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Asymmetric synthesis of 3,4-disubstituted pyrrolidines: 1,3-dipolar addition to chiral bicyclic lactams†

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Summary — The title compounds **1** are obtained in good yields from tricyclic lactams **2**, which are derived from the asymmetric [3+2] dipolar cycloaddition of azomethine ylides **4** to chiral bicyclic lactams **3**. Thus, treatment of tricyclic adducts **14** or **17** with methyllithium gives *N*-substituted bicyclic hydroxylactams **16** or **18**, respectively, as a consequence of abstraction of the kinetically acidic benzylic hydrogen followed by an anionic cycloreversion process. Alternatively, treatment of **14** or **48** with calcium metal in liquid ammonia gives *N*-unsubstituted bicyclic hydroxylactams **60** or **56** respectively. Through the intermediacy of these bicyclic hydroxylactams, illustrative examples of nonracemic monocyclic and bicyclic 3,4-disubstituted pyrrolidine 'building blocks' were synthesized bearing vicinal substituents which are amenable to facile chemical manipulation.

3,4-disubstituted pyrrolidine / asymmetric synthesis / 1,3-dipolar addition / bicyclic lactam / hydroxylactam

Résumé — **Synthèse asymétrique de pyrrolidines 3,4-disubstituées : addition 1,3-dipolaire sur des lactames bicycliques chiraux.** Les pyrrolidines 3,4-disubstituées sont obtenues avec de bons rendements à partir de lactames tricycliques qui proviennent d'une cycloaddition dipolaire [3+2] asymétrique d'ylures d'azométhines sur des lactames bicycliques chiraux. Ainsi le traitement des adduits tricycliques **14** ou **17** par le MeLi conduit respectivement aux hydroxylactames *N*-substitués **16** ou **18** par abstraction du proton benzylique suivie d'un processus anionique de rétrocyclisation. Par ailleurs, le traitement de **14** ou **18** par le calcium métallique dans l'ammoniac liquide conduit respectivement aux hydroxylactames bicycliques non substitués **60** ou **56**. Par l'intermédiaire de ces hydroxylactames bicycliques des exemples significatifs de synthèse de pyrrolidines 3,4-disubstituées mono- et bicycliques ont été obtenus aisément.

pyrrolidine 3,4-disubstituée / synthèse asymétrique / addition 1,3-dipolaire / lactame bicyclique / hydroxylactame

Chiral, nonracemic pyrrolidines have considerable utility as 'building blocks' for the synthesis of alkaloids possessing significant biological activity and their use as auxiliaries and ligands in asymmetric reactions is well documented [1]. Thus, the development of general methods for the synthesis of these chiral pyrrolidine derivatives bearing synthetically useful substitution patterns remains a continuing challenge.

The search for general methods to reach chiral pyrrolidines formed the basis for our continuing interest in exploring the synthetic utility of bicyclic lactams **3**. Due to the density of functional groups about this versatile chiral template, and due to the latent pyrrolidine ring present, a variety of highly diastereoselective C–C-bond forming reactions were developed that culminated in the synthesis of 2- [2, 3] and 3-monosubstituted [4, 5], and 2,2- [6] and 2,3-disubstituted [7] pyrrolidine derivatives. While now there are numerous methods described for the synthesis of substituted pyrrolidines [1], a much smaller subset of these methods are enantioselective. We note, however, that *there are remarkably few enantioselective routes to pyrrolidines having the 3,4-disubstitution pattern* **1** (fig 1) [8–13].

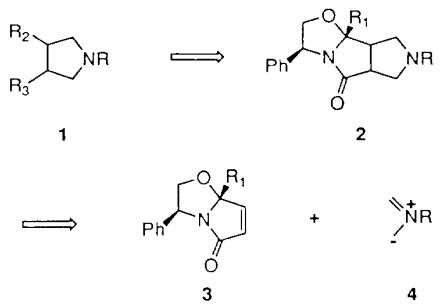

Fig 1

We have reported that chiral, unsaturated bicyclic lactams **3** are particularly useful dipolarophiles for diastereoselective azomethine ylide **4** cycloadditions,

† This paper is dedicated to Professor Henri Kagan for his outstanding contributions to asymmetric synthesis.

* Correspondence and reprints

affording tricyclic 3,4-disubstituted pyrrolidine derivatives **2** in excellent yield and selectivity. We were, therefore, interested in modifying the bicyclic lactam moiety of **2** to reveal substituents on **1** which would have a higher range of functionality and greater opportunities for variation than has been observed in the literature. In this context, we can now report that tricyclic lactams **2**, derived from phenylglycine, serve as precursors of nonracemic bicyclic hydroxylactams **5** (fig 2).

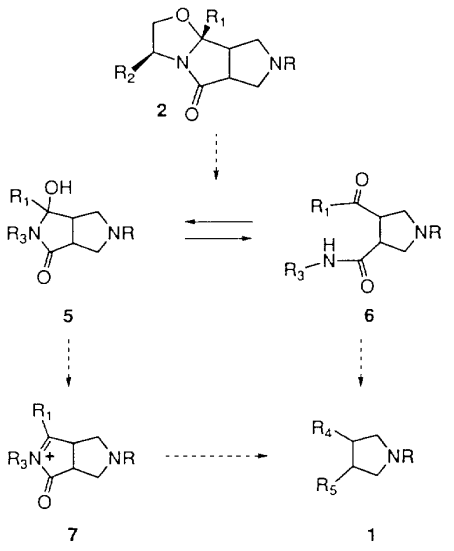

Fig 2

The synthetic utility of hydroxylactams **5** is based on, in part, its acid-catalyzed equilibrium with *N*-acyliminium ions **7** which are capable of inter- and intramolecular capture of a wide variety of nucleophiles [14–18], including hydrides [18–21]. Speckamp [22] has shown that hydroxylactams can exhibit their reactivity through their ketoamide tautomeric forms **6** under mildly basic conditions. The latent keto functionality has been shown to undergo chemoselective Wittig olefination and reduction reactions [21–24]. The iminium species **7** may be manipulated in several manners to produce optically active 3,4-disubstituted pyrrolidine derivatives **1**.

The most common method for the preparation of chiral, nonracemic hydroxylactams **5** involves selective nucleophilic addition (hydride or organomagnesium reagent) to one carbonyl group of a chiral [16–20, 24–28] or achiral [15, 21] cyclic imide. However, there are very few methods for the preparation of hydroxylactams from *non-imide* starting materials [15]. An example of the latter case has been observed in our laboratories [29], as shown in figure 3.

During an attempt to alkylate bicyclic lactam **8** with LDA and MeI, the unexpected formation of lithium alkoxide **11** was observed. It is probable that this process was initiated by abstraction of the kinetically acidic benzylic proton by a lithium base to form a transient dipole-stabilized [30] lithio anion intermediate **9**. The generation of benzylic, dipole-stabilized lithio anions has been shown to occur in preference to metalation at

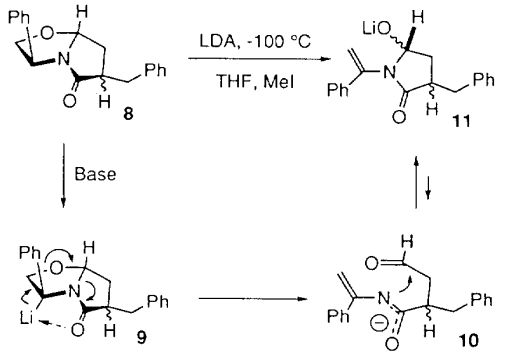

Fig 3

the site adjacent to the amide carbonyl in many cases [31, 32]. Since alignment of the C–Li bond with the σ^* orbital of the oxazolidine C–O bond is poor in a five-membered ring, it did not seem likely that oxazolidine C–O-bond cleavage was the result of β-elimination, but rather the result of a concerted 1,3-anionic cycloreversion [33] process to form an intermediate enamide anion **10** [34]. Enamide **10** then spontaneously cyclized to give the observed 5-lithioxy pyrrolidinone **11**.

An alternative method of hydroxylactam generation was reported [4] en route to the antidepressant (−)-Rolipram when the phenylglycine-derived lactam **12** was treated with excess calcium metal in liquid ammonia (fig 4). An 84% yield of the *N*-unsubstituted hydroxylactam **13**, was thus obtained.

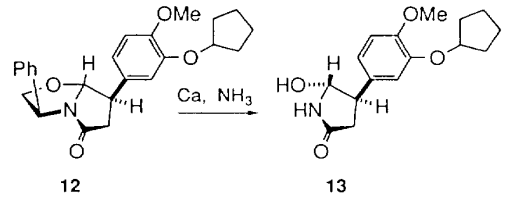

Fig 4

In view of the aforementioned synthetic utility of nonracemic hydroxylactams, attention was directed towards the optimization of the serendipitous anionic cycloreversion process previously illustrated in figure 3.

The tricyclic lactam **14** [11] was treated with methyllithium in ether-THF at −10 °C and after quenching with TFA led to an epimeric mixture of bicyclic carbinols, **16** in 62% yield (fig 5). These hydroxylactams appeared to be moderately stable to chromatographic purification; however, they were found to be prone to facile epimerization and thus difficult to isolate separately in pure form. Similarly, tricyclic lactam **17** underwent methyllithium-induced cycloreversion to give bicyclic hydroxylactam **18** in 63% yield (fig 6). The stereochemical assignment of **18** was based upon ^{1}H-NMR, which showed the lack of coupling between the carbinol methine proton (δ 5.71 (s, 1H)) and the adjacent methine proton at the ring fusion. This was consistent with a *trans* orientation for these protons.

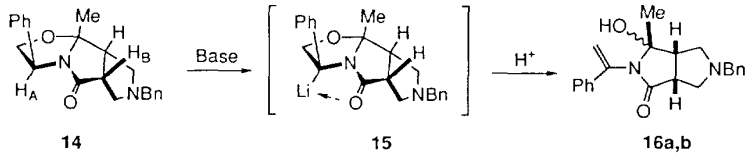

Fig 5

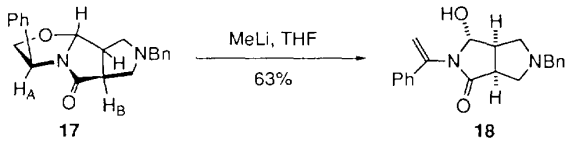

Fig 6

It is noteworthy that the addition of approximately one equivalent of methyllithium to phenylglycine-derived lactams **14** and **17** provided complete consumption of the starting material with immediate evolution of methane gas. This suggested that neither abstraction of the acidic hydrogen H_B nor nucleophilic addition of methyllithium to the carbonyl groups of **14** or **17** were rapid processes compared to the removal of H_A to provide the corresponding dipole-stabilized intermediate **15**. This lithiation process virtually failed using the bulkier *sec*-butyllithium or *tert*-butyllithium whereas nucleophilic addition to the carbonyl group was observed when *n*-butyllithium was used.

To evaluate the hydroxylactam utility toward the preparation of nonracemic 3,4-disubstituted pyrrolidine derivatives, the epimeric carbinolamines **16** were treated with three equivalents of methylidene triphenylphosphorane (fig 7) to give a single 3,4-disubstituted pyrrolidine **19** as a consequence of ring opening of the carbinolamine **16** to the ketoamide, followed by olefination of the more reactive carbonyl group. Pyrrolidine **19** was devoid of any stereochemical mixture since the carbinolamines gave only the methyl ketones. The presence of the 3,4-substituents in **19** allowed for facile chemical manipulation and structure determination.

It was now necessary to assess the enantiomeric purity of **19** as well as the relative 3,4-*trans* stereochemistry. In this regard, a synthesis of alcohol (±)-**25** was undertaken to provide racemic material for use with chiral stationary phase HPLC. As shown in figure 8, addition of methylmagnesium iodide to the known [35, 52] imide **20**, gave the intermediate hydroxylactams **21**, which was allowed to react with methylidene triphenylphosphorane to give racemic pyrrolidine **22** in 50% overall yield. Exposure of **22** to phenyl chloroformate and triethylamine gave exclusively the monocarbamoylated product **23**. *N*-acylation of **23** was accomplished by abstraction of the NH proton with *sec*-butyllithium (1.2 equiv) at −78 °C, followed by addition of phenyl chloroformate (3 equiv). After warming to room temperature, the biscarbamoylated intermediate **24** was isolated in 79% yield. The latter was treated with excess lithium triethylborohydride (2.5 equiv) to furnish the desired racemic alcohol (±)-**25** along with the phenyl

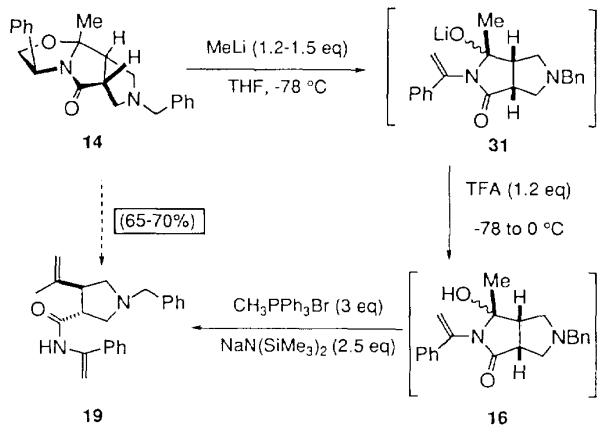

Fig 7

N-phenylcarbamate **26**. Due to the difficulties encountered in the separation of (±)-**25** from **26** by radial chromatography, mixed fractions were isolated along with pure (±)-**25**, which was isolated in 40% yield.

Figure 9 shows the corresponding enantioselective route to pyrrolidine **25**. Tricyclic lactam **14** (88% de) was treated with methyllithium as described before to afford hydroxylactams **16** after an aqueous work-up. The crude **16** was added to a THF solution containing methyl triphenylphosphonium bromide and $NaN(SiMe_3)_2$. This process provided pyrrolidine **19** as a single isomer in 53% overall yield. Exposure of **19** to phenyl chloroformate and triethylamine gave products derived from complete carbamoylation of the pyrrolidine nitrogen (with loss of benzyl chloride) and incomplete acylation of the amide nitrogen. The biscarbamoylated product **28**, obtained in 47% yield, was separated chromatographically from secondary amide **27**, which was produced in 40% yield. Subjection of pure **28** to reduction with excess $LiBHEt_3$ gave the desired alcohol **25** in 73% yield along with *N*-carbamoylated enamine of acetophenone **29**. Alcohol **25** was indistinguishable from the racemic version by ^{1}H-NMR. However, chiral stationary phase HPLC analysis of nonracemic **25** revealed an enantiomeric excess of only 60%.

It appeared that the basic conditions in the Wittig step caused rapid epimerization at C-3 and C-4 in **19** to generate the more stable *trans* enantiomers **30a** and **30b**. Whereas bis(trimethylsilyl)amine (1.0 equiv) had no apparent effect on hydroxylactams **16**, the more basic sodium bistrimethylsilylamide caused extensive decomposition over 24 h. Presumably, this decomposition might have been due to ring opening, epimerization, and intermolecular aldol reactions.

Therefore, to test this racemization hypothesis, nonracemic alcohol **25** was prepared using $NaN(SiMe_3)_2$

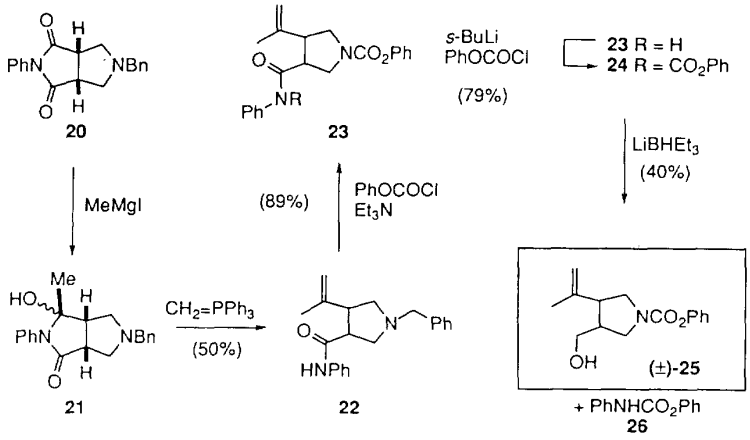

Fig 8

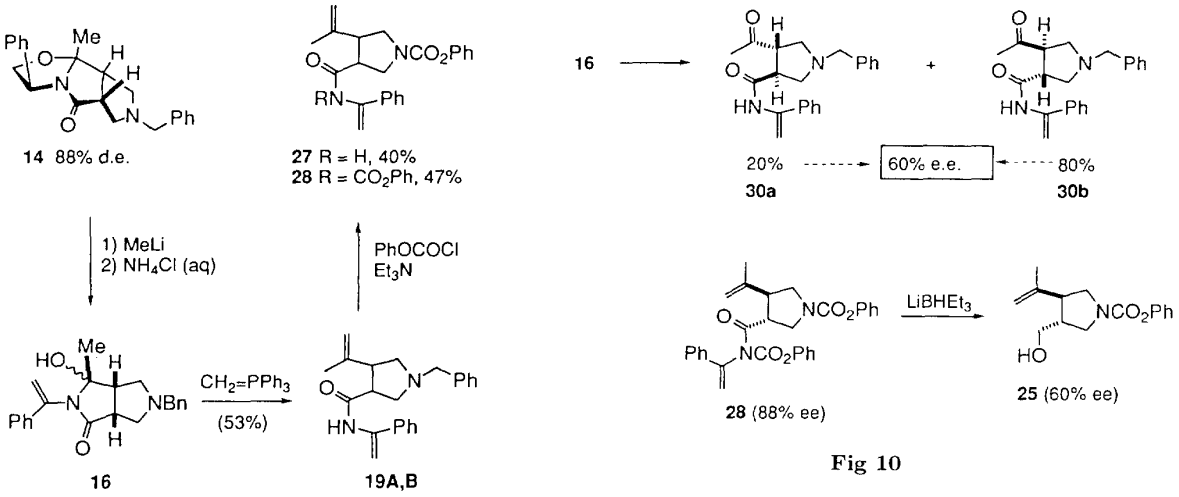

Fig 9

Fig 10

as the limiting reagent used to generate the Wittig reagent. In this new reaction mixture, excess methyl triphenylphosphonium bromide was used relative to the amount of $NaN(SiMe_3)_2$ required to form two equivalents of the Wittig reagent. In this manner, the $NaN(SiMe_3)_2$ should have been completely converted to $HN(SiMe_3)_2$. The Wittig reagent, thus obtained, was used to generate pyrrolidine **19** from hydroxylactams **16** (derived from tricyclic lactam **14**, which was 88% diastereomeric excess). Conversion of **19** to alcohol **25** was accomplished via the urethane **32** as illustrated in figure 10. Chiral stationary phase HPLC analysis of **25** indicated an enantiomeric excess of 88%, which demonstrated that *complete retention of enantiomeric enrichment was observed in this process.*

The conversion of tricyclic lactam **14** to nonracemic pyrrolidine **19** was optimized in the 'two-pot' chemical sequence as shown in figure 7. Treatment of **14** with methyllithium at −78 °C immediately gave the lithium alkoxide **31** with moderate effervescence caused by methane gas evolution. When a 0 °C THF solution of **31** was added to the Wittig reagent in THF, poor yields of pyrrolidine **19** resulted. This suggested that lithium alkoxide **31** might not have been in equilibrium with the reactive ketoamide tautomer in this reaction medium. In earlier runs, only moderate yields (30–53%) had been obtained when lithium alkoxide **31** was quenched with aqueous NH_4Cl and then subsequently subjected to an extractive workup before addition to the Wittig reagent. Since hydroxylactam **16** was more reactive to the Wittig reagent than lithium alkoxide **31**, an in situ conversion of **31** to **16** was performed by acidifying with TFA. The resulting solution of soluble lithium trifluoroacetate and hydroxylactam **16** was allowed to warm to 0 °C before its addition to the Wittig reagent. This modification led to significantly increased yields (65–70%) of pyrrolidine **19**.

The absolute configurations of **19** and derivatives were determined by chemical correlation to 3,4-disubstituted pyrrolidines derived from α-allokainic [12] and kainic acids [36]. In the sequence illustrated in figure 11, the 3-enamido substituent of **19** was first converted to the 3-hydroxymethyl substituent of **33**. Thus, quantitative acylation of **19** with Boc_2O gave **32**, which was treated with $LiBHEt_3$ to afford the alcohol **33** in 58% yield. Homologation of the 3-hydroxymethyl substituent of **33** was accomplished by the following synthetic sequence. Catalytic hydrogenation of **33** over

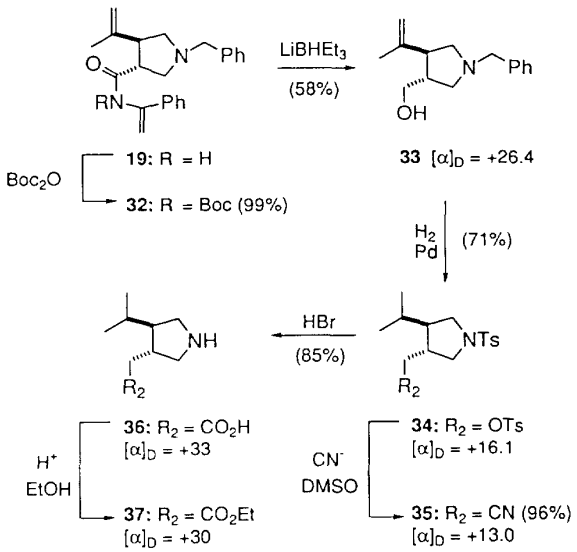

Fig 11

$Pd(OH)_2$ on carbon gave an intermediate aminoalcohol resulting from hydrogenation of the double bond and hydrogenolysis of the *N*-benzyl group. Reaction of this crude intermediate with *p*-toluenesulfonyl chloride in pyridine gave sulfonamide **34** in 71% yield for the two steps. Displacement of the tosyl group of **34** was accomplished with sodium cyanide in DMSO in 96% yield to afford nitrile **35**. Subjection of the latter to a refluxing biphasic mixture of 48% HBr and CH_2Cl_2 for 18 h allowed the concomitant hydrolyses of the *N*-tosyl and nitrile functionalities to give the optically active amino acid **36** in 85% yield after purification by ion-exchange chromatography.

Kennewell [36] had demonstrated that oxidative decarboxylation of *L*-α-kainic acid **38** gives a pyrroline intermediate which epimerizes at C-3 under the acidic conditions of a subsequent reduction ($NaBH_3CN$) step to give the thermodynamically more stable *trans* amino acid **39**. Oxidative decarboxylation of commercially available **38**, followed by reduction ($NaCNBH_3$), gave the *trans* amino acid (+)-**39**, which exhibited a positive rotation ($[\alpha]_D = +28$; lit [36]: $[\alpha]_D = +39.5$). Catalytic hydrogenation of (+)-**39** gave (+)-**36**, which was correlated to synthetic **36** (derived from **14**) by spectral and polarimetric comparison (fig 12). The absolute configurations of (+)-**36** and (+)-**33** were thus shown to be (3*R*,4*R*) and (3*R*,4*S*), respectively. Moreover, as shown in figure 11, acid-catalyzed esterification of (+)-**36** gave ethyl ester (+)-**37** whose ^{1}H-NMR spectrum was identical with the reported enantiomer [12], (−)-**37**, which was derived from natural α-allokainic acid. The absolute configuration of synthetic (+)-**37** was therefore assigned as (3*R*,4*R*).

It was now desirable to assess the feasibility of transforming **16** and **18** into the fused lactones, **41**, **42**. The lactone functional group is present in a number of naturally occurring compounds exhibiting pharmacological properties [37], and forms the structural core

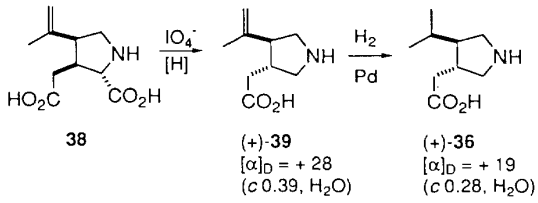

Fig 12

of many versatile synthetic intermediates [38]. For example, lactone-fused pyrrolidines were converted to azabicyclic derivatives that were useful as potential therapeutic agents for Alzheimer type dementia [39]. Accordingly, since hydroxylactams like **16** and **18** may be considered appropriate precursors for the lactone functional group, attention was directed towards this goal. Figure 13 shows a sequence of chemical events where nonracemic hydroxylactams *ent*-**16** were subjected to reductive conditions. Reacting through the ketoamide tautomer *ent*-**16c**, the hydride attacked the more electrophilic ketone carbonyl group to afford hydroxyamides **40**, which then cyclized in acid to form a mixture of bicyclic lactones (**41** and **42**) and acetophenone **43**. Table I reveals that the overall three-step sequence to the bicyclic lactones **41** and **42** was moderately efficient (42–52% yield) and that the diastereoselectivity of the ketone reduction ranged between 4 and 6:1, depending upon the hydride source.

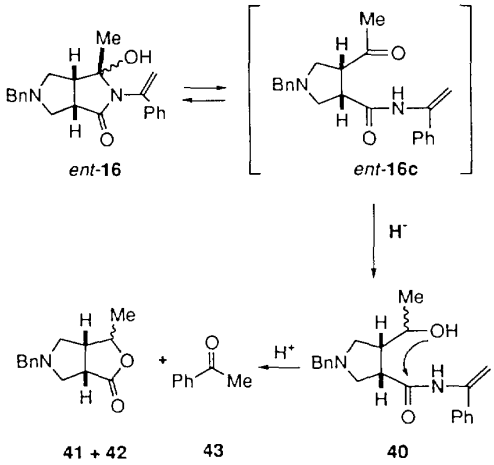

Fig 13

That the major lactone **41** was of high enantiomeric enrichment was shown by its optical rotation ($[\alpha]_D = +9.94$) and by its ee as determined by chiral stationary phase HPLC (fig 14). The level of enantiomeric enrichment of lactone **41** (94% ee) is within experimental error of the diastereomeric excess (88% de) of the precursor tricyclic lactam (*ent*-**14**), demonstrating that this process is indeed enantioselective. For comparison purposes, the racemic lactones (±)-**41** and (±)-**42** were prepared from racemic imide **20**, by the sequence shown in figure 15.

Table I. Selective reduction of ketoamide intermediate *ent*-**16c**.

Hydride	*Equiv*	*Temperature (° C)*	*Solvent*	*Reaction time*	***41/42** ratio*
$NaBH_4$	4.3	50–55	$EtOH/H_2O$	3.0	4.2:1[a]
$LiAl(O\textit{tert}\text{-}Bu)_3H$	3.0	0	THF	29	6.0:1[a]
$KBH(\textit{sec}\text{-}Bu)_3$	3.0	−30	THF	2.3	6.3:1[b]

[a] Determined by ^{1}H-NMR analysis on the crude lactone mixture. [b] Determined by GC/MC analysis on the crude lactone mixture.

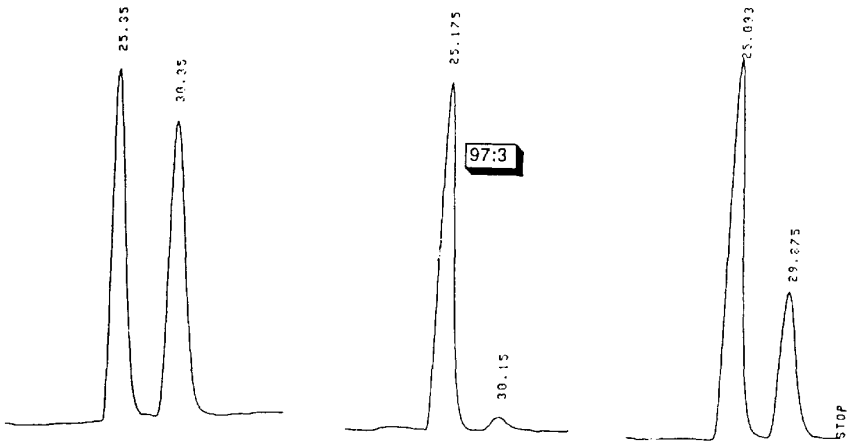

Fig 14. Chiral stationary phase HPLC trace of lactone **41** (Diacel, OJ Column, hexane/2-propanol, 90:10).

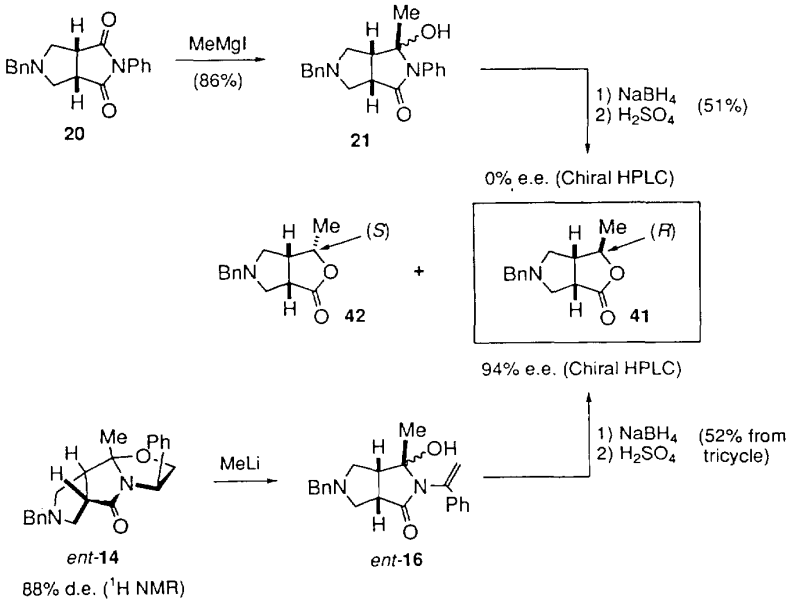

Fig 15

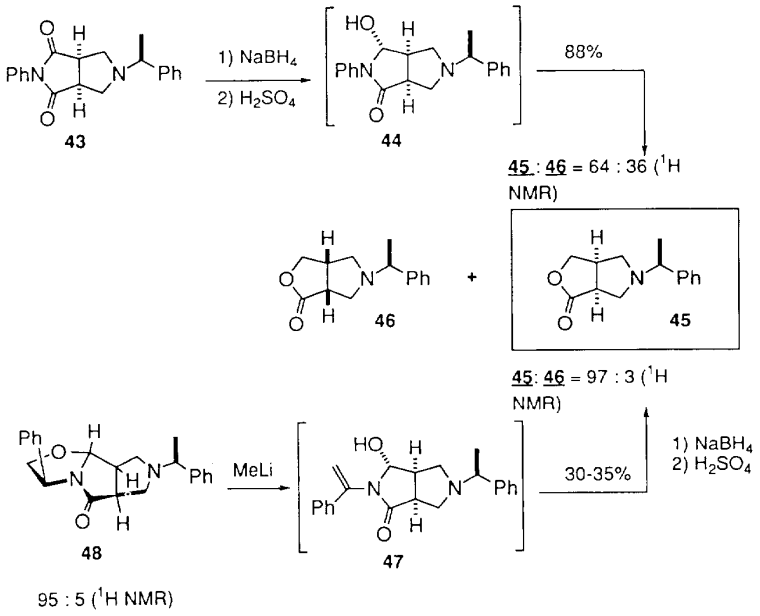

Fig 16a

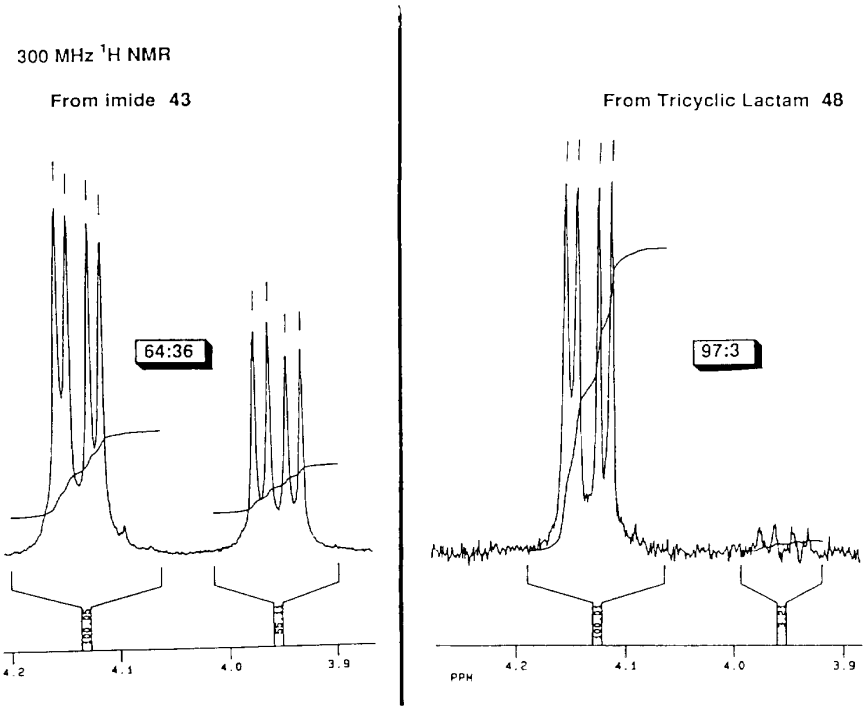

Fig 16b. Partial ^{1}H-NMR spectrum of diastereomeric mixtures of lactones **45** and **46**.

We next considered reaching the chiral bicyclic lactones **45** or **46** via the tricyclic adducts **48** (fig 16a). However, one could also, in principle, reach **45** via simple imides such as **43** with stereocontrolled reduction. Treatment of chiral bicyclic imide **43** with $NaBH_4$ gave hydroxyamides through the intermediacy of hydroxylactam **44**. Subsequent acidification gave an inseparable and disappointing 1.8:1 mixture of lactones **45** and **46** in 88% yield (fig 16b). In contrast, similar treatment of the chiral hydroxylactam, **47**, derived from diastereomerically enriched **48** (90% de), gave lactone **45** (94% de), but in poor yield (30–35%) accompanied by decomposition products. Evidently, the rate of ring opening of the carbinol amide **47** was affected by the enamine in the *N*-substituent and was slow when compared to the ring opening rate of the *N*-phenyl hydroxy-

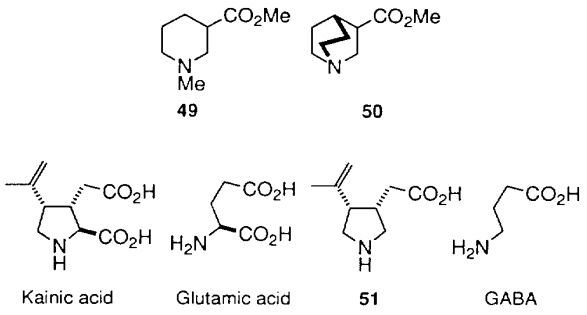

Fig 17

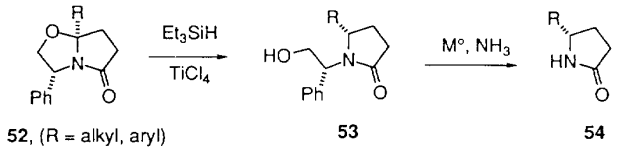

Fig 18

lactam **44** resulting in undesired side reactions. Several attempts to increase the yield had only limited success.

The strategy of using carbocyclic or heterocyclic rings as conformational constraints in the design of bioactive organic compounds has led to enhanced activity, selectivity, and stability to pharmacologically important substances [39, 40]. Conformationally constrained peptides were shown to be useful tools in developing peptide-derived pharmaceutic agents (fig 17) [41–44]. Conformational restriction in quinuclidine ester **50** resulted in a 40-fold increase in binding affinity to the muscarinic receptor as compared with the less rigid arecoline **49** [45].

Moreover, kainic acid and analogs exhibit powerful neuroexcitatory effects, which were ascribed to their acting as conformationally restricted analogs of glutamic acid [46]. Similarly, the 2-decarboxylated derivative of kainic acid **51** was of interest [47, 36] since it is a conformationally restricted analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).

Chiral bicyclic lactams **52** have recently been converted to optically active GABA precursors [3, 4, 6] as shown below. In the presence of titanium tetrachloride, bicyclic lactams **52** were converted to *N*-acyl iminium intermediates that were then reduced stereoselectively [48, 49] with triethylsilane to give pyrrolidinones **53**. Dissolving metal reduction of **53** gave chiral lactams **54** in good yields (see fig 18) and the conversion of the 2-pyrrolidinone substrates to the corresponding GABAs has been accomplished previously [50].

Reaction conditions were evaluated for the preparation of pyrrolidinone **59**, as shown in figure 19. Tricyclic lactam **48** was found to be unreactive in TFA in the presence of Et_3SiH at room temperature, and the addition of heat (reflux) promoted decomposition. Furthermore, treatment of **48** with $TiCl_4$ in the presence of Et_3SiH at −78 °C gave the water-soluble bicyclic pyrrolidinone **57** in poor isolated yields (11%).

Similar treatment of the more lipophilic bromotricyclic lactam **55** [11] gave improved isolated yields

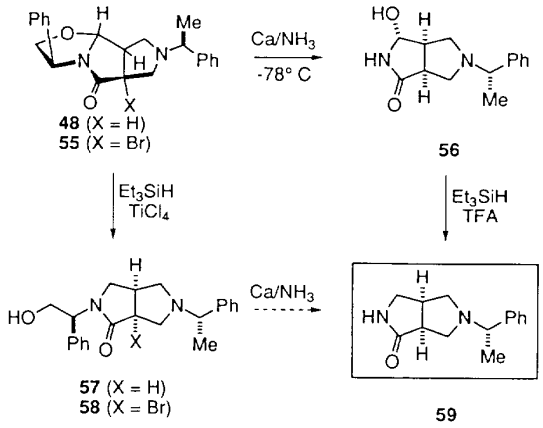

Fig 19

(51%) of **58**; however, mixtures of reduction products were observed upon dissolving metal reduction with calcium metal. Improved results were achieved through the intermediacy of hydroxylactams **56**. Thus, reaction of **48** with calcium in liquid ammonia at −78 °C gave crude hydroxylactam **56**, which was immediately treated with TFA and Et_3SiH. Chromatographic purification afforded **59** as a single diastereomer in 31% unoptimized yield for the combined steps.

As shown in figure 20, reductive cleavage of the oxazolidine C–O bond of **14** with $TiCl_4$ and Et_3SiH gave poor isolated yields (22%) of the polar diamino alcohol **61**. In contrast, metal-ammonia reduction of **14** gave *N*-unsubstituted hydroxylactam **60** [51] in excellent yield. Deoxygenation (Et_3SiH, TFA, room temperature) of **60** occurred in a highly stereoselective manner, affording **62** in 75% yield. The stereochemical assignment of **62** was based upon ^1H- and ^{13}C-NMR analysis and will be described below. Apparently, the observed stereochemistry arose from hydride delivery

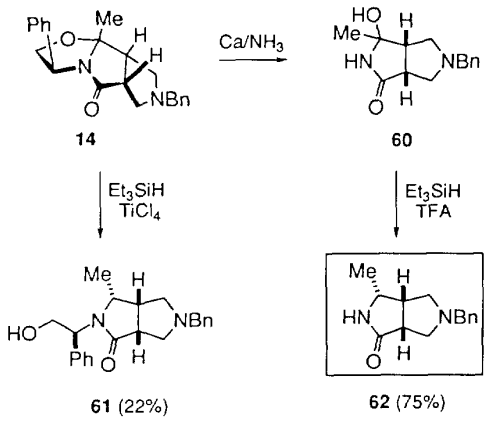

Fig 20

from the less hindered *exo* face of the bicyclic structure of **62**.

Structure assignments

The stereochemical assignments of bicyclic lactones **41** and **42** and pyrrolidinones **61** and **62** were based upon the ^{1}H- and ^{13}C-NMR data summarized in figure 21.

The ^{13}C-NMR signals corresponding to the methyl groups in the minor isomer **42** (δ 16.7), and in pyrrolidinone **62** (δ 17.2) were observed up-field relative to the methyl signal in major isomer **41** (δ 22.2). The up-field shift of the methyl group signals in the structurally similar compounds **42**, **62** and **64** was likely due to the steric compression of the methyl groups *syn* to the pyrrolidine ring. Thus, H_A and H_B in compounds **42**, **62** and **64** shared the same *syn* orientation. Moreover, the similarity in magnitude between the coupling constants (J_{AB}) of the corresponding ring-fusion hydrogens (H_A) and methine hydrogens (H_B) of minor isomer **41** (J_{AB} = 4.1 Hz) and that of the known [9] bicyclic lactone **63** (J_{AB} = 4.0 Hz) suggested that H_A and H_B in these compounds shared the same *anti* orientation.

In summary, the readily available chiral tricyclic lactams **14**, **17** and **48** may be considered synthons for nonracemic bicyclic hydroxylactams. The transformations described herein represent a novel tactic for the preparation of pyrrolidines bearing the manipulable 3,4-disubstitution pattern. In this context, the synthetic utility of these intermediates allowed control of the nature of the pyrrolidine ring substituents providing useful functional 'handles' for further synthetic work.

Experimental section

General

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker AC300 spectrometer. For ^{1}H NMR, chemical shifts are reported in ppm (δ) relative to the residual $CHCl_3$ signal (δ 7.24), or HDO signal (δ 4.64), downfield from tetramethylsilane (δ 0.00). Coupling constants (J) are reported in hertz and the data are presented in the form: chemical shift (multiplicity, number of protons, coupling constants). For ^{13}C NMR taken in $CDCl_3$, chemical shifts are reported in ppm (δ) relative to the middle resonance of the $CDCl_3$ triplet (δ 77.0). For ^{13}C NMR taken in D_2O, chemical shifts are reported in ppm relative to the signal (δ 51.6), provided by added CH_3OH (2 μL), downfield from the resonance corresponding to the trimethylsilyl group (δ 0.00) of sodium 3-(trimethylsilyl)-1-propanesulfonate in D_2O. Carbon resonances were assigned with the aid of distortionless enhancement by polarization transfer (DEPT) spectra obtained with phase angles of 135° and 90°. DEPT (135, 90) experiments in ^{13}C NMR differentiate between methyl, methylene, methine, and quaternary carbon signals and thus effectively provide C-H multiplicities which are indicated as s = singlet (quaternary), d = doublet (methine), t = triplet (methylene), and q = quartet (methyl). Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer and were calibrated from the 1601 cm^{-1} polystyrene absorption. Melting points were obtained using a Mel-temp apparatus and were uncorrected. Optical

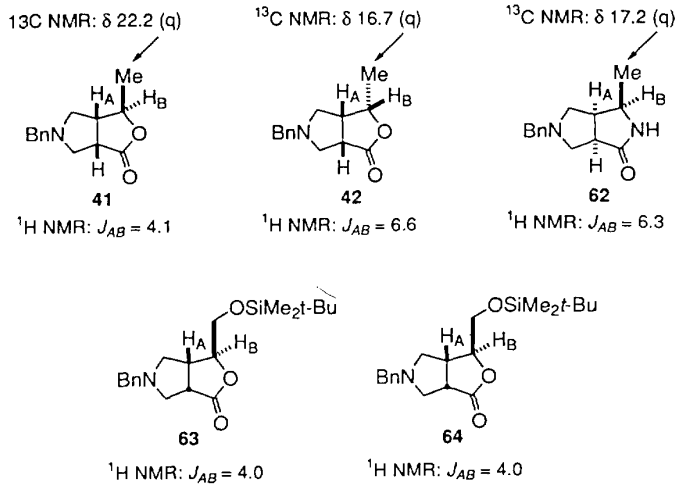

Fig 21. Stereochemical assignments of bicycles **41**, **42** and **62–64**.

rotations were taken at 25 °C on an Autopol III automatic polarimeter. Low-resolution mass spectra were measured on a HP 5890 gas chromatograph/HP 5970 mass spectrometer; column: 12 m × 0.2 mm ID HP1 column (100% dimethylpolysiloxane). Temperature program: 50 °C (1 min); ramp (20 °C/min to 280 °C). Elemental analyses were performed by Atlantic Microlab Inc, Norcross, GA, USA.

Reagents

Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl radical. Ethyl acetate (EtOAc) and hexanes were distilled prior to use. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 prior to use. Toluene, pyridine, triethylamine, and diisopropylamine were distilled from calcium hydride under argon. Trifluoroacetic acid (TFA) and other reagents were used without purification unless indicated.

Separations

Preparative flash column chromatography [53] was performed on Amicon Matrex (20–45 μm) or Aldrich 951 (58 μm) silica gel using a positive pressure of air. Radial chromatography was carried out using a preparative, centrifugally accelerated, radial, thin-layer chromatograph provided by Harrison Research (840 Moana Court, Palo Alto, CA, USA). Thin layer chromatography (TLC) was carried out on aluminum-backed silica gel $60F_{254}$ (0.2 mm thickness). Compounds were visualized by UV light or staining with solutions of: potassium permanganate (Na_2CO_3 (2 g)/$KMnO_4$ (1 g) in H_2O (100 mL)); ammonium molybdate ($(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1 g)/H_2SO_4 (2 mL)/H_2O (18 mL)), or vanillin (vanillin (5 g)/H_2SO_4 (2 mL)) in absolute ethanol (100 mL). Unless otherwise indicated, all reactions were carried out under an inert atmosphere of argon. Glassware was either dried in an oven (120 °C) for at least eight hours or was thoroughly flame dried and cooled under argon.

• *1(R),4(R,S),5(S)-7-Benzyl-4-hydroxy-4-methyl-3-(1-phenylethenyl)-3,7-diazabicyclo[3.3.0]octan-2-one* ***16a,b***

To a −10 °C solution of tricyclic lactam **14** (217 mg, 0.623 mmol) in THF (5 mL) was added 0.43 mL (0.685 mmol, 1.1 equiv) of a 1.6 M solution of MeLi in Et_2O. TLC analysis (EtOAc) of the clear, pale yellow solution indicated a trace of starting material, and when an additional portion of 1.6 M MeLi (0.10 mL, 0.16 mmol) was introduced the solution became dark red. After 50 min, the mixture was quenched by the addition of saturated aqueous NH_4Cl, extracted into Et_2O, dried (Na_2SO_4), and was concentrated to a crude yellow foam (223 mg). This foam was purified by column chromatography (1:1 to 100:0 EtOAc/hexanes) to afford 135 mg (62%) of oily hydroxylactams **16a** and **16b** as a 5:1 mixture of diastereomers.

For the major hydroxylactam **16a**: R_f 0.18 (EtOAc).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.2–7.6 (m, 10H), 5.84 (s, 1H), 5.39 (s, 1H), 3.60 (ABq, 2H, J = 12.9, $\Delta\nu$ = 82.9), 3.55 (d, 1H, J = 9.2), 3.22 (m, 1H), 2.98 (m, 1H), 2.83 (m, 1H), 2.43 (m, 1H), 2.30 (m, 1H), 1.70 (br s, 1H), 1.30 (s, 3H).

IR (film) for a 5:1 mixture of **16a** and **16b**: ν 3 357, 3 084, 3 060, 3 027, 1 678, 1 626 cm^{-1}.

MS (EI, 70 eV) *m/e* (relative intensity): 330 (57.7, M^+-H_2O, 302 (1.4), 253 (1.2), 239 (5.7), 211 (5.6), 158 (11.7), 133 (16.8), 132 (16.4), 103 (12.3), 91 (60.6), 77 (13.0), 65 (15.1), 42 (100).

For the minor hydroxylactam **16b**: R_f 0.36 (EtOAc).

Partial ^{1}H-NMR: δ 5.76 (s, 1H), 5.52 (s, 1H), 1.36 (s, 3H).

• *1(S),4(R),5(R)-7-Benzyl-3-(1-phenylethenyl)-4-hydroxy-3,7-diazabicyclo[3.3.0]octan-2-one* ***18***

To a −78 °C solution of tricyclic lactam **17** (20.0 mg, 0.0598 mmol) in THF (1 mL) was added 0.17 mL (0.24 mmol, 4 equiv) of a 1.4 M solution of MeLi in Et_2O. The resulting clear, pale yellow solution was left to stand at −20 °C for 27 h. TLC analysis (EtOAc) showed complete consumption of the starting material. The reaction was quenched at −78 °C by the addition of saturated, aqueous NH_4Cl (1 mL) and was allowed to warm to room temperature. The mixture was partitioned between Et_2O and H_2O and the organic extracts were combined, dried (Na_2SO_4), and concentrated to a pale yellow foam which was immediately purified by column chromatography (1:1–100:0 EtOAc/hexanes). Afforded was 12.5 mg (63%) of **18** as a colorless oil: R_f 0.33 (EtOAc).

^{1}H-NMR 300 MHz, $CDCl_3$) δ 7.5–7.2 (m, 10H), 5.71 (s, 1H), 5.39 (s, 1H), 4.91 (s, 1H), 3.61 (ABq, 2H, J = 12.8, $\Delta\nu$ = 98.3), 3.38 (d, 1H, J = 9.3), 3.19 (apparent t, 1H, J = 7.7), 2.91 (d, 1H, J = 9.7), 2.65 (apparent t, 1H, J = 7.8), 2.37 (m, 2H), 1.76 (br s, 1H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 175.7 (s), 140.4 (s), 138.7 (s), 134.9 (s), 128.8 (d), 128.6 (d), 128.6 (d), 128.4 (d), 127.2 (d), 126.3 (d), 114.3 (t), 89.0 (d), 59.4 (t), 58.9 (t), 57.6 (t), 45.7 (d), 44.3 (d);

IR (film): ν 3 355, 3 060, 3 027, 1 679, 1 629 cm^{-1}.

• *3(R),4(S)-1-Benzyl-4-isopropenyl-N-(1-phenylethenyl)pyrrolidine-3-carboxamide* ***19***

To a white suspension of dry methyltriphenylphosphonium bromide (1.90 g, 5.32 mmol) in THF (15 mL) was added a 1 M solution of $NaN(SiMe_3)_2$ in THF (4.2 mL, 4.2 mmol). The resulting yellow suspension was allowed to stir at room temperature for 30 min.

To a clear, colorless, −78 °C solution of tricyclic lactam **19** (587 mg, 1.68 mmol) in THF (20 mL) was added a 1.5 M solution of MeLi·LiBr complex in Et_2O (1.3 mL, 2.0 mmol) dropwise. The solution became tea-orange during the addition and moderate gas evolution was observed which subsided within 5 min. TLC analysis revealed complete consumption of the starting material. TFA (155 μL, 2.02 mmol) was added in one portion and the pale yellow solution of hydroxylactams **16** was allowed to warm rapidly to −10 °C.

After 20 min, the nearly colorless solution of hydroxylactams **16** was added to the methylidene triphenylphosphorane ylide suspension via cannula, followed by a THF rinse (5 mL), and the resulting yellow suspension was allowed to stir for 24 h at room temperature. TLC analysis (EtOAc) showed complete consumption of intermediate hydroxylactams and the formation of olefin products (R_f 0.60), triphenylphosphine oxide (R_f 0.27), and $MePPh_3OH$ (R_f 0.08). Saturated aqueous NH_4Cl (25 mL) was added and the aqueous phase was separated and extracted with CH_2Cl_2 (2 × 25 mL). The organic extracts were combined with the organic phase, dried (Na_2SO_4) and concentrated to a residue that was purified by column chromatography (1:5 EtOAc/hexanes) to afford 408 mg ((70.1%) of **19** as a yellow syrup: R_f 0.59 (EtOAc).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.00–7.45 (m, 10H), 5.91 (s, 1H), 5.01 (s, 1H), 4.84 (s, 1H), 4.79 (s, 1H), 3.60 (ABq, 2H, J = 12.6, $\Delta\nu$ = 29.5), 3.10 (m, 3H), 2.79 (m, 1H), 2.51 (dd, 1H, J = 7.4, 9.7), 2.24 (m, 1H), 1.77 (s, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 174.7 (s), 144.9 (s), 140.8 (s), 138.9 (s), 137.8 (s), 128.72 (d), 128.70 (d), 128.5 (d), 128.4 (d), 127.3 (d), 126.0 (d), 111.4 (t), 100.8 (t), 59.7 (t), 57.7 (t), 57.3 (t), 50.8 (d), 50.2 (d), 20.6 (q).

IR (film): ν 3 289, 3 060, 3 027, 2 965, 1 746, 1 690, 1 642, 1 601, 1 075, 668 cm^{-1}.

Anal calc for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.56; H, 7.61; N, 8.03.

• *1(S),4(RS),5(R)-7-Benzyl-4-hydroxy-4-methyl-3-phenyl-3,7-diazabicyclo[3.3.0]octan-2-one (±)-**21a,b***

Following the procedure of Speckamp [52], a solution of known bicyclic succinimide **20** [35] (117.3 mg, 0.383 mmol) in THF (2 mL) at room temperature was treated with a 3.0 M solution of methylmagnesium iodide in Et_2O (0.26 mL, 0.78 mmol). The previoulsly clear, colorless solution became a tan-yellow suspension. After 2 h, saturated, aqueous NH_4Cl was added (2 mL) and the mixture was partitioned between Et_2O and H_2O. The Et_2O extracts were combined, dried (Na_2SO_4) and concentrated to 106 mg (86%) of racemic hydroxylactams (±)-**21a,b** as a pale yellow syrup. ^{1}H-NMR analysis of this mixture showed a diastereomeric ratio of 2.2:1.

For the major isomer **21a**: R_f 0.27 (EtOAc).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.4–7.2 (m, 10H), 6.28 (br s, 1H), 3.67 (ABq, 2H, J = 12.7, $\Delta\nu$ = 29.7), 3.22 (m, 3H), 2.80 (dd, 1H, J = 4.8, 9.0), 2.46 (apparent, 1H, J = 9.8), 2.28 (dd, 1H, J = 4.7, 9.6), 1.32 (s, 3H).

For the minor isomer **21b**: R_f 0.41 (EtOAc).

Partial ^{1}H-NMR δ 1.25 (s, 3H).

• *trans-3(R,S),4(R,S)-1-Benzyl-4-isopropenyl-N-phenylpyrrolidine-3-carboxamide (±)-**22***

To a white suspension of methyltriphenylphosphonium bromide (1.75 g, 4.90 mmol) in THF (30 mL) at room temperature was added a 1 M solution of $NaN(SiMe_3)_2$ in THF (7.4 mL, 7.4 mmol) to form a yellow suspension that was allowed to stir for 18.8 h. A THF solution (5 mL) of crude hydroxylactams (±)-**21** (derived from 601 mg, 1.96 mmol of bicyclic succinimide **20**) was added dropwise to the above yellow ylide suspension. After 45 min, the suspension turned brown and TLC (EtOAc) analysis indicated complete consumption of (±)-**21**. The reaction was quenched with aqueous NH_4Cl and partitioned between H_2O and Et_2O. The Et_2O extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a red syrup. Column chromatography (1:1 EtOAc/hexanes), followed by radial chromatography (1:4 EtOAc/hexanes) gave an oil that was induced to crystallize with 1:5 Et_2O/hexanes. Trituration of the solids with 1:5 Et_2O/hexanes gave 316 mg (50%) of (±)-**22** as a white powder: R_f 0.56 (EtOAc); mp 89–89.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.50 (m, 2H), 7.27–7.37 (m, 7H), 7.06 (m, 1H), 4.85 (s, 1H), 4.80 (s, 1H), 3.70 (ABq, 2H, J = 12.7, $\Delta\nu$ = 21.6), 3.14 (m, 3H), 2.80 (m, 1H), 2.55 (dd, 1H, J = 7.1, 9.8), 2.34 (apparent t, 1H, J = 7.9), 1.78 (s, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 173.7 (s), 145.0 (s), 138.5 (s), 138.2 (s), 128.9 (d), 128.6 (d), 128.5 (d), 127.5 (d), 123.6 (d), 119.4 (d), 111.4 (t), 59.6 (t), 57.8 (t), 56.9 (t), 50.4 (d), 50.0 (d), 20.5 (q).

IR (film): ν 3 300, 3 062, 2 964, 1 660, 1 599, 1 500 cm^{-1}.

• *trans-3(R,S),4(R,S)-4-Isopropenyl-1-phenoxycarbonyl-N-phenylpyrrolidine-3-carboxamide (±)-**23***

A 25 °C solution of (±)-**22** (194 mg, 0.607 mmol) in CH_2Cl_2 (10 mL) was treated first with phenyl chloroformate (0.30 mL, 2.43 mmol), and then with Et_3N (85 μL, 0.61 mmol). After 32 h, the reaction mixture was applied directly onto a silica gel column presaturated with 1:1 EtOAc/hexanes. Elution of the R_f 0.42 component and final purification by radial chromatography (1:4 EtOAc/hexanes, 1 mm plate) gave 190 mg (89.3%) of (±)-**23** as a white crushable foam: R_f 0.42 (ET_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.09–7.46 (m, 10H), 4.99 (s, 1H), 4.96 (s, 1H), 3.68–4.03 (m, 3H), 3.18–3.50 (m, 2H), 2.89–3.07 (m, 1H), 1.81 (s, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 169.2 (s), 152.9 (s), 151.1 (s), 142.2 (s), 137.5 (s), 129.3 (d), 128.9 (d), 128.8 (d), 125.4 (d), 124.6 (d), 124.5 (d), 121.6 (d), 120.1 (d), 113.6 (t), 113.2 (t), 113.2 (t), 50.6 (t), 50.4 (t), 49.7 (t), 49.4 (t), 49.2 (d), 48.9 (d), 48.44 (d), 48.37 (d), 20.6 (q), 20.3 (q).

IR (film): ν 3 323, 3 138, 3 077, 2 971, 2 889, 1 725, 1 704, 1 666, 1 601 cm^{-1}.

• *trans-3-(R,S),4(R,S)-N,1-Bis(phenoxycarbonyl)-4-isopropenyl-N-phenylpyrrolidine-3-carboxamide (±)-**24***

To a −70 °C solution of (±)-**23** (175 mg, 0.499 mmol) in THF (10 ML) was added a 1.03 M solution of *sec*-butyllithium in cyclohexanes (0.64 mL, 0.66 mmol) dropwise to form a pale yellow solution. After 30 min, phenyl chloroformate (0.20 mL, 1.6 mmol) was added dropwise. After 3 h, TLC analysis showed complete consumption of starting (±)-**23** and the solution was allowed to warm to room temperature over 2 h. The reaction mixture was quenched with 1.8 weight% aqueous solution of citric acid and Et_2O and the aqueous phase was extracted with Et_2O. The Et_2O extracts were dried (Na_2SO_4), concentrated and the residue was purified by radial chromatography (1:4 EtOAc/hexanes) to afford 186 mg (79%) of (±)-**24** as a clear, colorless oil: R_f 0.62 (Et_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.00–7.50 (m, 15H), 4.95 (m, 2H), 4.08–4.36 (m, 2H), 3.68–4.00 (m, 2H), 3.35–3.52 (m, 2H), 1.82 (s, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$, doubling of signals are due to hindered rotation of carbamate groups) δ 175.0 (s), 152.9 (s), 152.7 (s), 151.2 (s), 150.1 (s), 142.8 (s), 142.5 (s), 137/6 (s), 129.5 (d), 129.2 (d), 128.8 (d), 128.0 (d), 126.5 (d), 126.4 (d), 125.2 (d), 121.7 (d), 121.1 (d), 112.7 (t), 112.6 (t), 50.2 (t), 49.9 (t), 49.0 (d), 48.8 (d), 47.9 (d), 20.9 (q).

IR (film): ν 3 067, 3 044, 2 972, 2 891, 1 751, 1 723, 1 649, 1 595 cm^{-1}.

• *trans-3(R),4(S)-4-Isopropenyl-1-(phenoxycarbonyl)pyrrolidine-3-methanol **25***

To a −10 °C solution of tertiary amide **28** (20.6 mg, 0.0415 mmol) in THF (2 mL) was added dropwise a 1.0 M solution of $LiBHEt_3$ in THF (0.10 mL, 0.10 mmol), and the reaction was allowed to warm to room temperature. After 2.5 h, the reaction mixture was quenched with saturated, aqueous NH_4Cl and Et_2O. The organic extracts were combined and co-evaporated with THF to give a residue that contained white solids. This residue was filtered through silica gel (CH_2Cl_2), and the UV-active components were separated by radial chromatography (1:4 EtOAc/hexanes) to provide 4.2 mg of enamide **29** and 7.9 mg (73%) of **25** both as clear, colorless oils. For **29**: R_f 0.25 (1:1 EtOAc/hexanes).

^{1}H-NMR (300 MHZ, $CDCl_3$) δ 8.46 (m, 1H), 7.24–7.52 (m, 9H), 4.94 (s, 2H).

For **25**: R_f 0.15 (1:1 EtOAc/hexanes).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.09–7.37 (m, 5H), 4.89 (s, 2H), 3.80 (m, 3H), 3.58 (dd, 1H, J = 6.6, 10.9), 3.37 (m, 2H), 2.71 (m, 1H), 2.44 (s, 1H), 1.76 (d, 3H, J = 3.6), 1.64 (s, 1H, D_2O exch).

^{13}C-NMR (75.5 MHz, $CDCl_3$ DEPT experiments 135 and 90; some doubling of signals due to hindered rotation of carbamate group) δ 129.2 (d), 125.2 (d), 121.7 (d), 113.1 (t), 63.2 (t), 50.5 (t), 49.2 (t), 48.3 (d), 47.4 (d), 44.0 (d), 43.2 (d), 19.7 (q).

IR (film): ν 3 454, 3 074, 1 724, 1 647 cm^{-1}.

• *trans-3(R,S),4(R,S)-4-Isopropenyl-1-(phenoxycarbonyl)pyrrolidine-3-methanol (±)-**25***

To a −10 °C solution of amide (±)-**24** (177 mg, 0.376 mmol) in THF (10 mL) was added dropwise a 1.0 M solution of $LiBHEt_3$ in THF (1.1 mL, 1.1 mmol) and the reaction was allowed to warm to room temperature. After 5 h, the reaction mixture was quenched with saturate, aqueous NH_4Cl and Et_2O. The organic extracts were combined and co-evaporated with THF to give a residue that contained white solids. The residue was taken up in CH_2Cl_2 and was filtered through silica gel. Radial chromatography on the filtered residue gave (±)-**25** (40.5 mg, 41%) along with an impure fraction (138 mg), which consisted of **26** and (±)-**25**.

• *3(R),4(S)-4-Isopropenyl-1-(phenoxycarbonyl)-N-(1-phenylethenyl)pyrrolidine-3-carboxamide **27** and 3(R),4(S)-N,1-bis(phenoxycarbonyl)-4-isopropenyl-N-(1-phenylethenyl)pyrrolidine-3-carboxamide **28***

To a 25 °C solution of **19** (91.8 mg, 0.265 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (75 μL, 0.538 mmol, 2 equiv), and then neat phenyl chloroformate (96 μL, 0.80 mmol, 3 equiv). The clear, colorless solution was allowed to stir for 12 h. The reaction mixture was applied directly onto a silica gel column presaturated with 1:1 EtOAc/hexanes. The UV absorbing components were eluted with 1:1 EtOAc/hexanes, concentrated and separated by radial chromatography (1:4 EtOAc/hexanes, 1 mm plate) to afford 37.6 mg (40%) of **27** as a clear, colorless film and 62.5 mg (47%) of **28** as a white crushable foam.

For **27**: R_f 0.12 (1:4 EtOAc/hexanes).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (m, 1H), 7.04–7.38 (m, 10H), 5.88 (s, 1H), 5.13 (s, 1H), 5.00 (s, 1H), 4.98 (s, 1H), 3.86 (m, 2H), 3.28 (m, 3H), 2.99 (m, 1H), 1.82 (s, 3H).

IR (film): ν 3 302, 3 060, 1 725, 1 595, 1 528 cm^{-1}.

For **28**: R_f 0.64 (Et_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.09–7.45 (m, 13H), 6.85 (m, 2H), 5.93 (s, 1H), 5.34 (s, 1H), 4.92 (s, 2H), 4.08–4.29 (m, 2H), 3.84–3.99 (m, 1H), 3.71 (m, 1H), 3.43 (m, 2H), 1.80 (s, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$, multiple signals are due to hindered rotation of the carbamate groups and accidental degeneracy) δ 147.1 (s), 145.7 (s), 144.6 (s), 138.1 (s), 137.7 (s), 137.5 (s), 131.5 (s), 125.6 (d), 125.4 (d), 125.2 (d), 125.0 (d), 122.83 (d), 122.8 (d), 121.6 (d), 118.4 (d), 117.8 (d), 112.0 (t), 110.3 (t), 110.1 (t), 52.1 (t), 52.0 (t), 51.1 (d), 50.9 (d), 50.8 (d), 50.1 (d), 25.1 (q), 24.9 (q).

IR (film): ν 3 064, 1 788, 1 751, 1 723, 1 640, 1 593, 1 494 cm^{-1}.

• *3(R),4(S)-1-Benzyl-N-tert-butoxycarbonyl-4-isopropenyl-N-(1-phenylethenyl)pyrrolidine-3-carboxamide **32***

To a room temperature solution of secondary amide **19** (373 mg, 1.08 mmol) in THF (6 mL) was added Boc_2O (941 mg, 4.31 mmol) and DMAP (52.5 mg). The resulting clear, yellow solution was allowed to stir for 20 h. The reaction mixture was then concentrated and the residue was directly purified by radial chromatography (1:3 EtOAc/hexanes) to afford 479 mg (99.4%) of **32** as a pale yellow oil: R_f 0.74 (Et_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) extra signals (δ 1.45, 1.51) are due to hindered rotation about imide bonds. δ 7.31 (m, 10H), 5.68 (s, 1H), 5.09 (s, 1H), 4.79 (s, 1H), 4.73 (t, 1H, J = 1.5), 3.98 (apparent q, 1H, J = 7.8), 3.63 (ABq, 2H, J = 13.1, $\Delta\nu$ = 49.1), 3.37 (apparent q, 1H, J = 7.6, 3.02 (t, 1H, J = 9.1), 2.87 (m, 2H), 2.53 (apparent, 1H, J = 8.1), 1.72 (s, 3H), 1.51 (s, 1.5H), 1.45 (s, 3H), 1.24 (s, 9H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) extra signals (δ 27.4, 27.9) are due to hindered rotation about imide bonds. One accidental degeneracy found in aromatic region. δ 176.9 (s), 152.3 (s), 145.7 (s), 144.3 (s), 139.12 (s), 136.97 (s), 128.6 (d), 128.4 (d), 128.2 (d), 126.9 (d), 125.4 (d), 113.4 (t), 111.1 (t), 83.1 (s), 59.9 (t), 58.5 (t), 58.4 (t), 49.3 (d), 48.7 (d), 27.9 (q), 27.5 (q), 27.4 (q), 20.3 (q).

• *(3R,4S)-1-Benzyl-4-isopropenylpyrrolidine-3-methanol **33***

To a −10 °C solution of tertiary amide **32** (462 mg, 1.03 mmol) in THF (10 mL) was added a 1 M solution of $LiBEt_3H$ in THF (3.1 mL, 3.1 mmol) dropwise over 2 min. The solution was allowed to stir for 18 h at room temperature. The reaction mixture was quenched with saturated, aqueous NH_4Cl and was extracted with CH_2Cl_2. The organic extracts were dried (K_2CO_3) and concentrated and purified by column chromatography (100% EtOAc) to provide 139 mg (58.4%) of **33** as a clear, colorless oil: R_f 0.29 (5.95 Et_3N/EtOAc); $[\alpha]_D^{25}$ = +26.4 (*c* 1.38 benzene).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.76 (m, 1H), 4.70 (m, 1H), 3.40 (dd, 1H, J = 3.9, 10.1), 3.52–3.62 (m, 2H), 2.97 (t, 1H, J = 8.6), 2.94 (br s, 1H), 2.73 (m, 2H), 2.53 (dd, 1H, J = 7.3, 9.2), 2.20 (m, 2H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 146.4 (s), 138.7 (s), 128.6 (d), 128.3 (d), 127.0 (d), 110.4 (t), 67.1 (t), 60.1 (t), 58.8 (t), 58.1 (t), 47.9 (d), 44.0 (d), 20.4 (q).

IR (film): ν 3 353, 3 066, 2 917, 2 794, 1 644, 1 051, 1 029, 699 cm^{-1}.

• *(3R,4S)-(4-Isopropyl-1-p-toluenesulfonylpyrrolidine-3-yl)methyl p-toluenesulfonate **34***

A mixture of alcohol **33** (119 mg, 0.514 mmol) and 20% $Pd(OH)_2$ on carbon (50 mg) in absolute EtOH (5 mL) was stirred at room temperature under an atmosphere of hydrogen for 18 h. The reaction mixture was filtered through celite and the catalyst was washed thoroughly with EtOAc and then EtOH. The filtrate was concentrated and the residue was coevaporated with benzene. The crude saturated amino alcohol was combined with *p*-toluenesulfonyl chloride (294 mg, 1.54 mmol) in pyridine (5 mL) and was allowed to stir at room temperature for 22 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic extracts were washed with 0 °C 1 N HCl, saturated, aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to a yellow syrup. Purification was accomplished by radial chromatography (1:4 EtOAc/hexanes) to give 164 mg (70.7%) of **34** as a pale yellow solid: R_f 0.49 (1:1 EtOAc/hexanes); Mp 88–93 °C; $[\alpha]_D$ = + 16.1 (*c* 1.66, benzene).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (apparent d, 2H, J = 8.3), 7.64 (apparent d, 2H, J = 8.3), 7.33 (apparent t, 4H, J = 8.1), 3.94 (dd, 1H, J = 5.1, 9.9), 3.73 (dd, 1H, J = 8.6, 9.8), 3.30 (dd, 1H, J = 8.0, 9.7), 3.04 (AB of ABX, 2H, J_{AB} = 10.1, J_{AX} = 8.8, J_{BX} = 4.2, $\Delta\nu$ = 46.2, 2.69 (dd, 1H, J = 7.7, 9.8), 2.44 (s, 3H), 2.43 (s, 3H), 2.19 (m, 1H), 1.56 (m, 1H), 1.44 (m, 1H), 0.78 (d, 3H, J = 6.7), 0.73 (d, 3H, J = 6.6).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 145.1 (s), 143.8 (s), 132.6 (s), 132.2 (s), 130.0 (d), 129.7 (d), 127.8 (d), 70.9 (t), 50.6 (t), 50.5 (t), 46.6 (d), 40.8 (d), 30.0 (d), 21.7 (q), 21.5 (q), 20.8 (q), 19.3 (q).

IR (film): ν 2 961, 2 875, 1 923, 1 738, 1 120, 1 018, 551 cm^{-1}.

Anal calc for $C_{22}H_{29}NO_5S_2$: C, 58.51; H, 6.47. Found: C, 58.60; H, 6.46.

• *(3R,4S)-4-Isopropyl-1-(p-toluenesulfonyl)-pyrrolidine-3-acetonitrile **35***

A mixture of tosylate **34** (139 mg, 0.308 mmol) and NaCN (75.0 mg, 1.54 mmol) in DMSO (1 mL) was stirred at room temperature for 22.3 h. The reaction mixture was diluted with saturated, aqueous NH_4Cl (25 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The organic extracts were combined and extracted with H_2O (5 × 20 mL), dried (Na_2SO_4) and concentrated to a light brown residue which was purified by radial chromatography (1:4 EtOAc/hexanes) to give 91.0 mg (96.4%) of **35** as clear, colorless oil: R_f 0.42 (1:1 EtOAc/hexanes); $[\alpha]_D$ = + 13.0 (*c* 1.11, benzene).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 2H, J = 8.3), 7.33 (d, 2H, J = 8.0), 3.30–3.40 (m, 2H), 3.03 (dd, 1H, J = 6.1, 10.1), 2.89 (dd, 1H, J = 7.6, 10.0), 2.42 (s, 3H), 2.35 (dd, 2H, J = 6.0, 8.1), 2.21 (m, 1H), 1.70 (m, 1H), 1.56 (hexaplet, 1H, J = 6.7), 0.87 (d, 3H, J = 6.7), 0.79 (d, 3H, J = 6.7).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 143.9 (s), 132.5 (s), 129.8 (d), 127.7 (d), 117.7 (s), 52.5 (t), 50.0 (t), 49.6 (d), 37.6 (d), 29.4 (d), 21.5 (t), 21.1 (q), 20.9 (q), 18.8 (q).

IR (film): ν 2 961, 2 875, 2 247, 1 598, 1 560, 1 091, 1 032, 816, 664 cm^{-1}.

• *(3R,4R)-4-Isopropylpyrrolidine-3-acetic acid* ***36***

A solution of nitrile **35** (39.8 mg, 0.130 mmol) in CH_2Cl_2 (1.0 mL) was added to 48% Hbr in H_2O (5 mL) to form a biphasic mixture (top layer: CH_2Cl_2). This mixture was refluxed for 18 h and TLC analysis of the organic layer showed complete consumption of the starting material. The aqueous phase was separated, washed with CH_2Cl_2, and then stirred with Dowex® 50W-X8, H^+ form, 20–50 mesh ion exchange resin. The resin was placed into a cylindrical column and was eluted with H_2O until neutral (300 mL), followed by 4 M NH_4OH. Isolation and co-evaporation of the appropriate fractions with THF gave 19.0 mg (85%) of **36** as a light yellow powder. $[\alpha]_D$ = 33 (*c* 0.56, H_2O.

^{1}H-NMR (300 MHz, D_2O) δ 3.33 (m, 2H), 2.89 (m, 2H), 2.38 (dd, 1H, J = 4.7, 14.7), 2.28 (m, 1H), 2.06 (dd, 1H, J = 8.7, 14.5), 1.74 (m, 1H), 1.65 (m, 1H), 0.81 (d, 3H, J = 6.6), 0.74 (d, 3H, J = 6.6).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 183.0 (s), 53.3 (t), 51.5 (d), 50.0 (t), 43.1 (t), 40.1 (d), 30.9 (d), 23.4 (q), 20.2 (q).

• *(3R,4R)-Ethyl-4-isopropylpyrrolidine-3-acetate* ***37***

Amino acid **36** (10 mg, 0.058 mmol) was diluted with EtOH (10 mL) and *p*-TsOH·H_2O (5 mg) was added. This mixture was brought to reflux. After 70 h, the reaction mixture was concentrated under reduced pressure. ^{1}H-NMR (D_2O, 300 MHz) analysis of the residue showed unreacted **36**, therefore additional *p*-TsOH·H_2O (100 mg) was introduced and the mixture was brought again to reflux for an additional 48 h. This mixture was concentrated under reduced pressure to a light-brown semi-solid residue that was diluted with EtOAc and washed with saturated $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated to give 5 mg (43%) of **37** as a light brown residue: $[\alpha]_D$ = + 30 (*c* 0.1, H_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.10 (q, 2H, J = 7.2), 3.08 (m, 2H), 2.73 (br s, 1H), 2.61 (m, 2H), 2.44 (dd, 1H, J = 4.4, 14.8), 2.10–2.30 (m, 2H), 1.58 (m, 1H), 1.44 (m, 1H), 1.23 (t, 3H, J = 7.1), 0.92 (d, 3H, J = 6.6), 0.85 (d, 3H, J = 6.6).

• *1(S),5(R),4(R)-7-Benzyl-4-methyl-3-oxa-7-azabicyclo[3.3.0]octan-2-one* ***41*** *and 1(S),5(R),4(S)-7-benzyl-4-methyl-3-oxa-7-azabicyclo[3.3.0]octan-2-one* ***42***

To a −78 °C solution of tricyclic lactam *ent*-**14** (105.8 mg, 0.304 mmol) in THF (5 mL) was added 0.87 mL of a 1.4 M solution of MeLi in Et_2O. The solution became pale yellow and was allowed to stir for 30 min. TLC analysis (EtOAc) showed complete consumption of the starting material. Saturated, aqueous NH_4Cl (2 mL) was added and the mixture was allowed to warm to room temperature. The mixture was partitioned between Et_2O and H_2O and the Et_2O extracts were combined and concentrated to a pale yellow residue of hydroxylactams (*ent*-**16**) which was diluted with 60% EtOH/H_2O (10 mL). Powdered $NaBH_4$ (50 mg, 1.3 mmol, 4.3 equiv) was added and the turbid white suspension was allowed to stir at room temperature for 5.5 h, and then at 50–55 °C for 3 h. To the solution was then added 1 M H_2SO_4 (10 mL) and the acidic mixture was allowed to stir for 1 h at room temperature. The smell of acetophenone was present and the mixture was poured into a mixture of saturated, aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the organic extracts were combined, dried (Na_2SO_4), and concentrated to a pale yellow syrup which was applied onto a silica gel column presaturated with CH_2Cl_2. The column was eluted with CH_2Cl_2 until the emergence of acetophenone, and then Et_2O was used as eluant until the emergence of both lactones (36.2 mg, 51%).

^{1}H-NMR analysis of the mixture indicated a 4.2:1 mixture of diastereomers.

Anal calc for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.49; H, 7.46.

For the major lactone **41** R_f 0.44 (Et_2O); $[\alpha]_D$ = −9.94 (*c* 1.66, CCl_4).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.35 (dq, 1H, J = 4.1, 6.4), 3.58 (ABq, 2H, J = 13.1, $\Delta\nu$ = 50.7), 3.25 (d, 1H, J = 9.5), 3.12 (ddd, 1H, J = 9.3, 7.9, 1.4), 2.79 (d, 1H, J = 9.5), 2.54 (m, 1H), 2.42 (apparent t, 1H, J = 8.5), 2.33 (dd, 1H, J = 6.6, 9.5), 1.36 (d, 3H, J = 6.5).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 179.2 (s), 138.3 (s), 128.4 (d), 128.3 (d), 127.1 (d), 82.7 (d), 59.5 (t), 58.7 (t), 57.2 (t), 45.4 (d), 44.7 (d), 22.2 (q).

IR (film): ν 3 028, 2 970, 2 824, 2 800, 2 360, 1 767, 1 495, 1 477, 1 454 cm^{-1}.

MS (EI, 70 eV) *m/e* (relative intensity): 231 (43, M^+), 216 (6.2), 186 (6.7), 160 (13), 140 (28), 132 (9.9), 91 (100), 65 (27), 42 (40).

For the minor lactone **42**: R_f 0.28 (Et_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.72 (quint, 1H, J = 6.6), 3.58 (ABq, 2H, J = 13.1, $\Delta\nu$ = 62.9), 3.17 (m, 2H), 2.95 (m, 2H), 2.51 (apparent t, 1H, J = 7.9), 2.22 (apparent t, 1H, J = 8.1), 1.33 (d, 3H, J = 6.5).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 179.1 (s), 138.3 (s), 128.4 (d), 128.3 (d), 127.2 (d), 77.6 (d), 59.1 (t), 57.4 (t), 54.1 (t), 45.9 (d), 41.6 (d), 16.7 (q).

MS (EI, 70 eV) *m/e* (relative intensity): 231 (33, M^+), 216 (4.9), 186 (10.2), 158 (6.1), 140 (28), 132 (12), 91 (100), 65 (19), 42 (43).

• *1(S),5(R)-7-(1-(S)-Phenylethyl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one* ***45*** *and 1(R),5(S)-7-(1-(S)-phenylethyl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one* ***46***

Chiral bicyclic succinimide **43** was prepared according to the method of Achiwa [35] in 52% yield. For **43**: R_f 0.44 (Et_2O).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.2–7.6 (m, 10H), 3.62 (d, 1H, J = 9.5), 3.14–3.37 (m, 4H), 2.49 (dd, 1H, J = 7.9, 9.0), 2.29 (dd, 1H, J = 7.7, 9.7), 1.35 (d, 3H, J = 6.5).

To a room temperature of imide **43** (89.6 mg, 0.280 mmol) in 60% EtOH/H_2O (v/v, 10 mL) was added $NaBH_4$ (106 mg, 2.80 mmol). The mixture was allowed to stir for 9.4 h. A 1 M aqueous solution of H_2SO_4 was

added dropwise cautiously (**gas evolution**) until the effervescence subsided. After 3 h of stirring at room temperature, TLC analysis (ET_2O) showed no formation of the expected by-product aniline. The mixture was then heated to reflux for 2 h, cooled to room temperature, and poured into a mixture of saturated, aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated to provide a yellow oil that was purified by radial chromatography (1:1 Et_2O/hexanes). This process yielded 56.7 mg (87.5%) of an inseparable 1.8:1 mixture of bicyclic lactones **45** and **46** as a clear, colorless oil.

For the major lactone **45**: R_f 0.45 (EtOAc).

^{1}H-NMR (300 MHz, $CDCl_3$, selected signals) δ 7.30 (m, 5H), 4.48 (dd, 1H, J = 8.1, 9.0), 4.13 (dd, 1H, J = 3.3, 9.1), 3.23 (q, 1H, J = 6.6), 2.97 (m, 3H), 2.42 (m, 2H), 2.31 (dd, 1H, J = 7.0, 9.5), 1.33 (d, 3H, J = 6.7).

MS (EI, 70 eV) m/e (relative intensity): 216 (62%, M^+-CH_3), 154 (28), 105 (85), 77 (85), 39 (100).

For the minor lactone **46**: R_f 0.45 (EtOAc).

^{1}H-NMR (300 MHz, $CDCl_3$, selected signals) (fig 16b) δ 7.30 (m, 5H), 4.41 (apparent t, 1H, J = 8.9), 3.94 (dd, 1H, J = 4.2, 9.1), 3.45 (d, 1H, J = 9.1), 3.19 (q, 1H, J = 6.4), 2.95 (m, 3H), 2.56 (d, 1H, J = 9.7), 2.20 (dd, 1H, J = 6.5, 9.8), 1.33 (d, 3H, J = 6.7.

MS (EI, 70 eV) m/e (relative intensity): 216 (67%, M+−CH_3), 154 (25), 105 (73), 77 (100).

• *1(S),4(R),5(R)-7-(1-(S)-Phenylethyl)-4-hydroxy-3,7-diazabicyclo[3.3.0]octan-2-one* ***56***

To a −78 °C blue solution of calcium metal (48.6 mg, 1.21 mmol) in liquid ammonia (~15 mL) was added a solution of tricyclic lactam **48** (60.2 mg, 0.173 mmol) in THF (1 mL), followed by a THF (1 mL) rinse. This solution was allowed to stir at −78 °C for 1 h before the addition of solid NH_4Cl (500 mg). The ammonia was allowed to evaporate slowly under a stream of argon overnight. The gray-white residue was triturated with EtOAc and the filtrate was concentrated to give 40.9 mg (96.0%) of hydroxylactam **56** as a white foam: R_f 0.24 (2:3 EtOAc/acetone).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (br s, 1H, D_2O exchange), 7.22 (m, 6H), 5.01 (s, 1H), 3.15 (q, 1H, J = 6.4), 2.95 (m, 2H), 2.72 (apparent (d, 1H, J = 9.2), 2.65 (m, 1H), 2.41 (apparent t, 1H, J = 9.0),2.23 (apparent t, 1H, J = 8.4), 1.31 (d, 3H, J = 6.5).

^{13}C-NMR (75.5 MHz, $CDCl_3$). One accidental degeneracy found in aromatic region: δ 144.2 (s), 128.4 (d), 127.1 (d), 85.0 (d), 64.5 (d), 57.1 (t), 54.8 (t), 46.9 (d), 44.9 (d), 22.6 (q).

IR (film): ν 3 282, 2 967, 2 927, 2 794, 1 694 cm^{-1}.

• *1(R),4(R),5(R)-1-Bromo-3-(2-hydroxy-1-(S)-phenylethyl)-7-(1-(S)-phenylethyl)-3,7-diazabicyclo[3.3.0]octan-2-one* ***58***

To a −78 °C solution of tricyclic bromolactam **55** [11] (56.1 mg, 0.131 mmol) and Et_3SiH (63μL, 0.394 mmol) in $CHCl_2$ (2 mL) was added dropwise a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.39 mL, 0.39 mmol). The resulting brown solution was allowed to warm to room temperature to become a turbid brown stirrable suspension. After 4 h, the reaction mixture was quenched with saturated Na_2EDTA solution and was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to an oil that was purified by radial chromatography (1:4 EtOAc/hexanes) to give 28.7 mg (51%) of **58** as a clear, colorless oil: R_f 0.49 (EtOAc).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.07 (dd, 1H, J = 4.7, 8.6), 4.05–4.30 (m, 2H), 3.77 (dd, 1H, J = 7.8, 10.2), 3.40 (d, 1H, J = 9.8), 3.29 (q, 1H, J = 6.6), 2.90–3.10 (m, 3H), 2.70–2.80 (m, 2H), 2.63 (d, 1H, J = 9.7), 1.31 (d, 3H, J = 6.6).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 172.8 (s), 143.8 (s), 136.2 (s), 128.8 (d), 128.6 (d), 128.0 (d), 127.3 (d), 127.1 (d), 126.8 (d), 64.1 (t), 63.6 (d), 62.5 (t), 60.3 (s), 60.0 (d), 59.1 (t), 50.3 (t), 44.5 (d), 22.4 (q).

IR (film): ν 3 356, 3 063, 3 027, 2 972, 1 687, 1 603, 1 060 cm^{-1}.

• *1(S),5(R)-7-(1-(S)-Phenylethyl)-3,7-diazabicyclo-[3.3.0]octan-2-one* ***59***

To a −78 °C blue solution of calcium metal (70.2 mg, 1.75 mmol) in liquid ammonia (~15 mL) was added a solution of tricyclic lactam **48** (61.5N mg, 0.176 mmol) in THF (2 mL). The mixture was stirred under argon for 1.5 h, quenched with solid NH_4Cl (530 mg, 9.9 mmol) and was allowed to warm slowly with evaporation of solvent under a stream of argon. The residual solids were collected and triturated with EtOAc and the filtrate was concentrated under reduced pressure.

This crude hydroxylactam residue was diluted with TFA (1 mL), and Et_3SiH (54 μL, 0.34 mmol) was added and the solution was left to stir at room temperature for 16 h. The mixture was concentrated and partitioned between saturated, aqueous $NaHCO_3$ and CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to an oily residue, which was purified by column chromatography (EtOAc) to afford 12.6 mg (31%) of **59** as a clear, colorless oil: R_f 0.14 (2:3 EtOAc/acetone).

^{1}H-NMR (300 MHz, $CDCl_3$). One accidental degeneracy found in aromatic region: δ 7.26 (m, 5H), 6.13 (br s, 1H), 3.56 (dd, 1H, J = 8.4, 9.5), 3.21 (q, 1H, J = 6.6), 3.14 (dd, 1H, J = 2.5, 9.6), 2.78–2.95 (m, 3H), 2.65 (dd, 1H, J = 3.4, 9.2), 2.50–2.60 (m, 2H), 1.35 (d, 3H, J = 6.6).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 179.5 (s), 144.7 (s), 128.4 (d), 127.0 (d), 64.5 (d), 59.7 (t), 55.4 (t), 47.4 (t), 44.9 (d), 36.8 (d), 22.9 (q).

IR (film): ν 1 694, 1 540, 1 168, 900 cm^{-1}.

• *1(R),4(R,S),5(S)-7-Benzyl-4-hydroxy-4-methyl-3,7-diazabicyclo[3.3.0]octan-2-one* ***60***

To a −78 °C blue solution of calcium metal (67 mg, 1.67 mmol) in liquid ammonia (15 mL) was added a solution of **14** (87 mg, 0.25 mmol) in THF (2 mL). The mixture was allowed to stir for exactly 1 h and then quenched by the addition of solid NH_4Cl (1 g). The ammonia was allowed to evaporate into a dry-ice/isopropanol cooled receiving flask. The remaining solid residue was triturated thoroughly with EtOAc and the filtrate was concentrated, co-evaporated with CH_2Cl_2, and finally concentrated by high vacuum to afford 59.2 mg (96.1%) of **60** as a white solid: R_f 0.16 (EtOAc); Mp 122–126 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.78 (br s, 1H), 5.66 (br m, 1H), 3.60 (ABq, 2H, J = 12.6, $\Delta\nu$ = 19.9), 3.13 (apparent t, 2H, J = 10), 2.98 (m, 1H), 2.71 (dd, 1H, J = 4.9, 8.8), 2.32 (t, 1H, J = 9.9), 2.15 (dd, 1H, J = 5.0, 9.6), 1.43 (s, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 177.6 (s), 137.2 (s), 128.61 (d), 128.55 (d), 127.5 (d), 86.4 (s), 58.8 (t), 54.9 (t), 54.7 (t), 47.4 (d), 45.7 (d), 27.4 (q).

IR (film): ν 3 187, 2 978, 2 816, 1 702, 1 479, 1 438 cm^{-1}.

• *1(R),4(R),5(R)-7-Benzyl-3-(2-hydroxy-1-(S)-phenylethyl)-4-methyl-3,7-diazabicyclo-[3.3.0]octan-2-one* ***61***

To a −78 °C mixture of tricyclic lactam **14** (21.3 mg, 0.0611 mmol) and Et_3SiH (30 μL, 0.18 mmol) in CH_2Cl_2 (2 mL) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2

(0.2 mL), 0.18 mmol). The resulting brown suspension was immediately allowed to warm to room temperature to give a greenish suspension that was stirred for 14.2 h under argon. The mixture was diluted with saturated, aqueous $NaHCO_3$ and was extracted into CH_2Cl_2. After drying (Na_2SO_4), the organic phase was concentrated and the oily residue was purified by column chromatography. Thus, the column was eluted with EtOAc until the emergence of unreacted **14** (4.7 mg), followed by elution with 1:1 EtOAc/acetone until the emergence of the more polar component. Concentration of the more polar component afforded 4.8 mg (22%) of **61** as a clear, colorless oil: R_f 0.15 (1:1 EtOAc/acetone.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 4.52 (m, 1H), 4.23 (m, 2H), 4.07 (m, 1H), 3.89 (quint, 1H, J = 6.8), 3.56 (ABq, 2H, J = 13.1, $\Delta\nu$ = 60.2), 3.27 (dd, 1H, J = 1.2, 9.1), 3.15 (ddd, 1H, J = 1.5, 7.5, 9.1), 2.84 (m, 2H), 2.47 (dd, 1H, J = 7.5, 9.2), 2.16 (dd, 1H, J = 7.8, 10.3), 0.93 (d, 3H, J = 6.7).

^{13}C-NMR (75.5 MHz), $CDCl_3$) δ 178.2 (s), 138.9 (s), 138.1 (s), 128.44 (d), 128.37 (d), 128.3 (d), 127.3 (d), 127.2 (d), 127.0 (d), 64.8 (t), 62.2 (d), 59.5 (t), 58.6 (d), 57.6 (t), 55.1 (t), 47.2 (d), 38.9 (d), 16.5 (q).

IR (film): ν 3 361, 2 966, 1 659, 1 071 cm^{-1}.

• *1(R),4(R),5(R)-7-Benzyl-4-methyl-3,7-diazabicyclo[3.3.0]octan-2-one* ***62***

To a room temperature of hydroxylactam **60** (28.0 mg, 0.114 mmol) in TFA (1.0 mL) was added neat triethylsilane (54 μL, 0.34 mmol). The pale yellow solution was stirred for 12 h and the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated, aqueous $NaHCO_3$. The organic extracts were dried (Na_2SO_4) and concentrated to an oil that was purified by column chromatography (100:0 to 95:5 EtOAc/MeOH) to afford 19.6 mg (75%) of **62** as a white microcrystalline solid: R_f 0.43 (1:10 Et_3N/CH_3CN); Mp 112–114 °C; $[\alpha]_D$ = 25.4 (c 1.21, benzene).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.82 (br s, 1H), 3.89 (quint, 1H, J = 6.3), 3.56 (ABq, 2H, J = 12.9, $\Delta\nu$ = 57.4), 3.01 (m, 2H), 2.89 (m, 1H), 2.72 (dd, 1H, J = 4.2, 9.9), 2.57 (apparent t, 1H, J = 8.4), 2.29 (dd, 1H, J = 7.5, 9.9), 1.15 (d, 3H, J = 6.9).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 178.6 (s), 138.8 (s), 128.6 (d), 128.2 (d), 127.0 (d), 59.6 (t), 56.8 (t), 54.6 (t), 50.4 (d), 46.6 (d), 40.9 (d), 17.2 (q).

IR (film): ν 3 218, 2 963, 1 693 cm^{-1}.

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