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Chiral bicyclic lactams: useful precursors and templates for asymmetric syntheses[1]

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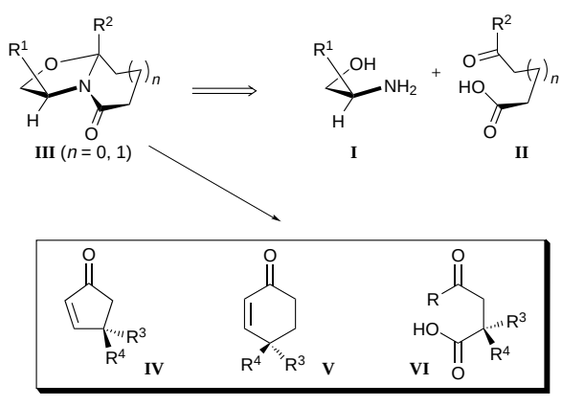
A survey of the utilitarian bicyclic lactams is presented. These chiral templates have provided, and continue to provide, access to a plethora of natural and unnatural carbocyclic products in high enantiomeric purity. Their synthetic versatility has recently grown with the development of new methods for the construction of heterocycles. In addition to the cyclopentenone, cyclohexenone and hexahydroindenone systems, products derived from bicyclic lactams now include optically active piperidines, pyrrolidines, pyrrolidinones and tetrahydroisoquinolines. These favourable properties make the bicyclic lactams highly adaptable tools for asymmetric synthesis.

Some recent progress achieved through the use of chiral, nonracemic bicyclic lactams **III** (n = 0,1) has demonstrated that they are extremely useful and versatile building blocks for the preparation of a host of enantiomerically enriched, natural and unnatural products.[2] The preparation of these templates from their corresponding enantiomerically pure amino alcohols **III**, and their earlier utility in the synthesis of compounds containing quaternary stereocentres such as cyclopentenones **IV**, cyclohexenones **V** and carboxylic acids **VI**, has been previously reviewed (Scheme 1).[2a,d]

The synthesis of enantiopure carbocycles, which until recently was the major focus of our program, continues to serve as a vital goal for the development of new synthetic methods *via* bicyclic lactams. Examples of these included in the present discussion will describe enantiopure hexahydroindenones, benzindenones and cyclohexenones containing contiguous stereogenic centres (Scheme 2). The discovery that nitrogen-containing heterocycles could also be efficiently generated from these chiral lactams stimulated recent studies directed toward the syntheses of optically active pyrrolidine and piperidine derivatives. Thus, the reader will find that a large portion of this brief outline has been dedicated to the development and application of methods for the syntheses of enantiopure heterocyclic compounds from 5,5- and 5,6-bicyclic lactams (*vide infra*).



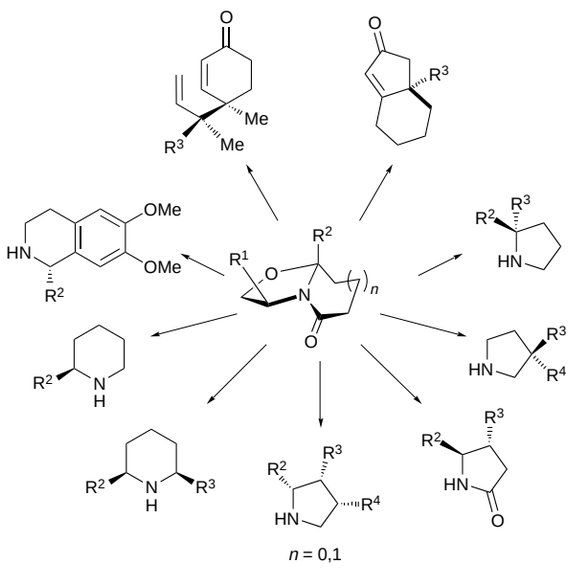
Scheme 1

Recent syntheses of chiral non-racemic carbocycles

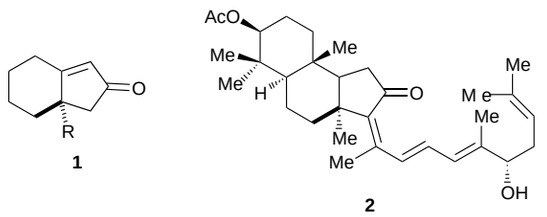
Hexahydroinden-2-ones and benz[e]inden-2-ones

The hexahydroindenone ring system **1**, present in a number of naturally occurring compounds (*e.g.* Stelliferin A **2**[3]) was identified as a viable target for the bicyclic lactams. Since the preparation of enantiopure 3,3-disubstituted cyclopentenones *via* the bicyclic lactam had already been accomplished,[2a,c,h] modifications to access this ring system were investigated (Scheme 3).[4] The requisite bicyclic lactam **3**, which could undergo intramolecular cyclization affording the intermediate alcohol **4**, would serve as a key precursor. After hydrolysis and condensation to **5**, this should provide the desired tetrahydroindenone **1**.

The bromo lactam **8** was prepared *via* a two step process shown in Scheme 4. Thus, alkylation of bicyclic lactam **6** with butenyl bromide, followed by a second *endo* alkylation with an appropriate electrophile, afforded good yields of dialkylated product **7**.[2a,4] The latter was converted to the bromide **8** *via* hydroboration–oxidation followed by bromination in good overall yields. Metal–halogen exchange yielded the alcohol **4** *via* the organolithium **3** (Scheme 3). Hydrolysis to the diketone **5**, followed by base-catalysed condensation, produced optically



Scheme 2



pure hexahydroindenones **1** in modest overall yields. Similarly, alkylation of **6** with the appropriate aryl bromides furnished lactams **9**, and the D ring of the Stelliferin class was accessed in a single step providing the benzindenones **10**. Because epimerization of the quaternary centres was not possible, diastereomerically pure lactams **8** and **9** provided enantiomerically pure products. Further elaboration of **10** should yield Stelliferin A **2**.

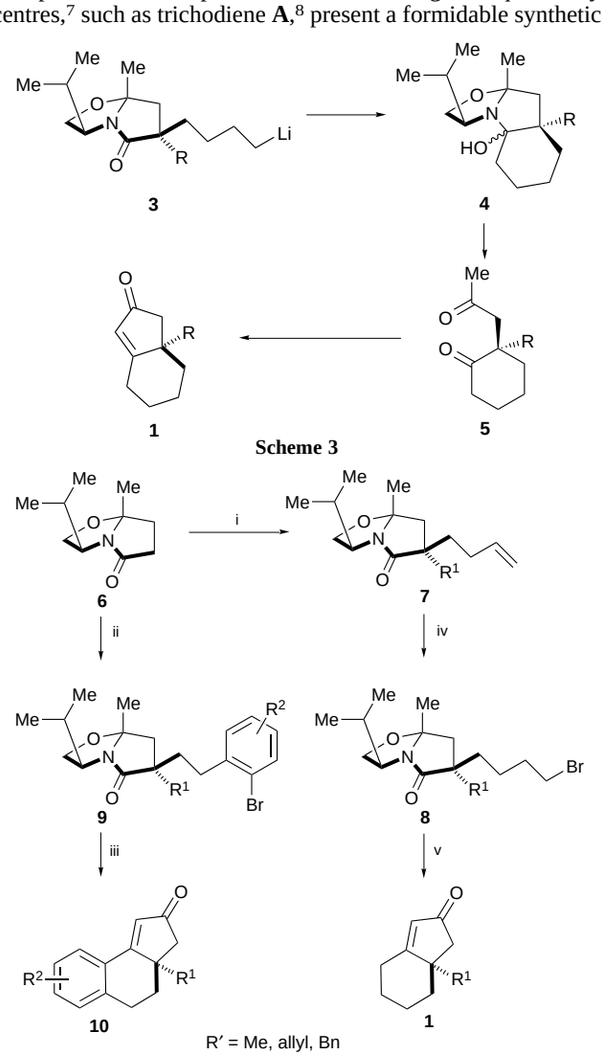
Application of hexahydroindenones to the magellanine framework

The above sequence leading to the hexahydroindenones has recently been applied to the construction of the Magellanine ring system **11** (Scheme 5).[5] The pivotal compound was the hexahydroindenone **1** (R = CH_2Py), which was obtained optically pure by hydrolysis–cyclization of diastereomerically pure lactam **7** (R = CH_2Py). Indenone **1** was cyclized *via* an intramolecular 1,4-addition of its enolate to the *N*-acylpyridinium salt and, after reoxidation, gave **12**. Successive stereoselective reductions provided the Magellanine framework **13**, whose structure was confirmed by single crystal X-ray analysis. The synthesis provided (−)-**13** in 13 steps from bicyclic lactam **6**, from which all of its six stereocentres had been derived.

4,4-Disubstituted cyclohexenones with vicinal stereocentres[6]

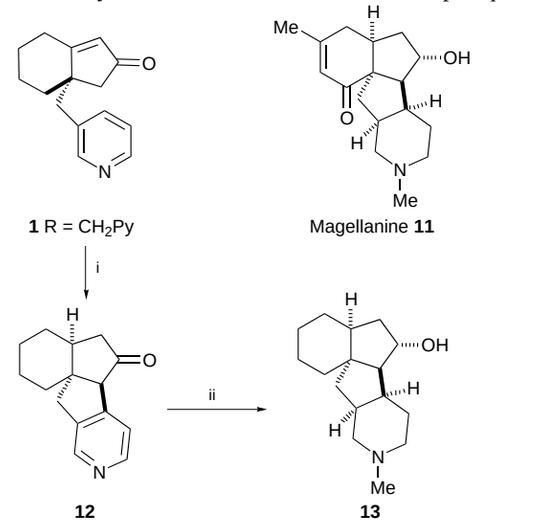
Compounds which possess vicinal stereogenic quaternary centres,[7] such as trichodiene **A**,[8] present a formidable synthetic challenge. Since one might imagine that this compound could be derived from the cyclohexenone **B**, it was envisioned that a bicyclic lactam might serve as a template for its synthesis (Scheme 6). Employment of the 5,6-bicyclic lactam, previously utilized in the synthesis of a number of optically active 4,4-disubstituted cyclohexenones,[2a,e] was feasible only if the properly substituted precursor **C** was available. Since the quaternary stereocentres could not be prepared through the usual dialkylation sequences, it was necessary to seek other means of installing these substituents with the correct stereochemistry. Undoubtedly, some form of the Claisen rearrangement (*e.g.* **D** → **C**) could produce the desired result. Unfortunately, lactam **14** could not, after numerous attempts, be directly *O*-alkylated to afford the Claisen precursor **16** (X = O) (Scheme 7). However, it was soon found that thiolactam **15**, obtained by treatment of **14** with Belleau's reagent,[9] underwent *S*-alkylation quite readily. Formation of the thioenolate with base, followed by addition of the appropriate allylic halides, produced the thioethers **16** (X = S) in good yields. The desired thio-Claisen rearrangement was smoothly implemented *via* thermal conditions to provide the rearranged thiolactams **17**.[10] The facial selectivity of the (3,3)-rearrangement was generally quite high, and the configuration of the new stereocentre was found to result from rearrangement on the *exo* face of the lactam. This is contrary to the *endo* selectivity normally observed during enolate alkylations of other 5,5- and 5,6-bicyclic lactams, however, this appears to be consistent with similar results obtained with these lactams of the type **14**.[2a,j] The subtle factors responsible for *exo* or *endo* selectivity with these lactams are still a matter of continuing investigation.†

The α,α-dialkylated thiolactams **17** were successfully transformed to the cyclohexenones **20** *via* the three step sequence

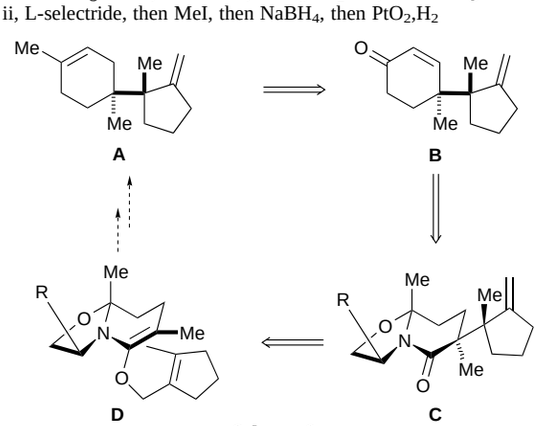


Scheme 3

Scheme 4 *Reagents*: i, LDA, butenyl bromide, then LDA, R^1X; ii, LDA, $Ar(CH_2)_2Br$, then LDA, R^1X; iii, Bu^tLi, then $Bu_4NH_2PO_4$, then NaOEt; iv, BH_3, H_2O_2, then NBS, PPh_3; v, Bu^tLi,$Bu_4NH_2PO_4$, KOH



Scheme 5 *Reagents*: i, PhOCOCl, $TiCl_4$, Pr^i_2NEt, then DDQ, then Pd–C, H_2; ii, L-selectride, then MeI, then $NaBH_4$, then PtO_2,H_2

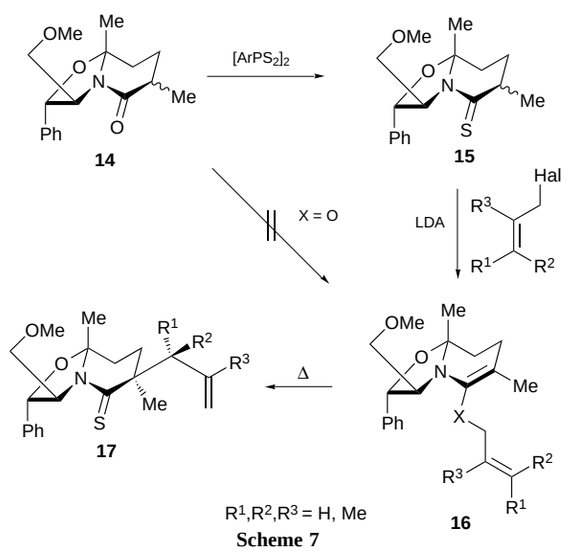


Scheme 6

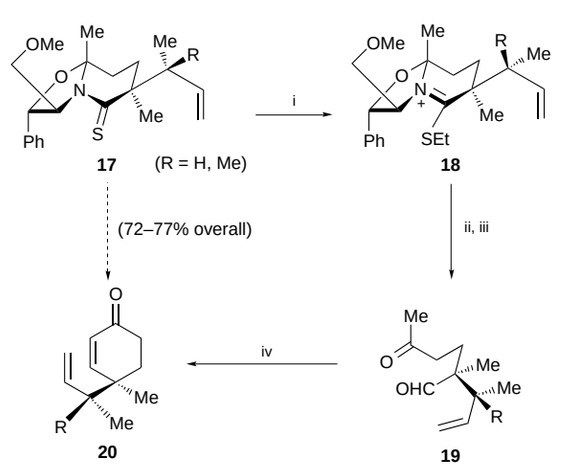
shown in Scheme 8. Generation of the thioiminium salts **18**, followed by reduction and hydrolysis, afforded the keto aldehydes **19** which were directly subjected to aldol cyclization to yield the optically pure ketone **20**, possessing vicinal quaternary centres in good overall yields.

Syntheses of chiral non-racemic heterocycles

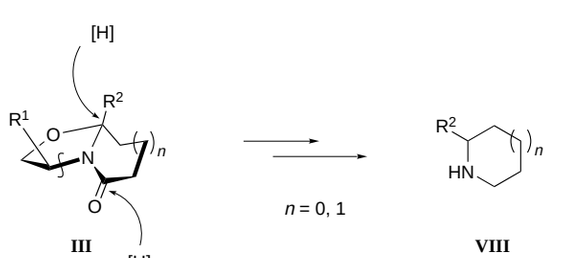
These highly useful[11a–c] substances should be readily obtained if the nitrogen atom present in the chiral auxiliary could be preserved in the final products **VIII** (Scheme 9). This was accomplished by simultaneous reduction of both the carbonyl and aminal centres in the lactams **III**, and was realized for both the 5,5- and 5,6-bicyclic systems. In this manner, enantiomerically pure pyrrolidines and piperidines **VIII** (n = 0,1) were prepared (*vide infra*).



Scheme 7



Scheme 8 *Reagents*: i, Et_3OBF_4; ii, Red-Al; iii, H_3O^+; iv, KOH, MeOH



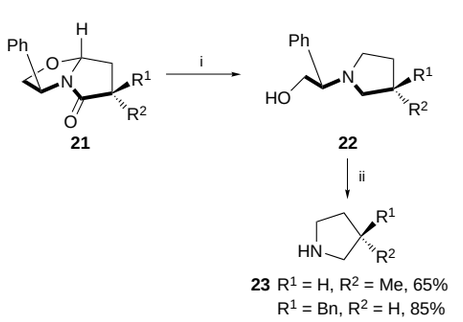
Scheme 9

Chiral pyrrolidines and pyrrolidinones

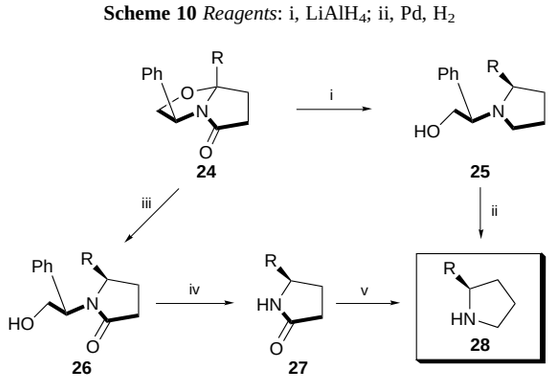
(i) *3-Substituted and 3,3-disubstituted pyrrolidines.* It was found that a number of angular hydrogen, dialkylated bicyclic lactams **21**,[2a] the utility of which had previously been demonstrated in the syntheses of chiral 5,5-disubstituted cyclopentenones,[2c] were simply and efficiently manipulated to provide enantiomerically pure 3,3-disubstituted pyrrolidines **23** (Scheme 10).[12] Specifically, the latter were obtained by reduction of lactams **21** with lithium aluminium hydride, followed by hydrogenolysis of the chiral auxiliary. It was noteworthy that monoalkylated lactams **21** (R^1 or R^2 = H) were also reduced, with no evidence of epimerization α to the lactam carbonyl group, to provide 3-substituted pyrrolidines **23** (R^1 or R^2 = H), in high optical purity.

(ii) *2-Substituted pyrrolidines and 5-substituted pyrrolidinones.* The angularly substituted, 5,5-bicyclic lactams **24** could be efficiently converted to 2-substituted pyrrolidines **28** and/or 5-substituted pyrrolidinones **27** by either of two short synthetic sequences (Scheme 11). Thus, treatment of lactam **24** directly with alane, or lithium aluminium hydride, reduced both the carbonyl and aminal centres to the pyrrolidines **25**, as single diastereomers. Hydrogenolysis of the nitrogen benzyl linkage then led to the free 2-substituted pyrrolidines **28** in good overall yields with greater than 98% enantiomeric purity.[11a] The utility of this sequence was recently demonstrated in the total asymmetric syntheses of the natural antibiotics (−)-irniine [R = $(CH_2)_9$Ph] and (−)-bgugaine [R = $(CH_2)_{13}$Me] by Jossang and co-workers.[13]

Alternatively, reduction of **24** by addition of triethylsilane and titanium tetrachloride to pyrrolidinone **26** (Scheme 11), followed by removal of the chiral auxiliary under dissolving metal conditions, provided the corresponding 5-substituted pyrrolidinones **27**, once again in high enantiomeric purity.[11a,14a,b] The pyrrolidinones, if desired, could be further reduced to the 2-substituted pyrrolidines **28**.[14c] Interestingly, both routes yielded pyrrolidines with the same absolute stereochemistry, namely, retention of configuration at the angular position in the lactams **21**.



Scheme 10 *Reagents*: i, $LiAlH_4$; ii, Pd, H_2



Scheme 11 *Reagents*: i, 'AlH_3'; ii, Pd, H_2; iii, Et_3SiH, $TiCl_4$; iv, Li^0–NH_3; v, $LiAlH_4$

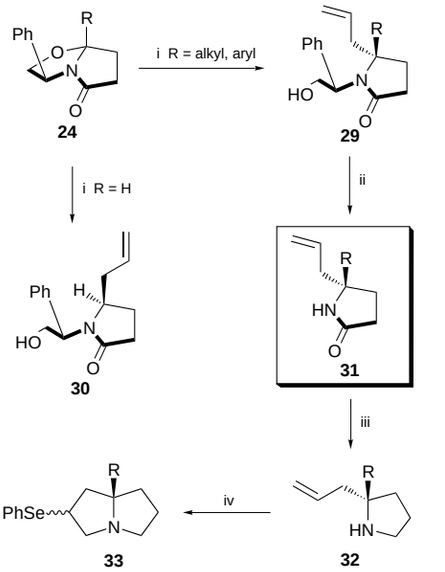
Although this stereochemical result was predictable for the alane reductions, having been previously observed in acetal cleavages,[15] it was surprising for the triethylsilane–titanium(iv) chloride system. Previous studies suggested that this reduction should have occurred in an S_N2 fashion to provide products with inversion of stereochemistry.[15] Fortunately, allylsilane additions to both angular hydrogen and angularly substituted bicyclic lactams **24** (Scheme 12) furnished some insight into the mechanism for these reductions (*vide infra*).

(iii) *2,2-Disubstituted pyrrolidines and 5,5-disubstituted pyrrolidinones.* In addition to hydride reductions, it was found that allylsilanes, under strong Lewis acidic conditions, could also be induced to add at the angular position of 5,5-bicyclic lactams **24** to furnish the disubstituted pyrrolidinones **29** and **30** (Scheme 12).[16] As seen for the hydride reductions, when R was either an alkyl or aryl substituent, the addition arose from *endo* entry to the lactam forming products with retention of configuration at the former angular position. Conversely, when the angular substituent was hydrogen, the observed stereochemistry was that from *exo* attack, or inversion of configuration. The chiral auxiliary in **29** may be cleaved under dissolving metal conditions to afford the 5,5-disubstituted pyrrolidinones **31** in good yield and with high enantiomeric excess. Again, if desired, pyrrolidinones **31** may be further reduced to pyrrolidines **32**. As an example of the utility of the newly installed allyl group, cyclization of pyrrolidines **32** was performed affording the backbone of the pyrrolizidine alkaloids **33**,[16b] an important class of natural products due to their potent biological activity.

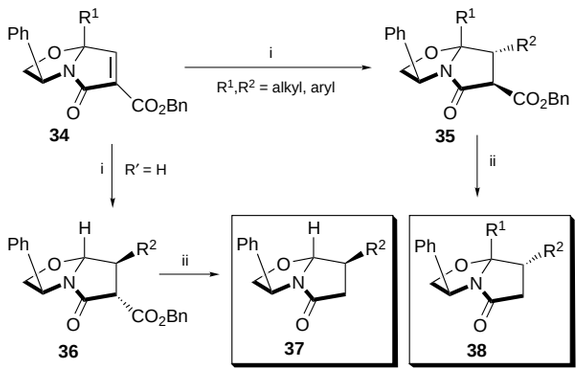
(iv) *Reactions with unsaturated 5,5-bicyclic lactams*. One of the most useful lactam substrates to date has been the unsaturated system **34** (Scheme 13)[2,17] The alkenic moiety has provided a functional handle on which a host of transformations have been carried out, including conjugate additions by various nucleophiles, pericyclic reactions,[2] and oxidations (*vide infra*). These transformations have proved invaluable in placing substituents in the 3- and 4-positions of both pyrrolidines and pyrrolidinones.

(v) *2,3*-trans-*Disubstituted pyrrolidines and 4-substituted and 4,5-disubstituted pyrrolidinones.* Lower order lithiocyanocuprates were found to efficiently add in a 1,4 fashion to activated unsaturated bicyclic lactams **34** producing **35** and **36** in good yields and high diastereoselectivities (Scheme 13).[18a,b] When the angular substituent in **34** was alkyl or aryl, addition proceeded mainly from the *endo* (α) face of the lactam, whereas the angular hydrogen lactams led to products resulting from *exo* (β) addition (**36**). This duality in the stereochemical outcome had been previously observed in cycloadditions to these unsaturated lactams,[2] and is believed to be primarily due to the steric effects created by the angular substituents. The benzyloxycarbonyl group (R^2 = CO_2Bn), which was found to be necessary for the cuprate additions, was efficiently removed *via* hydrogenolysis and decarboxylation. The resulting lactams **37** and **38** were subsequently converted to the corresponding pyrrolidines **39** and **41** respectively, or pyrrolidinones **40**, by one of the following sequences (Scheme 14).

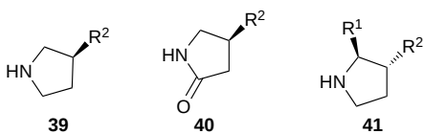
(vi) *2-Alkyl-3-amino- and 3,4-aziridino-pyrrolidines.* The 3-aminopyrrolidine **48** and 3,4-aziridinopyrrolidine **47** moieties are present in a diverse array of biologically active molecules,[19] and it was believed that these systems could be accessed *via* the unsaturated bicyclic lactam templates. It was observed that a series of primary and secondary amines efficiently added to the β-position of unsaturated lactams **42** to give the amino lactams **44** (Scheme 15).[19a] As previously seen with the cuprate additions, lactams bearing angular substituents (R = alkyl, aryl) led to products resulting from *endo* attack. The groups on the amine could be either chiral or achiral with no effect on the stereoselectivity. Surprisingly, the reaction was found to be irreversible. Thus, if the amino lactam adduct **44** was treated with base, generating the enolate, expulsion of the amine was



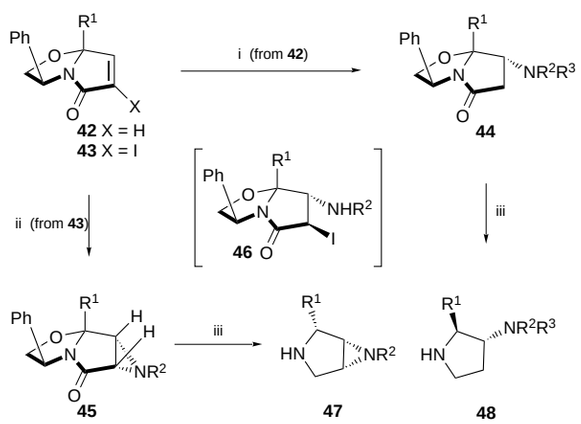
Scheme 12 *Reagents*: i, (allyl)$SiMe_3$, $TiCl_4$; ii, Li^0–NH_3; iii, 'AlH_3'; iv, PhSeSePh



Scheme 13 *Reagents*: i, $R^2{}_2CuLiCN$; ii, Pd, H_2



Scheme 14 *Reagents*: i, 'AlH_3', then Pd, H_2; ii, Et_3SiH, $TiCl_4$, then Li^0–NH_3



Scheme 15 *Reagents*: i, R^2R^3NH; ii, R^2NH_2; iii, 'AlH_3', then Pd, H_2

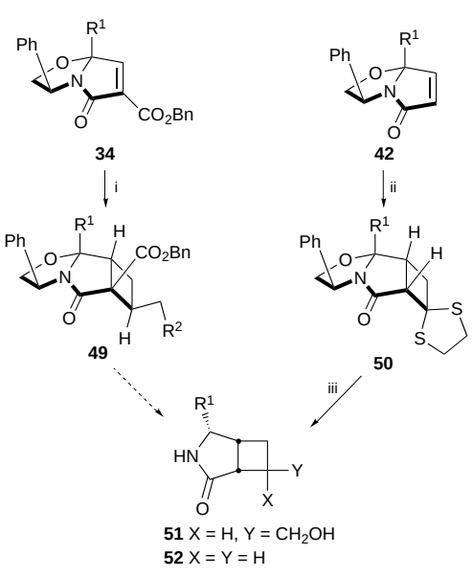
not observed, yet the enolate could be alkylated with an electrophile. This behaviour allowed for further elaboration of the pyrrolidine products (*vide infra*). However, by incorporating an α-halogeno substituent on the unsaturated lactam **43**,[17a] such as iodine, additions of primary amines efficiently led to aziridino products **45**, resulting from nucleophilic displacement of the halide *via* adduct **46**.[19b]

Both the amino and aziridino lactams were transformed to *trans*-2-alkyl-3-aminopyrrolidines **48** and *cis*-2-alkyl-3,4-aziridinopyrrolidines **47**, respectively, by the procedure identical to that used for the preparation of the other chiral pyrrolidine systems (*vide supra*).

(vii) *5-Alkyl-3,4-cyclobutanopyrrolidinones.* Organocuprate reagents and amines were not the only nucleophiles found to efficiently add to the unsaturated bicyclic lactams in a Michael fashion. During continuing studies to develop a diverse array of optically active pyrrolidines, the annulations of 2-methylenedithiolanes and allylsilanes with chiral bicyclic lactams were also investigated (Scheme 16).[20]

2-Methylenedithiolane, in the presence of dimethylaluminium chloride, added to unsaturated lactams **42** affording cyclobutanes **50** in high yields and as single diastereomers after chromatography.[20a] Although the removal of the thioketal to give the cyclobutanone derivatives failed, the dithioacetal could be reduced to the cyclobutane fused lactam, which was readily converted to the pyrrolidinones **52** *via* standard auxiliary removal procedures (*vide supra*). This Lewis acid-mediated annulation is complementary to the earlier photochemical additions of ethylene,[2a] and furthermore, these chiral cyclobutanopyrrolidinones **52** are potentially useful constrained GABA analogues.

Additions of allylsilanes to the unsaturated ester lactams **34** unexpectedly led to cyclobutane adducts **49** (Scheme 16).[20b] This was surprising in view of earlier reports of allylsilane annulations leading only to cyclopentanes. In fact, the silacyclobutane fused lactams **49** were among the first confirmed examples of this reaction manifold, which until recently was seriously questioned.[21] Although the cyclobutanes derived from triisopropylallylsilane (R^2 = Pr^i_3Si) are resistant to further chemical manipulation, the trityldimethylsilacyclobutanes (R^2 = Ph_3CMe_2Si) should allow ready substitution of the silicon moiety by a hydroxy substituent[22] to access chiral hydroxycyclobutanes of type **51**. Studies are currently in progress to evaluate these systems.

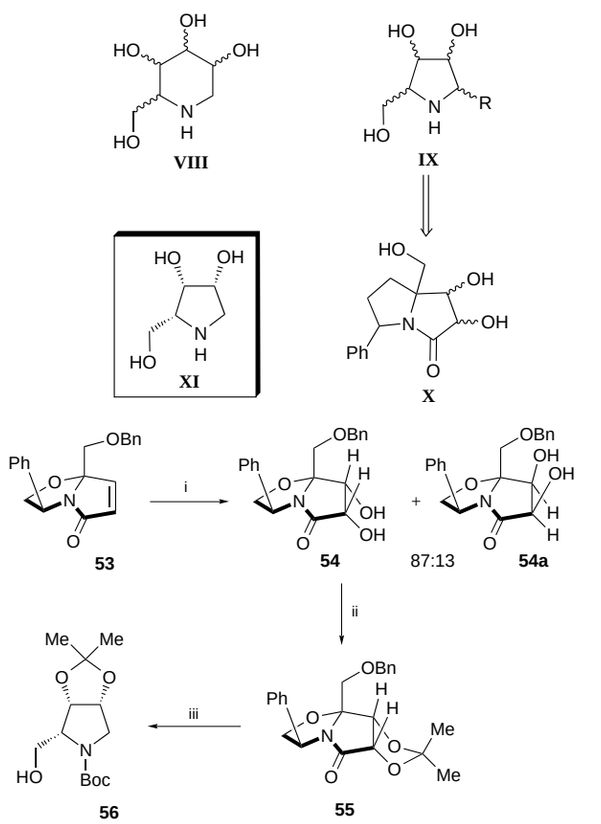


Scheme 16 *Reagents*: i, (allyl)R^2 (R^2 = $SiPr^i_3$, $SiMe_2CPh_3$), $TiCl_4$; ii, 2-methylenedithiolane, Me_2AlCl, iii, Raney Ni, then Et_3SiH, $TiCl_4$, then Li^0–NH_3

(viii) *Chiral azasugars.* Azasugars **VIII** and **IX** are representative of a general class of compounds that have been reported to exhibit many biological properties including antitumour and anti-HIV activity. As a result, a great deal of interest has recently been generated in developing methods for their efficient syntheses.[23]

In view of this, 1,4-dideoxy-1,4-imino-d-lyxitol **XI** was selected as a target. In order to establish the correct absolute and relative stereochemistry of the hydroxymethyl and hydroxy substituents, the appropriate unsaturated lactam **53** was prepared (Scheme 17). The key step required installation of the *vic*-hydroxy groups in a *syn* fashion to the *endo* face of the lactam. This *cis* dihydroxylation was indeed accomplished, using *N*-methylmorpholine *N*-oxide (NMO) as an oxidant with a catalytic amount of osmium tetroxide, furnishing an 87 : 13 mixture of diastereomers **54** and **54a**. The major product **54**, predicted to be *endo* based on previous additions to unsaturated lactams, was readily separated from its *exo* epimer **54a** providing diastereomerically pure material. After protection of the diol as the acetonide **55**, the key reduction step was addressed. The reduction at the aminal centre required that inversion of configuration take place, in a stereoselective manner, to afford the correct stereochemistry of the hydroxymethyl substituent in **56**. Inversion at the angular position during reductions had been previously observed in the syntheses of cyclobutanes **51** and aziridines **47** (*vide supra*). It was anticipated that the cyclic acetonide **55** would serve as a blocking group and force reduction from the β-face. This was indeed the case, as reduction of **55** with 9-BBN produced, after hydrogenolysis of the auxiliary and protection of the nitrogen, the all-*cis* pyrrolidine **56** as a single diastereomer. Thus **56**, simply a protected version of **XI**, was prepared in a total of eight steps in 12% overall yield in high enantiomeric purity.

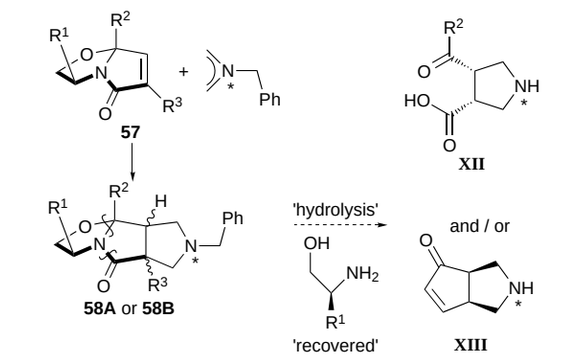
(ix) *3,4*-cis-*Disubstituted pyrrolidines.* It was anticipated that by fusing a pyrrolidine ring to the bicyclic lactam, *via* some type



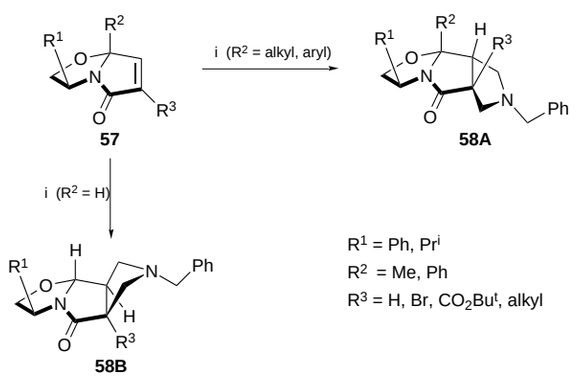
Scheme 17 *Reagents*: i, OsO_4, NMO; ii, 2,2-dimethoxypropane, iii, 9-BBN, then Pd, H_2, Boc_2O

of [3 + 2] cycloaddition process, recovery of the amino alcohol auxiliary would be possible while still maintaining a nitrogen heteratom in the product. Thus, hydrolysis of the lactam adducts **58**, as previously demonstrated in earlier examples,[2a] would lead to the keto acids **XII** or cyclopentenones **XIII** (Scheme 18). In this manner, the requisite pyrrolidine ring would be in hand, and the amino alcohol auxiliary would not have to be sacrificed.

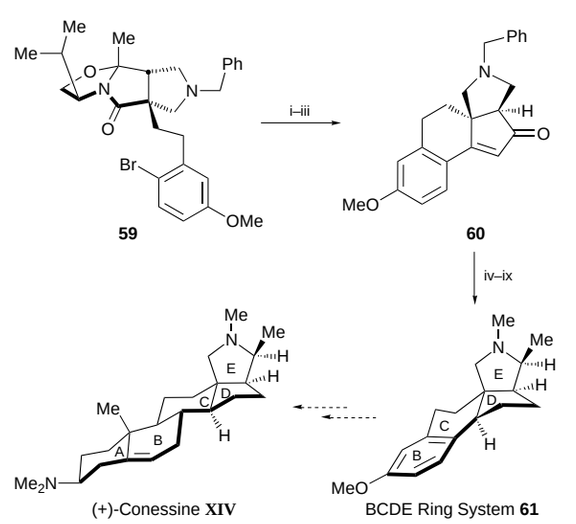
To this end, a study of the cycloaddition of azomethine ylides to chiral unsaturated bicyclic lactams was undertaken.[24] The ylides[25] led to high yields of cycloadducts **58A** and **58B** after addition to a variety of substituted bicyclic lactams **57** (Scheme 19). Once again, the angular substituent R^2 was the primary factor in determining *endo* or *exo* selectivity.



Scheme 18

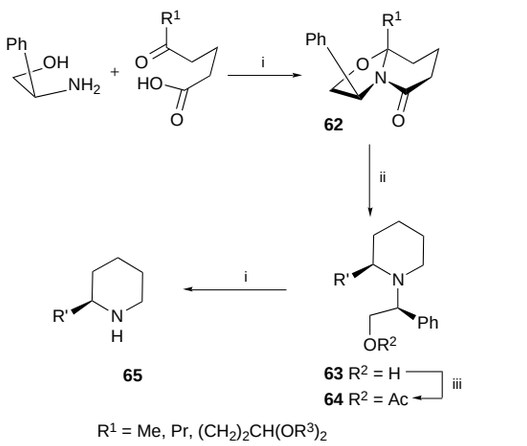


Scheme 19 *Reagents*: i, $(Me_3SiCH_2)(MeOCH_2)(Bn)N$, TFA

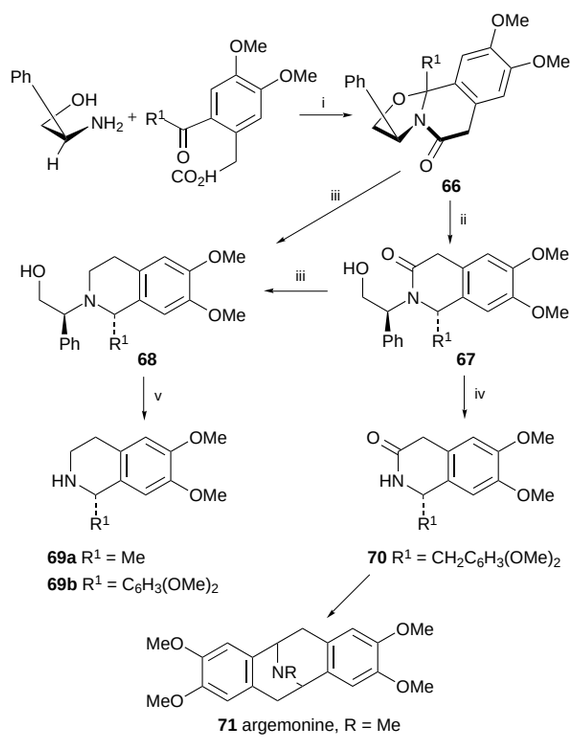


Scheme 20 *Reagents*: i, Bu^tLi; ii, $Bu_4NH_2PO_4$; iii, NaOEt; iv, 'AlH_3'; v, PhOCOCl; vi, Bu^tOK; vii, Pd, H_2; viii,Bu^sLi, MeI; ix, $LiAlH_4$

(x) *Asymmetric synthesis of conanine BCDE ring system.* (+)-Conessine **XIV**, a known amebicide, is just one in a family of alkaloids isolated from *Holarrhena antidysenterica*.[26] Common to each alkaloid in this family is the Conanine BCDE framework **61**, which contains a 3,4-disubstituted pyrrolidine subunit. A successful asymmetric synthesis of this structure would aptly demonstrate the versatility and utility of the chiral lactam template in pyrrolidine syntheses (Scheme 20).[27] The key step in implementing this sequence was the formation of cycloadduct **59**, containing the necessary bromoaryl side chain and the newly installed pyrrolidine E ring. The latter came directly from an azomethine cycloaddition to the appropriately functionalized unsaturated lactam **57** [$R^2 = (CH_2)_2Ar$].[18b] Other key steps in the synthesis involved construction of the BCD rings. This was accomplished *via* a method previously demonstrated for the preparation of the benz[*e*]inden-2-one ring system.[3] Metal–halogen exchange of aryl bromide **59**, followed by spontaneous cyclization, hydrolysis and aldol condensation, provided the requisite benzindenone **60** in high yield and in enantiomerically pure form. Reduction of the carbonyl group,



Scheme 21 *Reagents*; i, heat; ii, Red-Al, heat; iii, Ac_2O; iv, $Pd(OH)_2$, H_2



Scheme 22 *Reagents*: i, heat; ii, Red-Al; iii, $LiAlH_4$; iv, Na^0–NH_3; v, Pd, H_2

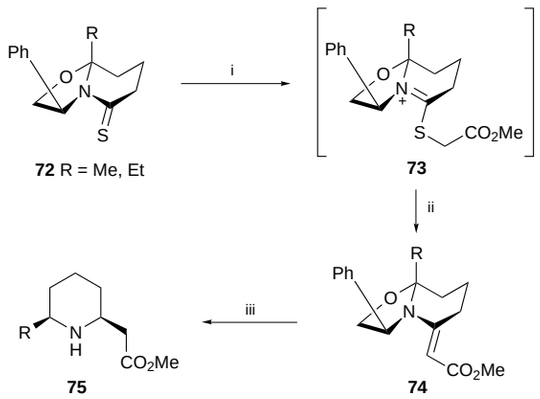
selective hydrogenation of the unsaturated C–D ring fusion and stereoselective alkylation of the pyrrolidine E ring resulted in the first asymmetric synthesis of the conanine BCDE framework **61**, in optically pure form and in 8% overall yield from **57**. Further elaboration of this framework to (±)–conessine **XIV** has previously been demonstrated.[26]

Piperidines and tetrahydroisoquinolines

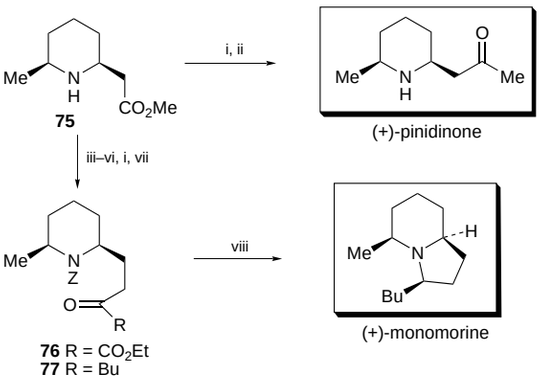
(i) *2-Substituted piperidines.* The presence of the piperidine ring system in a host of naturally occurring and biologically active alkaloids has generated considerable interest in the development of new methods for the preparation of these compounds in optically pure form.[11b,c,28a] Due to the success in the preparation of a number of enantiomerically pure pyrrolidines from 5,5-bicyclic lactams **III** (n = 0), it was felt that similar techniques could be applied to the related 5,6-bicyclic lactam.

Red-Al reduction of a number of angular alkyl 5,6-bicyclic lactams **62**, derived from δ-keto acids as shown, furnished the piperidine derivatives **63** in good yields and with high diastereomeric excess (Scheme 21).[28b] Retention of configuration of the angular substituent in **62** was again maintained in the major piperidine products **63**. In all cases, the diastereomers, once converted to the acetates **64**, could be purified to provide, after hydrogenolysis of the chiral axuiliary, the enantiopure 2-substituted piperidines **65** in only two steps from the bicyclic lactam **62**. The efficient and versatile nature of this piperidine synthesis was featured in the total synthesis of natural (−)-pipecoline **65** (R^1 = Me), (+)-coniine **65** (R^1 = Pr), and the 1-azabicyclic system, (−)-coniceine.[28b,c]

(ii) *1-Substituted tetrahydroisoquinolines.* Owing to the successful preparation of 2-substituted piperidines from simple angular alkyl 5,6-bicyclic lactams **62**, it was proposed that 1-substituted tetrahydroisoquinolines **69** could also be obtained from an appropriately functionalized 5,6-bicyclic lactam (Scheme 22). Although there are a number of routes to the 1-alkylisoquinolines, there are relatively few which install 1-aryl substituents.



Scheme 23 *Reagents*: i, $BrCH_2CO_2Me$; ii, $P(OMe)_3$, Et_3N, heat; iii, $Pd(OH)_2$, H_2



Scheme 24 *Reagents*: i, MeNHOMe·HCl, $AlMe_3$; ii, MeMgBr; iii, 2Cl; iv, OH^-; v, $(COCl)_2$; vi, CH_2N_2, AgO; vii, BuMgBr; viii, Pd, H_2

The requisite 5,6-bicyclic lactam **66** was simply prepared from the corresponding 2-acylphenylacetic acid and (*S*)-phenylglycinol, and the previously utilized reduction sequence for the piperidines was employed. Thus, reduction of **66** with $LiAlH_4$ to the tetrahydroisoquinoline derivatives **68** occurred with high diastereomeric excesses (Scheme 22). Again, the major products (> 95% de) were those with retention of configuration at the angular position of **66**. After purification of the diastereomers by chromatography, hydrogenolysis of the chiral auxiliary provided the tetrahydroisoquinolines **69** in optically pure form.[29a,c] The efficiency of this process was aptly demonstrated in the syntheses of both 1-alkyl- and 1-aryl-tetrahydroisoquinolines, (−)-salsolidine **69a** and (+)-cryptostyline II **69b**, respectively.

Treatment of bicyclic lactam **66** [$R^1 = CH_2C_6H_3(OMe)_2$] with Red-Al reduced only the aminal carbon to produce lactam **67** (Scheme 22). Removal of the chiral auxiliary under dissolving metal conditions afforded the free lactam **70** which was further elaborated, *via* reduction and cyclization, to enantiomerically pure (−)-argemonine.[29b]

(iii) *2,6-Disubstituted piperidines.* The presence of biologically active piperidines **71**, containing substitution at both the 2- and 6-positions, has prompted a number of laboratories to pursue new and efficient methods to access these systems in enantiomerically pure form.[11b,c]

If the thiolactam **72** could be induced to undergo an Eschenmoser contraction,[30] a means of transforming the carbonyl group to a carbon–carbon linkage, a useful intermediate for further elaboration might be in hand. In this regard, addition of methyl α-bromoacetate to thiolactams **72**, prepared from oxolactam **62** *via* the Belleau reagent,[9] afforded the intermediate thioiminium salts **73** which, on treatment with triethylamine and trimethyl phosphite, gave the vinylogous urethanes **74** in high yield (Scheme 23). Hydrogenation of **74** with concomitant reduction of the aminal carbon, the C=C, and the benzylic carbon was achieved in a single step using palladium hydroxide to afford the *cis*-2,6-disubstituted piperidines **75** as single enantiomers. The reducible centres were attacked from the *endo* face of the lactam to provide only the *cis* isomers, with net retention of configuration at the former aminal centre. It was also shown that the unsaturated linkage is reduced prior to the aminal linkage.

The synthetic value of piperidines **75** (Scheme 24) was clearly demonstrated in the efficient syntheses of two alkaloids, (+)-pinidinone and the ant trail pheromone (+)-monomorine.[11c,31]

Conclusions

Bicyclic lactams **III** (n = 0,1) have, once again, proven themselves to be extremely versatile in preparing a host of optically active products (*vide supra*). Their utility is perhaps best exhibited by the shear diversity of compounds (*e.g.* Schemes 1 and 2) that may be accessed through this single set of chiral templates. The ready availability of these building blocks,‡ and their inherent ability to provide a variety of enantiomerically pure carbocycles and heterocycles, makes these bicyclic lactams both an important and general tool for asymmetric synthesis.

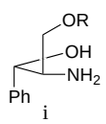
Professor Meyers is a native of New York City and was educated at New York University where he received his Bachelors (1954) and PhD (1957) degrees. He was an NIH Special Fellow at Harvard University with Professor E. J. Corey and joined the faculty of Louisiana State University (New Orleans) where he rose to the rank of Boyd Professor. He was Professor of Chemistry at Wayne State University before joining Colorado State University in 1972. His research interests are new

synthetic methods, asymmetric synthesis, heterocycles and total synthesis of natural products. He has been the recipient of the ACS Award in Creativity in Organic Synthesis (1985), an Arthur C. Cope Scholar (1987), and elected to the National Academy of Sciences (1994). He has been Associate Editor of the *Journal of the American Chemical Society* **and currently is a University Distinguished Professor and holder of the John K. Stille Chair in Chemistry.**

Gregory Philip Brengel was born on Long Island, New York in 1968. He received a Bachelors of Science in Chemistry (with honours) from Indiana University in 1990, and carried out research with Professor Jeffrey M. Stryker. He then moved to Colorado State University where he began his doctoral studies with Professor Albert I. Meyers. His dissertation work has resulted in the stereoselective syntheses of cycloalkanols *via* **allylsilane annulations to electron deficient alkenes and unsaturated bicyclic lactams. Gregory received his PhD in the autumn of 1996 and is currently employed with Union Carbide in New Jersey.**

Footnotes

† It has been recently found that 5,5-bicyclic lactams **III**, derived from the Parke–Davis amino alcohol **i** (R = Me, $SiPh_2Bu^t$), undergo almost exclusive *exo* alkylation. The diastereoselectivities in these cases are extremely high and the results of the study will be reported in due course; A. I. Meyers and M. Seefeld, *J. Org. Chem.*, 1996, **61**, 5712. See also G. Roth *et al.*, *J. Org. Chem*., 1996, **61**, 5710. For *exo* selective alkylations of 5,6-bicyclic lactams, see ref. 2(*j*).



i

‡ A wide selection of saturated and unsaturated 5,5-bicyclic lactams **III** (*n* = 0) and **57**, respectively, are now commercially available from either Aldrich Chemical Co. or Salford Ultrafine Chemicals & Research Ltd., Research Park, Manchester (UK).

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