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A Synthesis of Enantiomerically Pure 3- and 3,3-Disubstituted Pyrrolidines

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Summary: *Enantiomerically pure bicyclic lactam **1**, derived from (S)-phenylglycinol, underwent diastereoselective mono- and dialkylation affording substituted lactams **2** and **3** bearing tertiary and quaternary stereocenters. Reduction with $LiAlH_4$ furnished N-(2'-hydroxy-1'-phenylethyl) pyrrolidines **4** which were efficiently debenzylated by catalytic hydrogenolysis to afford enantiomerically pure 3-mono- and 3,3-disubstituted pyrrolidines **5**.*

The pyrrolidine ring and its substituted analogs are found in a variety of natural[1] and synthetic[2] products. Enantiomerically pure pyrrolidines have been efficiently employed as chiral auxiliaries[3] and intermediates[4] for the synthesis of a variety of chiral, nonracemic compounds. It is of interest therefore to have methods on hand to construct variously substituted pyrrolidines with the desired absolute configuration.

Syntheses of racemic 3-substituted pyrrolidines have been reported.[5] However, methods for the preparation of enantiomerically pure pyrrolidines substituted exclusively at the 3-position are scarce[6a] and have only recently been reported from this laboratory.[6b] In contrast, methods abound for the substitution of proline and pyroglutamic acid, many of which do include substitution at the 3-position on the ring, but these remain polysubstituted pyrrolidines.

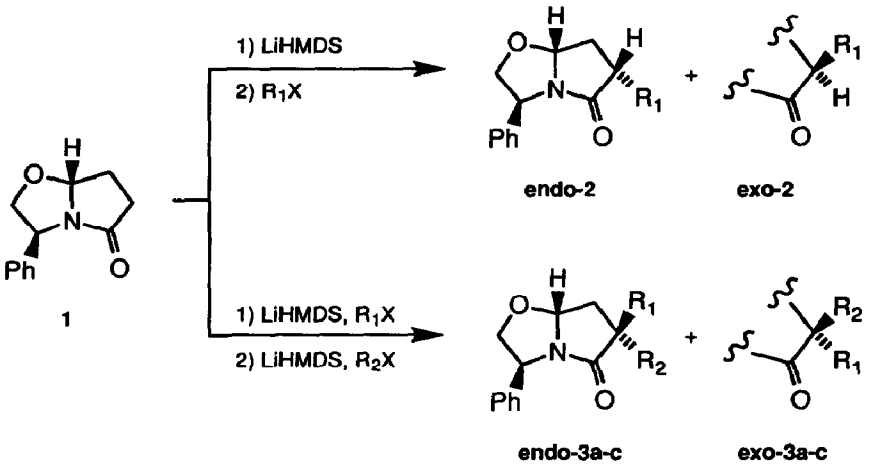
We recognized that a bicyclic lactam structure bearing an angular hydrogen at C-7a, with an auxiliary that could be deaminated, should be exploitable as a latent pyrrolidine or pyrrolidinone structure. The preparation of nonracemic 2-substituted pyrrolidines and pyrrolidinones has already been reported. The present work will describe the facile synthesis of enantiomerically pure 3-mono- and 3,3-disubstituted pyrrolidines via stereoselective enolate alkylation of lactam **1**.[7]

We envisioned (Scheme 2) that a diastereomerically pure mono- or disubstituted bicyclic lactam such as **2** or **3** could be reduced to furnish N-(2'-hydroxy-1'-phenylethyl)pyrrolidine **4**. This would then be relieved of the pendant phenylethanol by catalytic hydrogenolysis to afford an enantiomerically pure pyrrolidine **5**. This method afforded high enantiomeric purity, but, unlike previous bicyclic lactam strategies, did so in exchange for the loss of the stereogenic center of phenylglycine.

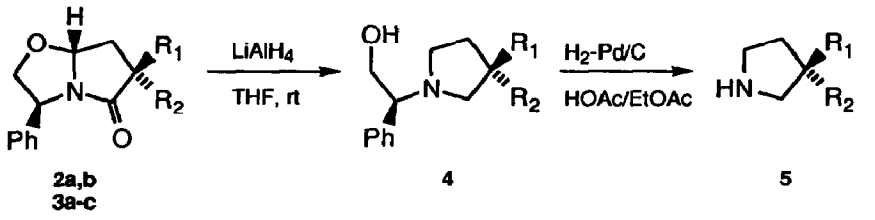
The lactams were deprotonated with lithium hexamethyldisilylamide (LiHMDS) in THF and then treated with neat alkyl halide (Table 1), all at -78°C. Lithium diisopropyl amide (LDA) was

satisfactory as a base for unsubstituted lactam **1** but proved unsuitable in forming the tertiary enolate (second alkylation) owing to a rapid loss of the benzylic methine proton on the phenylglycinol auxiliary. This was followed by irreversible opening of the oxazolidine ring by elimination of the ring oxygen affording an N-stryenyl compound. Potassium hexamethyldisilylamide evidently afforded a highly basic enolate. The product mixture from the monosubstituting alkylation of **1** gave a mixture of **1**, monosubstituted, and disubstituted lactam in a ratio of approximately 1 : 2 : 1, respectively, indicating rapid proton exchange between enolate and lactam. These difficulties were entirely overcome through the use of LiHMDS.

Scheme 1



Scheme 2



Diastereoselectivity from the first alkylation was usually modest (Entry 1, 46 % de) with the interesting exception of methylation (Entry 2, 66 % de). Alkylation with LiHMDS/allyl bromide gave an endo/exo product ratio of 60 : 40 (20 % de) and an isolated yield of 76%. The disubstituting alkylation typically resulted in better selectivity (Entries 3-5), probably due to higher steric congestion around the tertiary enolate. After alkylation the lactams were obtained *diastereomerically pure* (HPLC) by flash column chromatography. The diastereoselective propensities of bicyclic lactam enolates have been reported earlier.[8]

Table 1. Mono- and disubstituted bicyclic lactams **2** and **3**.

Entry	R_1X	R_2X	endo : exo	Yield %[a]	endo/exo Products[c]
1	$PhCH_2Br$	—	73 : 27	95	**2a**
2	CH_3I	—	83 : 17	97	**2b**
3	CH_2=$CHCH_2Br$	CH_3I	84 : 16	98[b]	**3a**
4	$PhCH_2Br$	CH_3I	82 : 18	95[b]	**3b**
5	CH_3I	4-(CH_3O)-$PhCH_2Br$	82 : 18	99[b]	**3c**

[a] Combined endo and exo products. [b] Yield of second alkylation. [c] HPLC conditions to assess de were column: DuPont Zorbax, 0.4 x 25 cm; 15% EtOAc in Hexane; 2 mL/min.

Diastereomerically pure lactams **endo-2a**, **exo-2a**, and **endo-2b** were elaborated to the enantiomeric 3-monosubstituted pyrrolidines **5a**, **5b**, and **5c** by reduction with excess LAH in THF at room temperature for 6 h. The crude amino alcohols **4**[9] were taken up in 1 : 1 ethyl acetate in glacial acetic acid and submitted to catalytic hydrogenolysis using 25 mol % of 10 % Pd on carbon under 3 atm of H_2 for 24 h to afford the pyrrolidines in Table 2. The volatility of **5c** precluded its efficient isolation so it was trapped from the crude product with phenylisothiocyanate. As a precaution against the remote chance that the monosubstituted lactams might epimerize when exposed to LAH reduction conditions, the (R)-α-methoxy-α-(trifluoromethyl)phenylacetamido diastereomers of **5a** and **5b** were prepared and each showed no trace of the other by ^{19}F-nmr.

Table 2. Enantiomerically pure pyrrolidines **5**.

Entry	Lactam	R_1	R_2	Yield %[a]	Pyrrolidine[b]	$[\alpha]_D$[c]
1	**endo-2a**	H	$PhCH_2$	83	**S-(-)-5a**	-18.2° (c 1.52, EtOH)
2	**exo-2a**	$PhCH_2$	H	85	**R-(+)-5b**	+19.1° (c 1.53, EtOH)
3	**endo-2b**	H	CH_3	65	**S-5c**	+8.92° (c 0.74, THF)[c]
4	**endo-3a**	$CH_3CH_2CH_2$[d]	CH_3	89	**R-(+)-5d**	+0.49° (c 3.27, THF)
5	**endo-3b**	$PhCH_2$	CH_3	86	**R-(+)-5e**	+2.33° (c 2.19, EtOH)
6	**endo-3c**	CH_3	4-(CH_3O)-$PhCH_2$	80	**S-(-)-5f**	-1.88° (c 2.45, EtOH)

[a] Yield from corresponding lactam. [b] Elemental analysis was performed on the phenylthiourea derivatives and all were satisfactory [c] Owing to the volatility of **5c** the phenylthiourea derivative was prepared, from which the yield was calculated and optical rotation taken. Otherwise, the signs and rotation values refer to the pyrrolidine. [d] During hydrogenolysis the allyl group was reduced to n-propyl.

The propensity of bicyclic lactam enolates to undergo predominantly endo alkylation was exploited to give all of the pyrrolidine products except **5b** (Table 2, Entry 2). This was derived from minor alkylation product **exo-2a** using LDA as the base. LDA gave endo/exo ratios closer to unity and thus was a more efficient source of this minor diastereomer. The major (endo) diastereomer of **2a** could be epimerized by treatment with LiHMDS (1.0 equiv, -78° C) followed by addition of solid ammonium chloride to give a 1: 1 ratio of endo/exo compounds.

From the disubstituted lactams were isolated the diastereomerically pure products **endo-3a-c** and these were submitted to the same LAH reduction conditions as above. The intermediate amino alcohols were taken directly to hydrogenolysis to furnish enantiomerically pure 3,3-disubstituted pyrrolidines **5d-f**.

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7. The synthesis of the phenylglycinol-derived lactam **1** has been described earlier: Meyers, A.I.; Lefker, B.A.; Sowin, T.J.; Westrum, L.J. *J. Org. Chem.*, **1989**, *54*, 4243.
8. Romo, D.; Meyers, A.I. *Tetrahedron*, **1991**, *47*, 9503, and references therein.
9. The reaction mixture was doubled in volume with THF, then quenched with finely powdered sodium sulfate decahydrate (5 water equivalents) and stirred until all traces of grey had disappeared and only a white flocculent solid remained. The solid was filtered away and the filtrate concentrated, whereupon a quantity of benzene was added and any water present was removed azeotropically on the rotary evaporator. This was repeated to afford quite dry amino alcohol.

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