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A novel stereocontrolled synthesis of enantiopure bicyclic lactams

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Abstract—A study on the reactivity of 3,4-dihydro-2-pyridones **9**, derived from (*S*)-phenylglycinol, toward different bases is presented. Using a catalytic amount of bases, the *cis* bicyclic lactams were obtained with excellent diastereoselectivities.

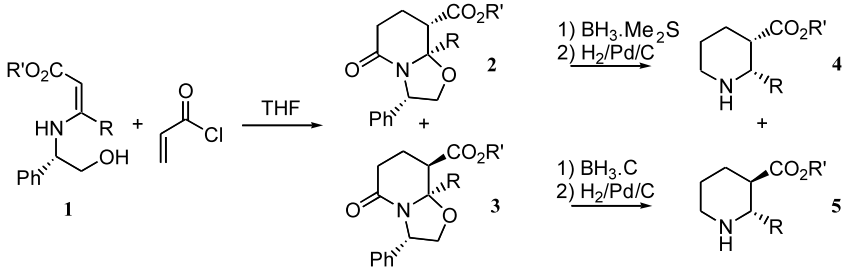
As regards the enantioselective synthesis of polysubstituted piperidines,[1] chiral non-racemic bicyclic lactams,[2] derived from homochiral β-amino alcohols, are commonly considered as most useful starting materials. In these syntheses, the bicyclic ring system is usually generated by cyclocondensation of δ-oxoacid derivatives with suitable β-amino alcohols. Amat et al. recently described an alternative procedure involving a diastereoselective oxidation of a (*R*)-phenylglycinol-derived 2-pyridone and its subsequent conversion into an enantiopure trihydroxypiperidine.[3] Gnecco et al. described a similar cyclisation starting from a (*R*)-phenylglycinol-derived 3,4-dihydro-2-pyridone.[4]

In a previous paper, we described the synthesis of chiral non-racemic disubstituted piperidines[5] **4** and **5** from respectively chiral bicyclic lactams **2** and **3**.[6] These compounds were obtained by aza-annulation[7] of β-enaminoesters **1** derived from (*S*)-phenylglycinol with acryloyl chloride (Scheme 1).

These original bicyclic lactams allowed an efficient access to piperidines **4** and **5** substituted at C-3 on the piperidines. A problem in this approach was the lack of stereoselectivity during the formation of the bicyclic lactams. In all experiments, these compounds were obtained in the form of two epimers **2** and **3**, differing by the configuration of the carbon bearing the carbonyl group.

Here we wish to present a new strategy towards advanced precursor lactams **2** and **3**, which can be used for the synthesis of *cis* and *trans* 2,3-disubstituted piperidines. This strategy is based on a study of the cyclization of 3,4-dihydro-2-pyridones **9** bearing an internal hydroxyl function. To our knowledge, such an internal Michael addition on β-enaminoesters has not been reported so far.

In order to prepare substrates **9** (Scheme 2) by an aza-annulation process, condensation of TBDMS-pro-



Scheme 1.

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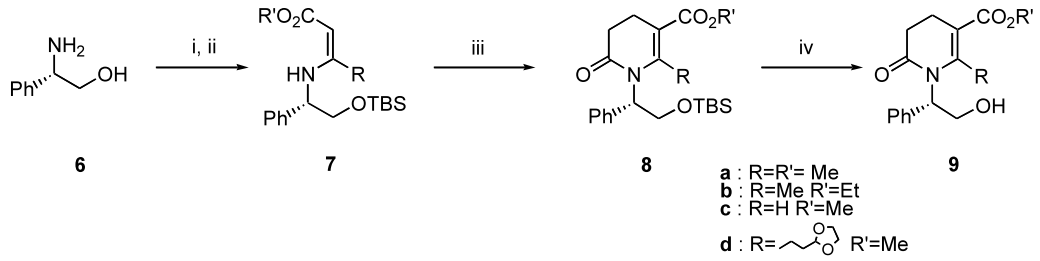


Scheme 2. *Reagents and conditions*: (i) imidazole 2.5 equiv., TBDMSCl 1.2 equiv., CH_2Cl_2; (ii) methylpropiolate or β-ketoesters, MeOH or EtOH; (iii) acryloyl chloride, THF; (iv) HF·pyridine, THF.

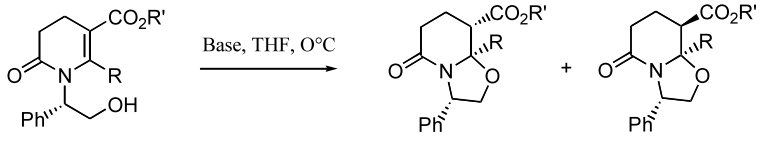
tected (*S*)-phenylglycinol with β-ketoesters (R = alkyl) or methylpropiolate (R = H) yielded β-enaminoesters **7** which were used unpurified in the next step.

The aza-annulation reaction was performed by adding 1.2 equiv. of acryloyl chloride derivatives to β-enaminocarbonyl compounds **7** in THF at room temperature. The cyclization with acryloyl chloride was successful and yielded good amounts of the expected TBDMS-protected 3,4-dihydro-2-pyridones **8**. Deprotection of compounds **8** with HF·pyridine worked properly and excellent yields of compounds **9** were obtained.

At this stage the alcohols **9** were purified by chromatography on silica gel. The overall yield with R = alkyl was higher than 80%, but it was only 45% with substrate **9c** (R = H) due to the poor yield of the condensation step between the protected (*S*)-phenylglycinol and methylpropiolate. In neutral and acidic media, dihydropyridones **9** were stable. Intramolecular Michael addition were then performed in basic media using LiHMDS, NaHMDS and KHMDS as bases, in THF at 0°C. Thereafter, the reaction mixtures were treated with an aqueous saturated ammonium chloride solution and extracted with dichloromethane. The results are presented in Table 1.

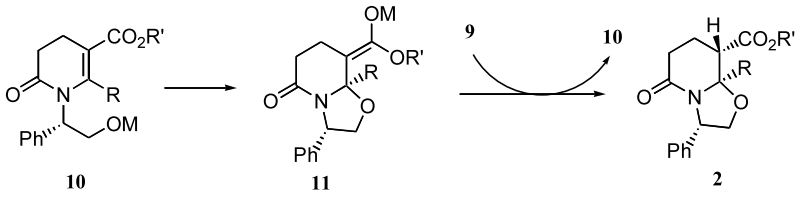
In all the experiments where R = alkyl (substrates **9a**,**b**,**d**) bicyclic lactams were formed quantitatively. The reactions were completed within 2 h. Study of the stereoselectivity of the newly formed stereocenter on the oxazolidine ring showed that only a *cis* configuration for the oxazolidine ring could be detected in the ^{1}H NMR spectrum of the crude product. This is in agreement with our previous experiments on the reaction of β-enaminoesters **1** with acryloyl chloride (Scheme 1).[5]

Table 1. Cyclization of 3,4-dihydro-2-pyridones **9**



Entry	Substrate	R	R'	Base (eq.)	Time hours (h)	Ratio **2**/**3**[a]
1	**9a**	Me	Me	LiHMDS, 0.5	2	94 / 6
2	"	"	"	NaHMDS, 0.5	"	86 / 14
3	"	"	"	KHMDS, 0.5	"	55/ 45
4	"	"	"	LiHMDS, 1.2	"	>98 / 2
5	"	"	"	LiHMDS, 0.1	"	>98 / 2
6	"	"	"	NaHMDS, 0.1	"	>98 / 2
7	"	"	"	KHMDS, 0.1	"	85/ 15
8	"	"	"	"	1	>98/ 2
9	**9b**	"	Et	NaHMDS, 0.1	2	>98/ 2
10	**9c**	H	Me	"	"	>98/ 2
11	**9d**		"	"	"	75/ 25
12	"	"	"	"	0.5	>98/ 2

a Ratios determined by ^{1}H NMR analysis of the crude mixture.



Scheme 3.

When 0.5 equiv. of base was used, the metal cation of the base employed during intramolecular Michael addition had a dramatical effect on the stereoselectivity of the reaction (entries 1–3). The best selectivity was obtained with the less reactive base (LiHMDS, entry 1). It is noteworthy that when an excess of LiHMDS was used such as in entry 4 the conversion was low (57%). A large increase in the diastereoselectivity of the 2 h reaction was observed when a catalytic amount of bases (10%) was used (entries 5–7). A total diastereoselectivity was observed with KHMDS when the reaction was stopped after 1 h (entry 8).

When KHMDS (0.5 equiv.) was used (entry 3), the reaction was thermodynamically controlled, since it appears that when *cis* stereomer **2a** was exposed to 0.5 equiv. of KHMDS, the ratio of the diastereomers **2a** and **3a** was approximately equivalent to the ratio obtained in entry 3 (52/48). Thus, under kinetic control (1–2 h reaction with 0.1 equiv. of base), *cis* bicyclic lactams **2** were obtained with high diastereoselectivity.

The cyclization was extended to substrates **9b–d**, using 0.1 equiv. of NaHMDS as standard conditions. The same stereoselectivity was observed in favor of the *cis* stereomers **2b–d**. Changing methyl ester to ethyl ester did not modify the d.e. (entry 9). On the contrary, a reaction starting from **9c** was not complete, since only 40% conversion was obtained (entry 10). In this case, the resulting enolate **11** formed by Michael addition was expected to be less stable than the intermediate alcoholate **10** (Scheme 3). Starting from substrate **9d**, partial epimerisation was observed after 2 h (entry 11). When the reaction was quenched after 40 minutes, the stereoselectivity was total (entry 12).

Absolute configurations of the *cis* lactams **2** and *trans* lactams **3** were deduced from the stereochemistry of compounds **2a** and **3a** already established by NOE ^{1}H NMR experiments and X-ray analysis. It was observed that the chemical shift of the proton α to the ester moiety in the major *cis* lactam diastereoisomers **2** was found up field (2.6–2.7 ppm) from that of *trans* isomers **3** (3.1–3.2 ppm).

Rationalization of the stereochemical outcome in intramolecular Michael addition is presented in Scheme 3. Following addition of alcoholate **10**, the resulting enolate **11** abstracts an acidic hydrogen on alcohol **9**. Protonation takes place from the less crowded *endo* diastereoface (*anti* to R and Ph). Upon exhaustion of the acidic hydrogen in the medium, (after 1–2 h with 0.1 equiv. of base), epimerization takes place, due to the abstraction of the hydrogen α to the amidic function.[8] This equilibration is even faster when 0.5 equiv. of bases are used.

In summary, we have found an easy and efficient route to chiral non-racemic *cis* bicyclic lactams **2** in five steps, starting from (*S*)-phenylglycinol. Complete diastereocontrol allows easy purification of compounds **2**. The overall yield, when R = alkyl, are >80%. This protocol has allowed the synthesis of 10 g of bicyclic lactam **2a**, with 83% overall yield and one purification by chromatography on silica gel of the 3,4-dihydro-2-pyridone **9**.

References

1. For recent applications, see: (a) Amat, M.; Canto, M.; Llor, N.; Ponzo, V.; Perez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335; (b) Amat, M.; Perez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787; (c) Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343; (d) Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661; (e) Amat, M.; Perez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611.
2. For reviews, see: (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843; (b) Meyers, A. I. Brengel, G. P. *Chem. Commun.* **1997**, 1.
3. Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257.
4. Teran, J. L.; Gnecco, D.; Galindo, A.; Juarez, J.; Bernes, S.; Enriquez, R. G. *Tetrahedron: Asymmetry* **2001**, *12*, 357.
5. Agami, C.; Dechoux, L.; Ménard, C.; Hebbe, S. *J. Org. Chem.* **2002**, *67*, 7573.
6. Agami, C.; Dechoux, L.; Hebbe, S. *Tetrahedron Lett.* **2002**, *43*, 2521.
7. (a) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 1358; (b) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 2112.
8. When the reaction was quenched after 12 h with MeOD, the α-amidic position was partially deuterated.