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An efficient route to chiral, non-racemic 3-alkyl-3-arylpyrrolidines. Improved stereoselectivity in alkylation of bicyclic lactams and the effect of leaving groups

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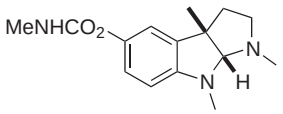
Abstract

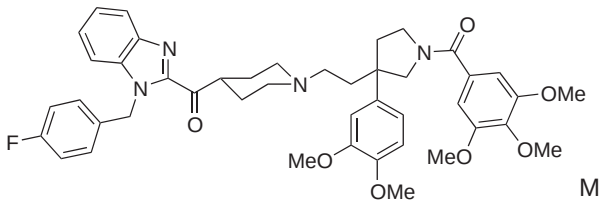
Chiral 3-alkyl-3-arylpyrrolidines were prepared from the substituted bicyclic lactams. Stereoselectivity in the alkylation of bicyclic lactams was improved by using an alkyl triflate or tosylate as the electrophile.

Keywords: alkyl triflates; diastereoselective alkylation; aminal reduction.

3-Alkyl-3-arylpyrrolidines are valuable constituents of a variety of natural products and medicinally important compounds.[1,2] For example, physostigmine[1] and MDL103,896[2b] are representative of this class possessing these heterocycles.



(-)-physostigmine



MDL103,896

To date only a few enantioselective synthesis of the 3-alkyl-3-arylpyrrolidines have been reported. Thus, 2-alkyl-2-arylmalonate was desymmetrized by hydrolysis with pig liver esterase, which resulted in half esters that were converted into chiral 3-alkyl-3-arylpyrrolidines by Fadel et al.[3] However, the optical purity of the materials was only 71–97% ee due to the variable

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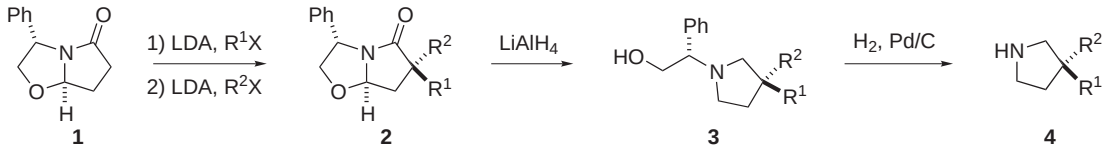
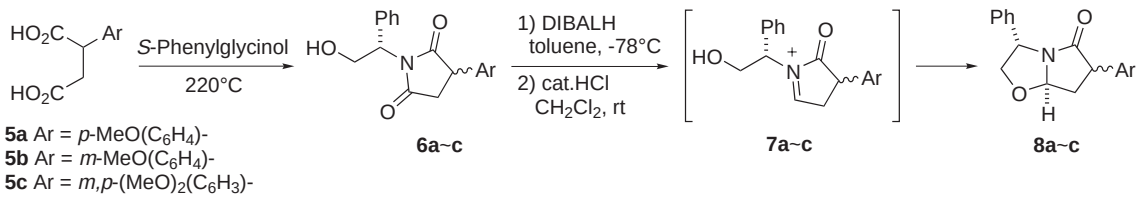
enantioselectivity of the enzymatic hydrolysis. On the other hand, direct alkylation of enolates of chiral 2-pyrrolidinones has been reported and has led to some chiral 3-substituted 2-pyrrolidinones.[4,5] Utilizing this approach, Royer et al.[5] produced chiral 3,3-dialkylpyrrolidinone derivatives from 1-(2-hydroxy-1-phenylethyl)-1,5-dyhydropyrrol-2-one, which was prepared from *R*-phenylglycinol and 2,5-dimethoxy-2,5-dihydrofuran. Despite the high diastereoselectivity, the yield in the second alkylation step was modest. This method has not yet been applied to the synthesis of 3-alkyl-3-arylpyrrolidines.

We have described the synthesis of chiral 3,3-dialkylsubstituted pyrrolidines **4** by successive alkylation of the bicyclic lactam **1**, followed by removal of the chiral auxiliary in **3** to pyrrolidines **4** (Scheme 1).[6] This process occurs in good overall yields, however, the diastereoselectivity in the alkylation of **1** has been erratic and, at times unsatisfactory. In order to extend the above procedure to 3-alkyl-3-arylpyrrolidines **4** (R^1 = alkyl, R^2 = aryl), the process required alkylation of angular hydrogen bicyclic lactam **1** to be substituted by both an alkyl and an aryl group.



Scheme 1. Synthesis of chiral 3,3-disubstituted pyrrolidines

The angular hydrogen bicyclic lactam **1** was prepared in good overall yield, from its succinimide derivative, which in turn, was prepared from *S*-phenylglycinol and succinic acid or anhydride.[6] The requisite aryl substituted bicyclic lactams **8a–c** were prepared from the corresponding 2-arylsuccinic acids **5a–c**.[7] Condensation of *S*-phenylglycinol and **5a–c** furnished the succinimide derivatives **6**, which were regioselectively reduced[8] and cyclized via the intermediate *N*-acyliminium species[9] **7** to afford the bicyclic lactams **8a–c** (overall yields of **5–8** were 38–62%, Scheme 2).

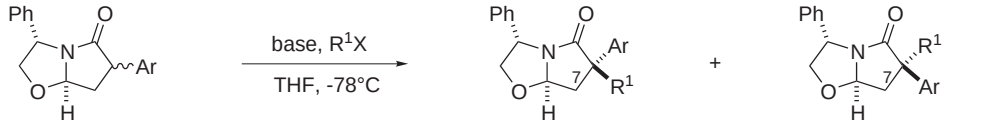


Scheme 2. Preparation of aryl substituted bicyclic lactam

Alkylation of bicyclic lactams (e.g. **8a–c**) has been shown to occur predominantly from the *endo* (concave) face, and the basis of this stereochemical result has been discussed.[6a] There is still some question regarding the major factor responsible for predominant *endo* alkylation. It is possible that, in addition to others, the steric repulsion between the angular substituent and approaching electrophile may be one of the more important factors determining *endo* selectivity. Since the alkylation of angular hydrogen lactams leads to generally lower diastereoselectivity than that of angular alkyl lactams,[6a] we felt the present case may shed some light on this issue.

Alkylation of bicyclic lactam **8a** with iodomethane and LHMDS in tetrahydrofuran at −78°C gave an *endo*/*exo* ratio of 86:14 for **9a** and **10a**, respectively, in 94% yield (Table 1, entry 1). Furthermore, the alkylation with allyl bromide proceeded to give an *endo*/*exo* ratio of 82:18 for **11a** and **12a**, respectively, in 81% yield (Table 1, entry 5). These ratios were determined by ^{1}H NMR and are assumed to be accurate to ±3%. The protons at the C-7 methylene in the major isomer **9a** appear separately at 2.25 and 2.94 ppm as a *dd*. On the other hand, these protons in the minor isomer **10a** appear much closer at 2.60 and 2.63 ppm. The stereochemistry of the major isomers was initially confirmed by converting them into compounds known in the literature. Due to the modest 6:1 ratio observed for **9a**:**10a**, a detailed study was initiated to try to improve the stereoselectivity.

Table 1
Alkylation of bicyclic lactam **8**



8a~c **9** R^1=Me or **11** R^1=Allyl **10** R^1=Me or **12** R^1=Allyl

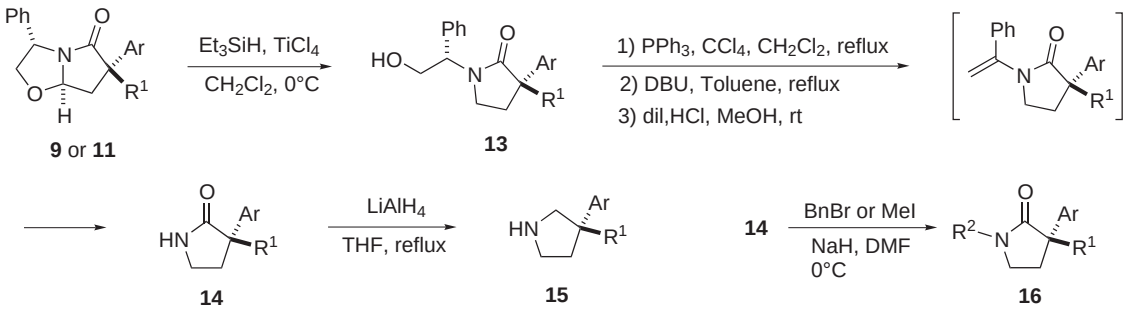
Entry	Substrate	Base	R^1X	Reaction time	Yield (%)	*endo*/*exo* (**9**/**10** or **11**/**12**)
1	**8a**	LHMDS	MeI	1 h	94	86/14
2	**8a**	LHMDS[a]	MeOTf	20 min	99	95/5
3	**8b**	LHMDS[a]	MeOTf	20 min	98	96/4
4	**8c**	LHMDS[a]	MeOTf	20 min	96	96 /4
5	**8a**	KHMDS	AllylBr	15 min	99	83/17
6	**8a**	KHMDS	AllylOTs	30 min	90	90/10
7	**8b**	KHMDS	AllylOTs	1 h	98	91/9
8	**8c**	KHMDS	AllylOTs	30 min	97	91/9

[a] The reaction was allowed to warm to −60°C for 20 min and was then recooled to −78°C prior to addition of the electrophile.

Addition of HMPA or increasing the reaction temperature in the alkylation of **8** had little or no effect on the stereoselectivity. The metal cation of the base employed during the alkylation (NaHMDS or KHMDS) also had no effect. Since the nature of the leaving group in the electrophile had received only little attention in the past,[10] this was, therefore, examined. Interestingly, the ratio of **9a**:**10a** increased considerably to 95:5 when methyl triflate was substituted for methyl iodide (Table 1, entry 2). Alkylation of the related lactams, **8b** and **8c**, with methyl triflate showed similar improvements in stereoselectivities. Improvements were also observed in the allylation of the lactams. Although the stereoselectivity is slightly lower than that of methylation, the best result was again obtained using the sulfonate derivative, i.e. allyl tosylate (Table 1, entries 6–8). An attempt to utilize allyl triflate was not practical due to the instability of the latter.

In contrast to the above, alkylation using ethyl triflate gave lower selectivity (*endo*/*exo* = 81:19, 93% yield). It appears, as of now, that the more bulk present in the electrophile, the more sensitive it will be to potentially existing steric bias on bicyclo[3.3.0] system. The fact that triflates and tosylates are usually poor electrophiles in ether solvents, resulting in a lower rate of alkylation of **8**, could be responsible for the increased selectivity in facial alkylation.[10b]

A representative number of bicyclic lactams (e.g. **9**, **11**) were converted into 3,3-disubstituted pyrrolidinone derivatives **13** in good yield by reductive ring opening with triethylsilane and titanium(IV) chloride at 0°C.[11] The minor diastereomer (4–9%) was readily eliminated by column chromatography at this stage to obtain pure pyrrolidinone **13**. Removal of chiral auxiliary was accomplished by an elimination–hydrolysis procedure. Thus, alcohol **13** was converted into the corresponding chloride with carbon tetrachloride and triphenylphosphine, followed by elimination of hydrogen chloride with DBU. Acid hydrolysis of the enamine (*N*-styryl pyrrolidinone) afforded optically pure 3,3-disubstituted pyrrolidinones **14** in high overall yield (Scheme 3, Table 2). Reduction of **14** with lithium aluminium hydride furnished the 3,3-disubstituted pyrrolidines **15** in quantitative yields.



Scheme 3. Conversion of bicyclic lactams into pyrrolidines and pyrrolidinones

Table 2

Lactam				**13** yield (%)	**14**		**15** $[\alpha]_D$
	Ar	R^1	Purity[a]		Yield (%)	$[\alpha]_D$	
9a	*p*-MeO(C_6H_5)	Me	95	93	90	−69.4	+11.1
9b	*m*-MeO(C_6H_5)	Me	>99	98	99	−79.4	+11.8
11b	*m*-MeO(C_6H_5)	Allyl	91	80[b]	97	89.0	+5.9
11c	*m*,*p*-$(MeO)_2(C_6H_4)$	Allyl	>99	>99	93	81.0	+3.1

16				Reported[3,12] $[\alpha]_D$ (% ee)
Ar	R^1	R^2	$[\alpha]_D$	
p-MeO(C_6H_5)	Me	Bn	−9.3	−8 (97)
m-MeO(C_6H_5)	Me	Me	−91.0	−79.9
m-MeO(C_6H_5)	Allyl	Bn	−21.4	−21 (86)
m,*p*-$(MeO)_2(C_6H_4)$	Allyl	Bn	−10.8	−8.5 (71)

[a] Percent content of major isomer (**9** or **11**) in the mixture of **9** and **10**, or **11** and **12**. Pure **9b** and **11c** were obtained by recrystallization.

[b] Yield after recrystallization.

To further address the absolute stereochemistry at C-3 of the pyrrolidines, the known corresponding lactams were accessed. Treatment of **14** with methyl iodide or benzyl bromide, and sodium hydride gave *N*-methyl or *N*-benzyl lactams **16**, whose optical rotation had been reported.[3,12] The sign of $[\alpha]_D$ was in agreement with the absolute configuration reported and was also consistent with the predicted entry of the electrophile to the bicyclic lactams. It is noteworthy that *N*-methyl lactam **16** (Ar = *m*-MeO(C_6H_5), R^1 = Me, R^2 = Me) is identical to the synthetic intermediate for (–)-physostigmine prepared by Takano et al.[12]

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