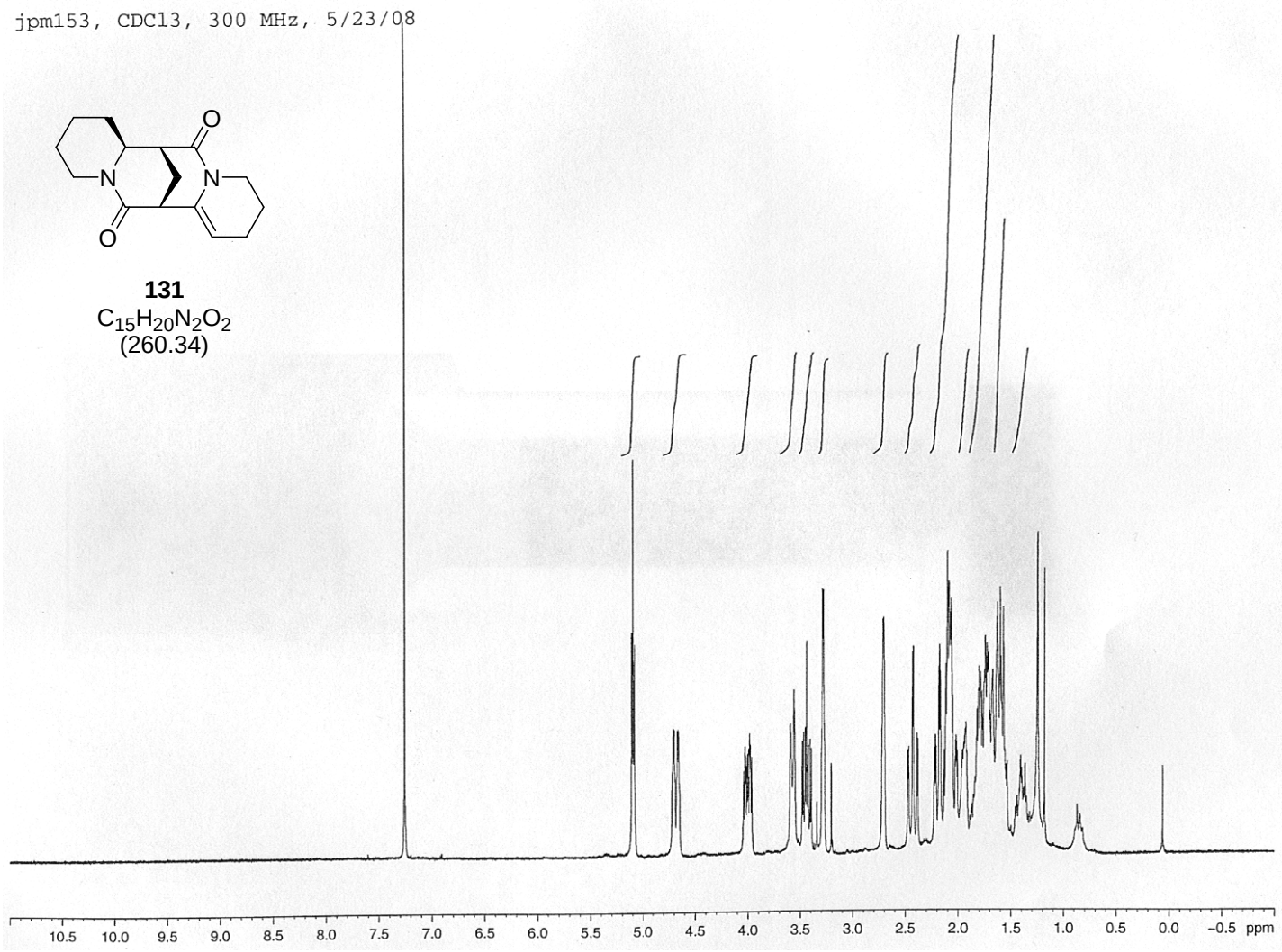
jpm149B, 13C, CDCl3, 75 MHz, 11/15/07




**130**

$C_{15}H_{22}N_2O_3$

(278.35)

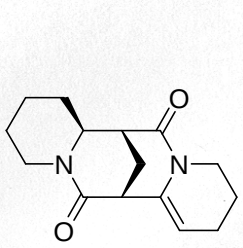



**131**

$C_{15}H_{20}N_2O_2$

(260.34)

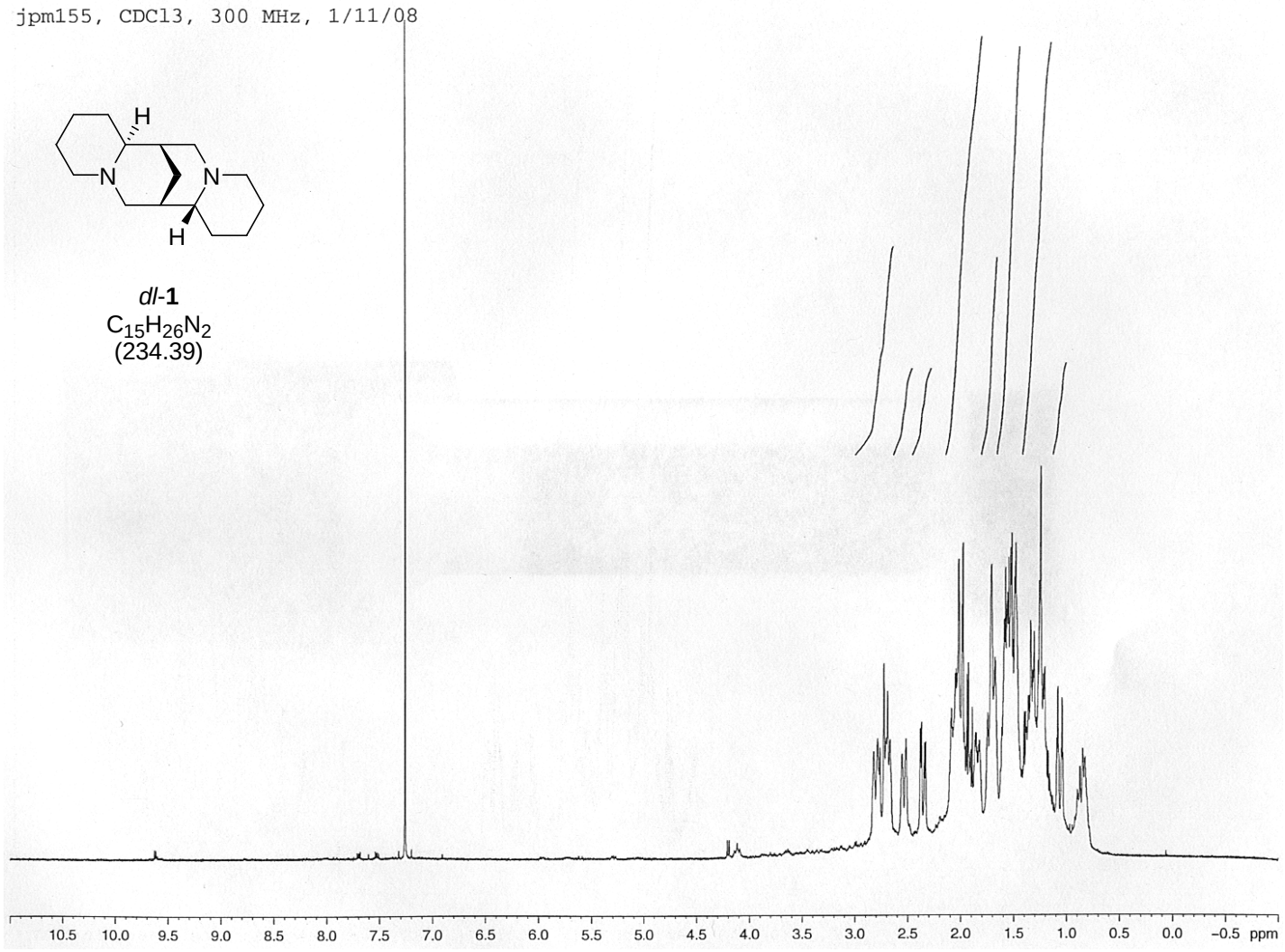
jpm153, 13C, CDCl3, 75 MHz, 5/23/08




**131**

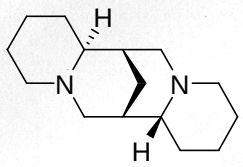
$C_{15}H_{20}N_2O_2$

(260.34)

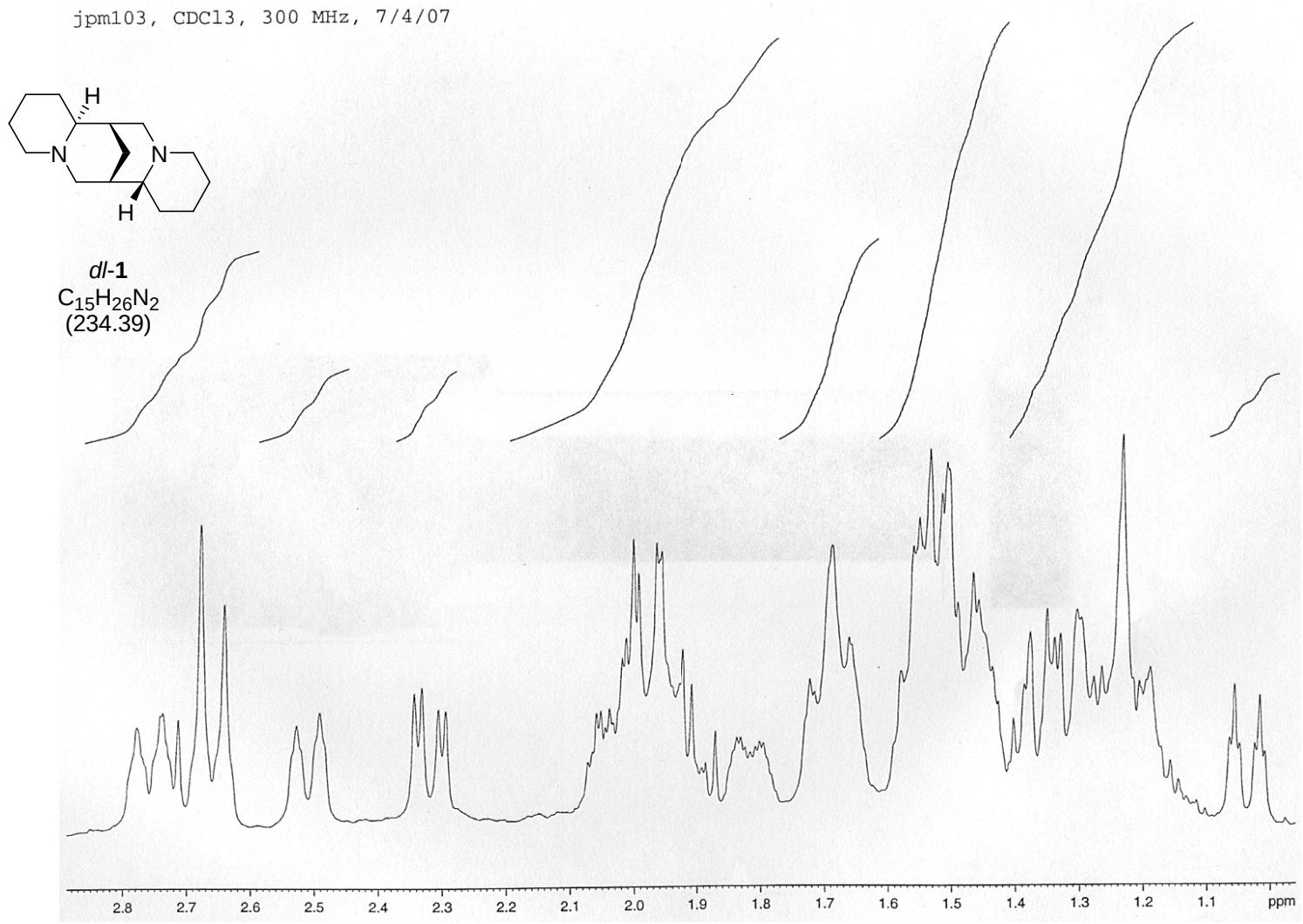


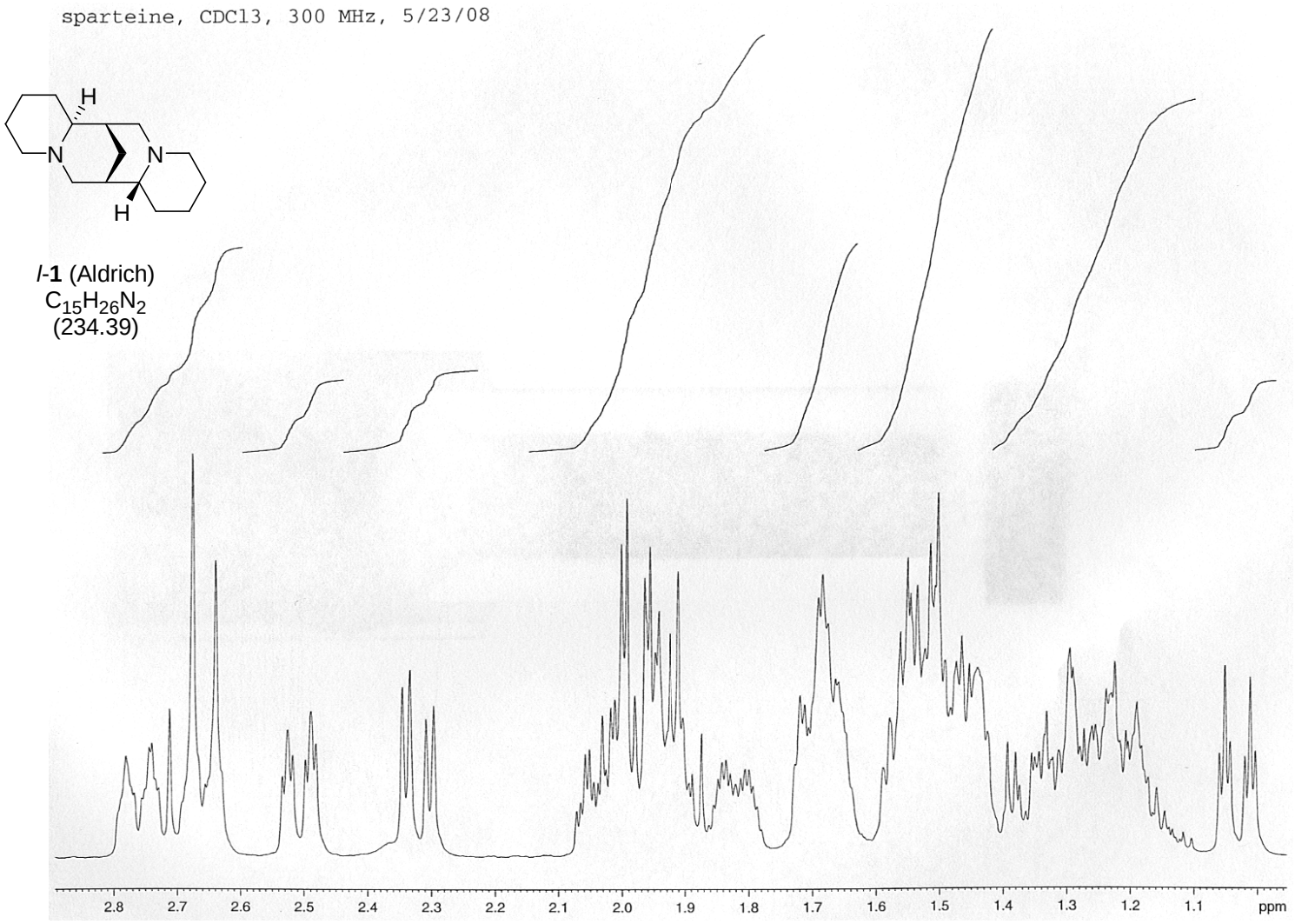

*dl*-**1**
$C_{15}H_{26}N_2$
(234.39)

jpm155, CDCl3, 400 MHz, 1/8/08

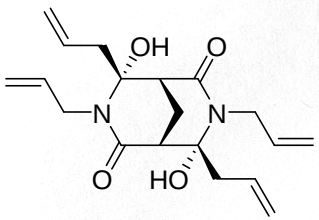



*dl*-**1**
$C_{15}H_{26}N_2$
(234.39)


jpm103, CDCl3, 300 MHz, 7/4/07
H
N
N
H
dl-1
C15H26N2
(234.39)
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
ppm


sparteine, CDCl3, 300 MHz, 5/23/08
H
N
N
H
*l*-**1** (Aldrich)
$C_{15}H_{26}N_2$
(234.39)
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
ppm

jpm35rec, 32 scans, CDCl3, 400 MHz, 5/26/07

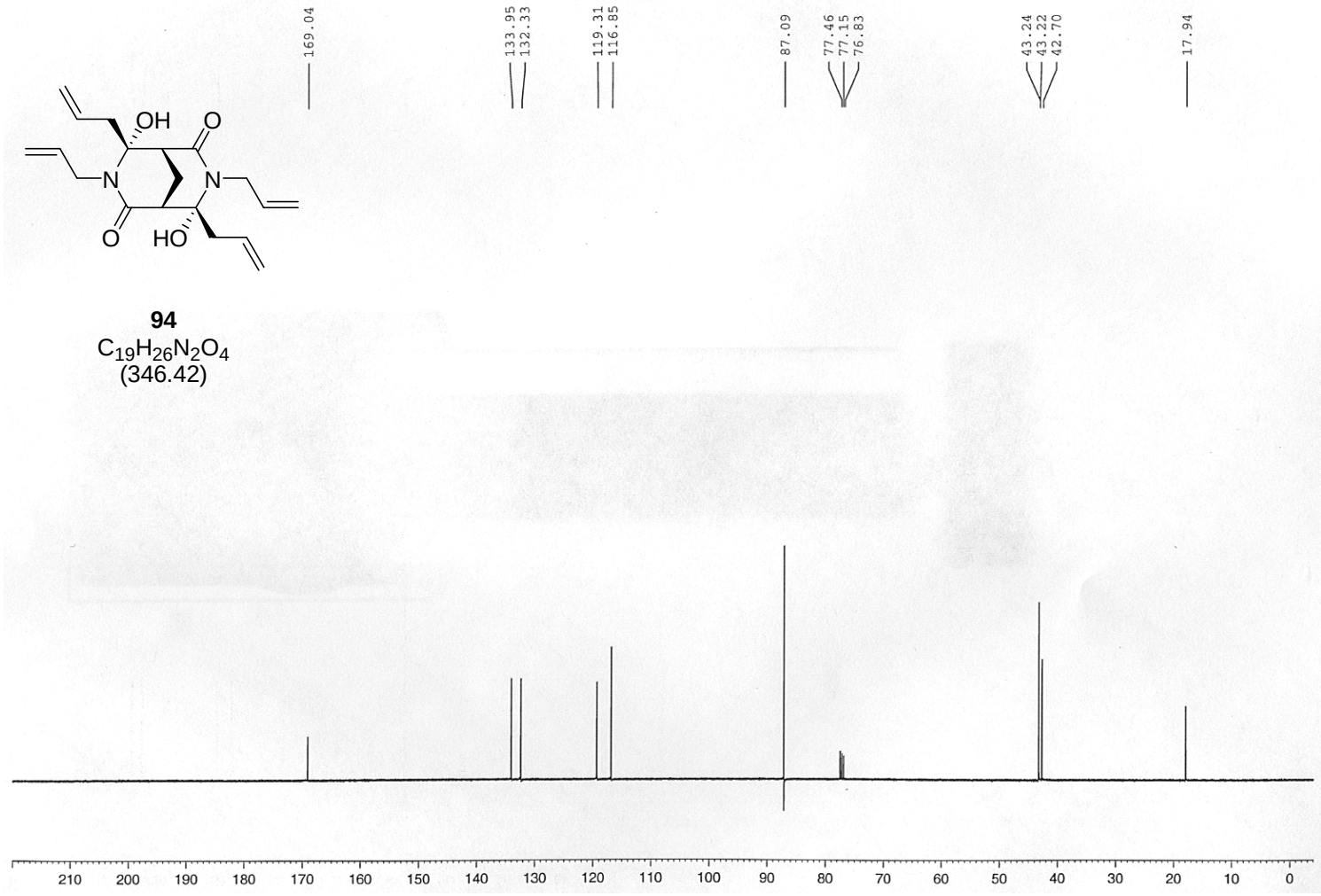



**94**

$C_{19}H_{26}N_2O_4$

(346.42)

jpm35rec, 13C, CDCl3, 75 MHz, 5/26/07

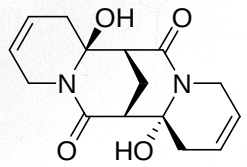



**94**

$C_{19}H_{26}N_2O_4$

(346.42)

jpm41rec, 32 scans, DMSO, 300 MHz, 6/18/07

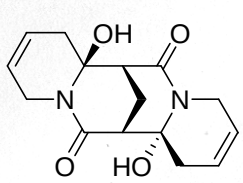



**95**

$C_{15}H_{18}N_2O_4$

(290.32)

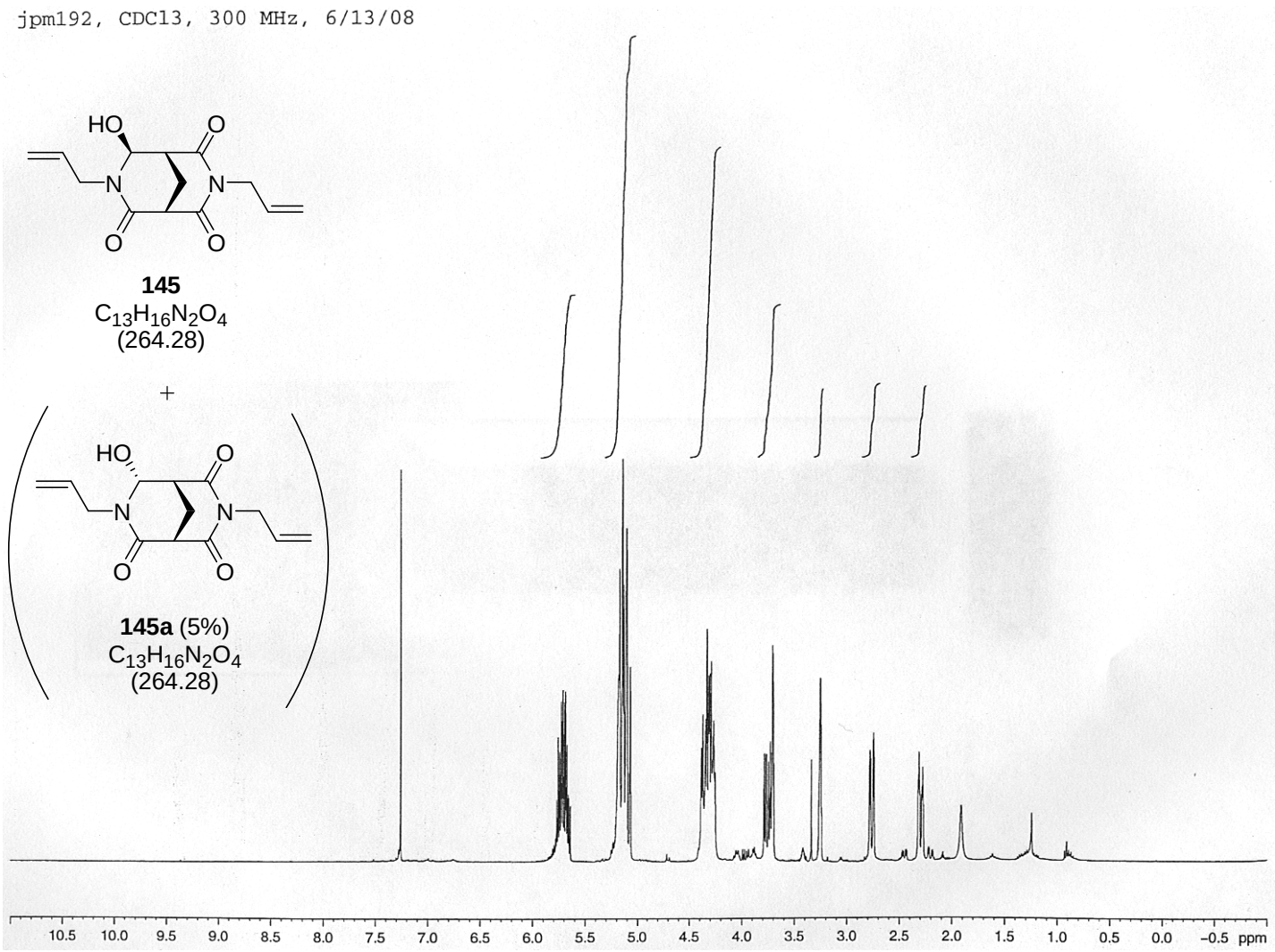
jpm41rec, 13C, DMSO, 75 MHz, 6/18/07

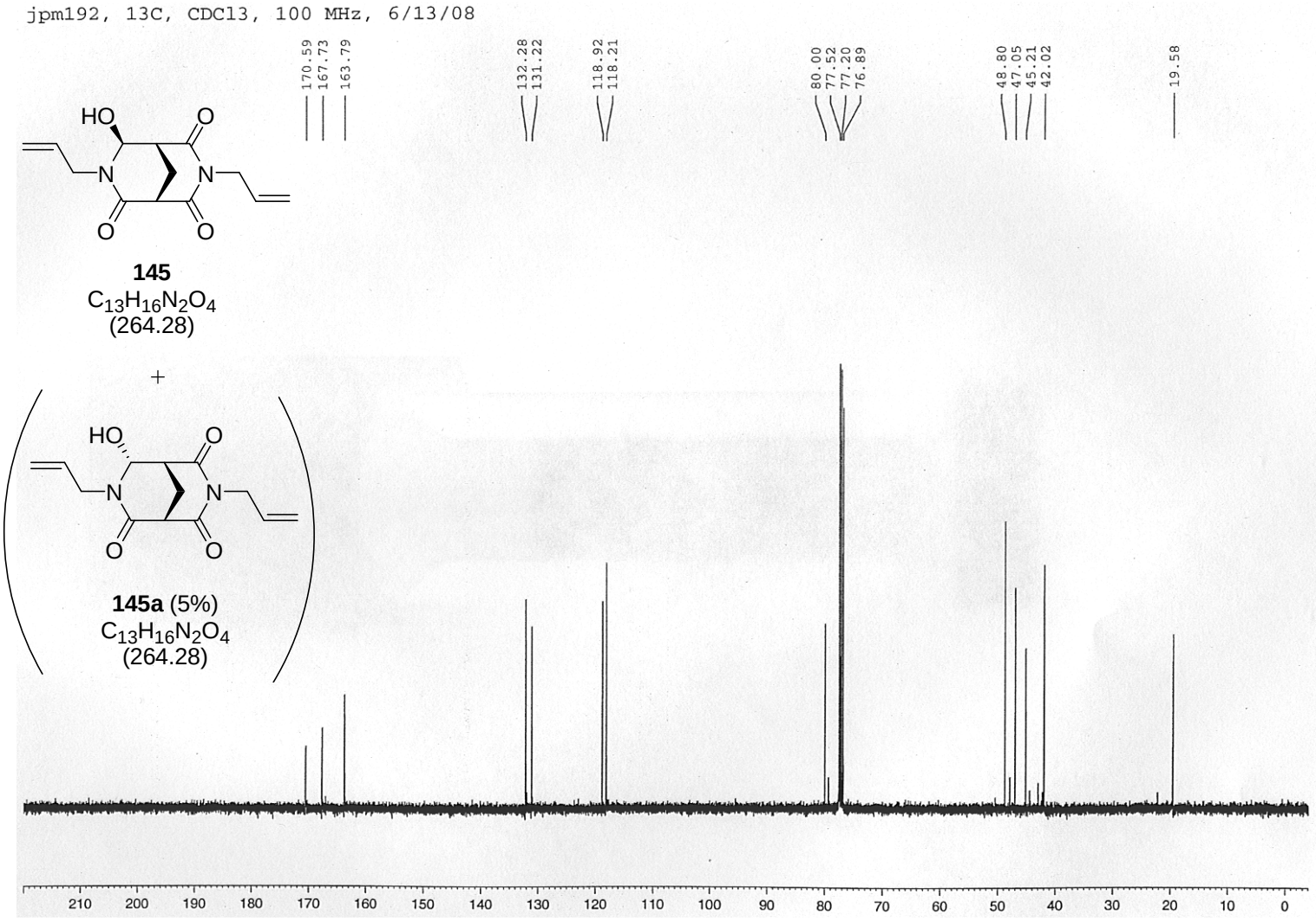



**95**

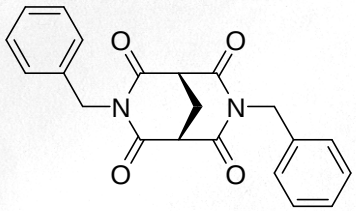
$C_{15}H_{18}N_2O_4$

(290.32)


jpm192, CDCl3, 300 MHz, 6/13/08
HO
O
N
N
O
O
145
C13H16N2O4
(264.28)
+
HO
O
N
N
O
O
145a (5%)
C13H16N2O4
(264.28)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 ppm


jpm192, 13C, CDCl3, 100 MHz, 6/13/08
170.59
167.73
163.79
132.28
131.22
118.92
118.21
80.00
77.52
77.20
76.89
48.80
47.05
45.21
42.02
19.58
HO
O
N
N
O
O
145
C13H16N2O4
(264.28)
+
HO
O
N
N
O
O
145a (5%)
C13H16N2O4
(264.28)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

jpm31, CDCl3, 300 MHz, 10/24/06

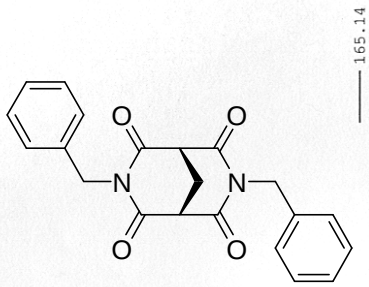


**149**

$C_{21}H_{18}N_2O_4$

(362.38)

jpm31, 13C, CDCl3, 100 MHz, 6/13/08

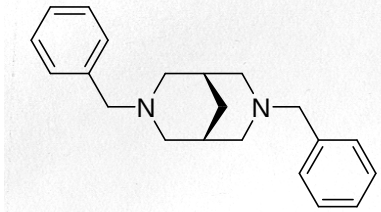


**149**

$C_{21}H_{18}N_2O_4$

(362.38)

jpm197, CDCl3, 300 MHz, 7/18/08

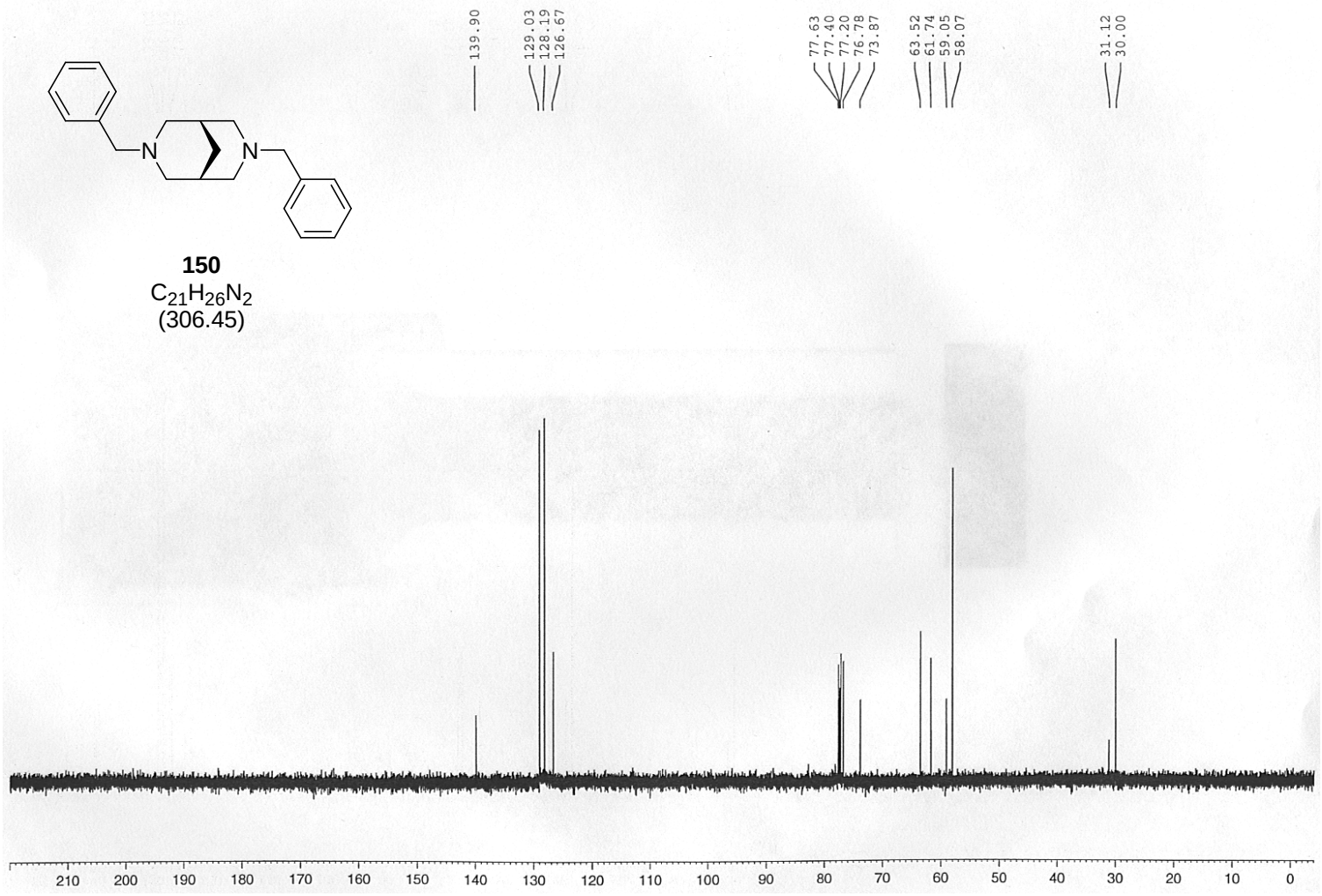



**150**

$C_{21}H_{26}N_2$

(306.45)

jpm197wet, 13C, CDCl3, 75 MHz, 7/15/08




**150**

$C_{21}H_{26}N_2$

(306.45)