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Asymmetric synthesis of 1,3- and 1,3,4-substituted pyrrolidines

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Abstract

Diastereoselective alkylation of *N*-acylnorbornene sultams **2** afforded a variety of enantiomerically pure products **3a**–**3e**. Reduction with $LiAlH_4$ (LAH) followed by ditosylation furnished chiral 1,4-ditosylates **5a**–**5e** which underwent a cyclization reaction with primary amines to afford chiral 1,3- and 1,3,4-substituted pyrrolidines.

Keywords: asymmetric synthesis; sultams; cyclization; pyrrolidines.

Chiral pyrrolidines are common structural subunits found in a variety of natural and unnatural products which possess interesting and diverse biological activities.[1] In addition, several enantiopure pyrrolidines have been used as auxiliaries for a number of important transformations.[2] As a result, the development of asymmetric methods for the synthesis of nonracemic substituted pyrrolidines has drawn the attention of many investigators.

We recently described the design and synthesis of the enantiopure norbornene sultams **1**. Subsequently, their use as effective chiral auxiliaries in asymmetric Diels–Alder and alkylation reaction has been demonstrated.[3,4] In particular, outstanding diastereoselectivity was consistently obtained from the alkylation of *N*-acylnorbornene sultams **2a**–**2c** with α-bromoacetate.[4] Enantiopure alkylated products **3a**, **3d**, *ent*-**3d** and **3e** were obtained (Scheme 1). These results are reminiscent of the findings of Oppolzer's sultams.[5] However, we have demonstrated the outstanding chiral induction of our auxiliaries during asymmetric alkylations. When *N*-acylnorbornene sultams were alkylated with α-alkyl α-bromoalkanoates, two new stereogenic centers were generated in a highly stereoselective manner. Thus, under the experimental conditions, enantiopure **3b**, *ent*-**3b** and **3c** were obtained as single alkylated products from the corresponding reactions.[4]

LAH reduction of **3a**–**3e** gave the corresponding chiral diols **4a**–**4e** in 72–92% yield, together with the regeneration of the chiral auxiliaries **1** or *ent*-**1** in over 65% yield. The optical integrity of the recovered norbornene sultams was proved to be intact, as indicated by optical measurements. Furthermore, because some of the diols are known compounds, their optical purity and the absolute configuration of the

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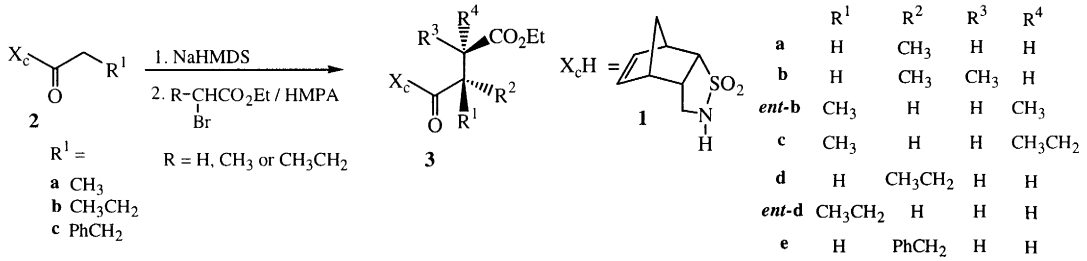
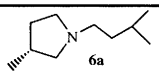
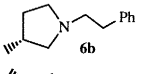
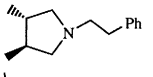
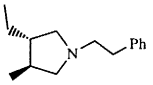
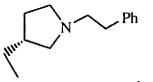
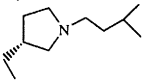
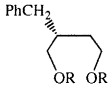
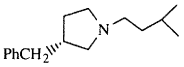


	R^1	R^2	R^3	R^4
a	H	CH_3	H	H
b	H	CH_3	CH_3	H
***ent*-b**	CH_3	H	H	CH_3
c	CH_3	H	H	CH_3CH_2
d	H	CH_3CH_2	H	H
***ent*-d**	CH_3CH_2	H	H	H
e	H	$PhCH_2$	H	H

Scheme 1.

stereogenic center were established by comparison with the literature. The new diols **4c** and **4e** prepared by this work were adequately characterized by NMR spectroscopic methods and elemental analysis. To set the stage for pyrrolidine ring formation, diols **4a**–**4e** were further transformed into the corresponding ditosylates by treating with tosyl chloride in pyridine. When the diols were allowed to react with excess tosyl chloride at −5°–0°C for 5 h, good to excellent yields of the ditosylates were obtained (Table 1).

Table 1
Synthesis of enantiomerically pure pyrrolidines

Entry	Alkylated products	Diols			Ditosylates			
		Yield (%)	R = H		R = Ts	Yield (%)	Product	Yield (%)
1	**3a**	72	**4a** [a]		**5a**	84	 **6a**	40
2	**3b**	81	**4b** [a]		**5b**	75	 **6b**	53
3	***ent*-3b**	93	***ent*-4a** [a]		***ent*-5b**	78		57
4	**3c**	77	**4c**		**5c**	74		77
5	**3d**	93	**4d** [b]		**5d**	67		79
6	***ent*-3d**	81	***ent*-4d** [b]		–	–		53
7	**3e**	80	**4e**		**5e**	85		80

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To demonstrate the feasibility of preparing chiral substituted pyrrolidines, treatment of ditosylates **5a**–**5e** with 4 equivalents of either phenylethylamine or 3-methylbutylamine in refluxing triethylamine for 16 h afforded the desired cyclization products in good yield (Table 1).

In summary, our synthetic approach provides a facile access to chiral 1,3-disubstituted and 1,3,4-trisubstituted pyrrolidines. Two naturally occurring pyrrolidines **6a** and **6b** were synthesized for the first time and our results supported the absolute configuration assignment proposed by Veith et al.[6]

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