Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7667–7669

TETRAHEDRON LETTERS

Synthesis of new enantiomerically pure α,β-unsaturated bicyclic lactams

Claude Agami, Alice Beauseigneur, Sébastien Comesse and Luc Dechoux*

Laboratoire de Synthèse Asymétrique (UMR 7611), Université P. et M. Curie, 4 place Jussieu, 75005 Paris, France

Received 2 July 2003; revised 18 July 2003; accepted 6 August 2003

Abstract—New enantiomerically pure *cis*-unsaturated bicyclic lactams were synthesized from phenylglycinol-derived 2-pyrrolinones in a two-step procedure.

α,β-Unsaturated bicyclic lactams[1] have been shown to be valuable substrates for asymmetric conjugate additions with various nucleophiles,[2] cycloadditions[3] and oxidations.[4] For example, these chiral templates have been widely used in the asymmetric synthesis of polysubstituted pyrrolidines. In these syntheses the bicyclic framework is usually generated by cyclocondensation of a γ-oxoacid derivative with phenylglycinol. The subsequent introduction of the unsaturation is carried out, either by treatment with methylsulfinate and LiHMDS,[5] followed by thermal elimination of the intermediate sulfoxides or by treatment of the generated enolate with phenylselenenyl bromide and further oxidation.

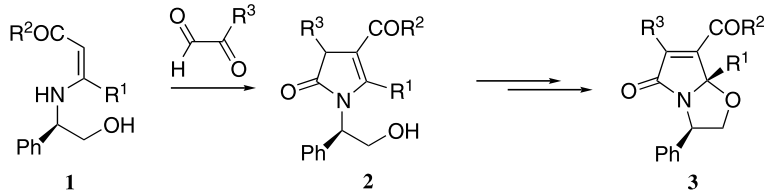
Here, we describe an alternative procedure involving the unprecedented diastereoselective transformation of (*R*)-phenylglycinol derived 2-pyrrolinones **2** into the unsaturated γ-bicyclic lactams **3** (Scheme 1). Moreover, this approach allows the introduction of a carbonyl moiety on the C4 position of the lactam ring.

The starting pyrrolinones **2** were obtained from the reactions between chiral non-racemic β-enaminocarbonylated compounds **1** with glyoxal ($R^3=H$) or phenylglyoxal ($R^3=Ph$).[6]

The reactions between glyoxal (or phenylglyoxal) and non-chiral *N*-substituted β-enaminoesters were originally described by Caballero et al.[7] As reported by the authors, pyrrolinones **2** were the main reaction products (30–40% isolated product yields). The reactions were carried out by addition of 1.5 equiv. of glyoxal in refluxing methanol or ethanol ($R^2=OEt$) and could be achieved on a multi-gram scale.

With compounds **2** in hand, we focused our attention on their electrophilic cyclisation using *N*-bromosuccinimide (NBS),[8] which would afford bicyclic compounds **4**, i.e. the potential intermediates in the synthesis of the expected lactams **3**.

Bromocyclisation of **2a** ($R^1=Me$, $R^2=OMe$, $R^3=H$, Scheme 2) was attempted in dichloromethane at 0°C using NBS. Unfortunately a large number of products were formed and no bicyclic lactams **4a** could be detected in the ^1H NMR spectrum of the crude



Scheme 1.

Keywords: β-enaminoesters; unsaturated bicyclic lactams; 2-pyrrolinones; oxazolidines; *N*-acyl-iminium.
* Corresponding author. E-mail: dechoux@ccr.jussieu.fr

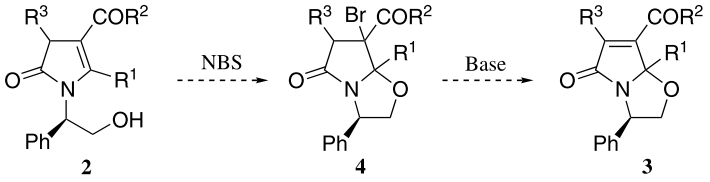
0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.08.017

product. Modifying the reaction conditions by adding base (NaOH, K_2CO_3, NEt_3) did not result in the formation of **3a** or **4a** (Scheme 2).

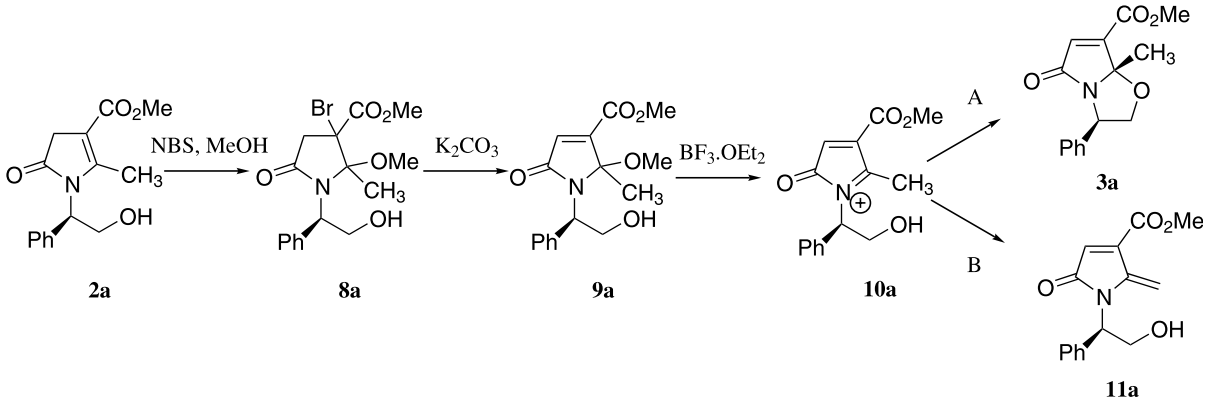
In contrast, treatment of pyrrolinone **2a** with 1.1 equiv. of NBS in methanol at room temperature afforded, within 10 min, haloether **8a** as two diastereomers in nearly quantitative yield. When potassium carbonate was added to the medium, 2-pyrrolinone **9a** was formed and could be isolated after chromatography on a silica gel column. It should be noted that the crude mixture of diastereomers **9a** could be used in the next step without purification: treatment of **9a** with an equimolar amount of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 produced the expected γ-bicyclic lactam **3a** in 64% overall yield starting from **2a** (Scheme 3).

Formation of the bicyclic lactam **3a** from intermediate **9a** (Scheme 3) can be considered by the initial acid–base reaction between the alkoxy group of **9a** and the Lewis acid followed by C–O bond cleavage to give the *N*-acyliminium ion **10a**, which can undergo intramolecular attack by the hydroxyl function to provide the expected product **3a** (pathway A). The presence of enamine **11a** as a secondary product, which was isolated by chromatography on a silica gel column, might be the result of abstraction of hydrogen from the methyl group (pathway B).

Five pyrrolinones **2a–e** were transformed into bicyclic lactams **3a–e** using this two-step procedure.[9] The yields presented in Table 1 correspond to combined yields over the two steps, without the purification of the intermediates **9**.

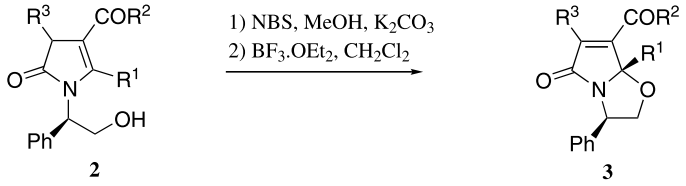


Scheme 2.



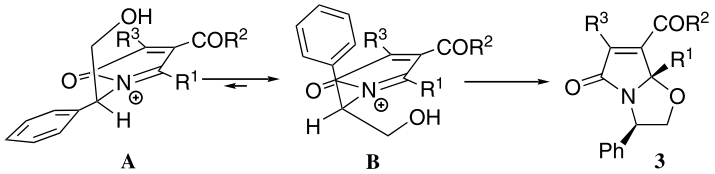
Scheme 3.

Table 1. Synthesis of compounds **3**



Entry	Substrate	R^1	R^2	R^3	Yield (%)[a]
1	**2a**	Me	OMe	H	64
2	**2b**	Me	Me	H	84
3	**2c**	$(CH_2)_4OBn$	OMe	H	96
4	**2d**	Me	OMe	Ph	50
5	**2e**	Me	OEt[b]	H	22

[a] The d.e. was always >95%, as determined by ^1H NMR analysis of the crude mixture.
[b] The first step was carried out in ethanol



Scheme 4.

In all cases, lactams **3** were formed as single diastereomers (entries 1–5). The stereochemistry of **3a** was determined by ^{1}H NMR spectroscopy (NOE experiments). The overall yields range from 50 to 96% when R^2 = OMe or Me (entries 1–4) and are satisfactory. The low yield obtained in entry 5 is due to the difficulty in obtaining the intermediate **9e** starting from **2e**.

The best result was obtained with substrate **2c** in which $R^1 = (CH_2)_4OBn$. In this case, the reaction exclusively follows pathway A (Scheme 3) as **3c** was the only compound observed in the ^{1}H NMR spectrum of the crude mixture.

The stereochemical outcome of the $BF_3{\cdot}OEt_2$ mediated intramolecular cyclisation can be rationalised by considering an allylic strain between the phenyl and the carbonyl in conformation **A**. This interaction is minimised in conformation **B**, thus favouring the formation of the *cis* diastereomers (Scheme 4).

In summary, a stereoselective synthesis of the chiral non-racemic unsaturated bicyclic lactams **3** has been developed starting from pyrrolinones **2**. The originality of structures **3** resides in the presence of a carbonyl moiety on the C4 position of the lactam rings. The reactivity of the double bond present in **3** towards nucleophilic agents should be modified compared to the already widely described bicyclic lactams. We are currently investigating this reactivity in terms of regio- and stereoselectivity. Thus compounds **3** should have potential as versatile building blocks for the enantioselective preparation of polysubstituted pyrrolidines.

References

1. 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.
2. (a) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *Tetrahedron* **2001**, *57*, 2635; (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett*. **1999**, *40*, 4639.
3. (a) Fray, A. H.; Meyers, A. I. *J. Org. Chem*. **1996**, *61*, 3362; (b) Kopach, M. E.; Fray, A. H.; Meyers, A. I. *J. Am. Chem. Soc*. **1996**, *118*, 9876.
4. Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; Mclaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931.
5. Resek, J. E.; Meyers, A. I. *Tetrahedron Lett*. **1995**, *36*, 7051.
6. The stereoselective synthesis of β-enaminocarbonylated compounds has already been described. See: Agami, C.; Dechoux, L.; Hebbe, S.; Moulinas, J. *Synthesis* **2002**, 79.
7. Caballero, E.; Puebla, P.; Domercq, M.; Medarde, M.; Lopez, J. L.; San Feliciano, A. *Tetrahedron* **1994**, *50*, 7849.
8. A related reaction was recently reported by Amat et al. In their article, the authors present the unprecedented oxidation of a phenylglycinol-derived 2-pyridone, leading to a chiral non-racemic unsaturated hydroxylated bicyclic lactam, which has been used as a precursor in the formal synthesis of the azasugar epiisofagomine. See: Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett*. **2001**, *3*, 3257.
9. *General procedure for the formation of bicyclic lactams* ***3***. To a solution of pyrrolinone **2a** (210 mg, 0.75 mmol) in MeOH (7 mL) was added, at 0°C, NBS (146 mg, 0.8 mmol). After 10 min K_2CO_3 (200 mg, 1.5 mmol) was added as a solid. The mixture was stirred for 1 h at room temperature and quenched with an aqueous solution of NaOH (10 mL, 0.5 M). The aqueous was extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was diluted in 10 mL CH_2Cl_2. To this solution was added $BF_3{\cdot}OEt_2$ (0.095 mL, 0.75 mmol) at room temperature. The mixture was stirred for 1 h at room temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous was extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/cyclohexane: 2/8) to furnish 131 mg of lactam **3a** (oil, yield, 64%). Anal. calcd for $C_{15}H_{15}NO_4$; C, 65.92; H, 5.33; N, 5.13. Found: C, 65.03; H, 5.54; N, 5.07. ^{1}H NMR (250 MHz, $CDCl_3$): 1.74 (s, 3H), 3.91 (s, 3H), 4.37 (dd, J = 7.0 and 9.0 Hz, 1H), 4.78 (dd, J = 8.2 and 9.0 Hz, 1H), 5.13 (dd, J = 7.0 and 8.2 Hz, 1H), 6.73 (s, 1H), 7.31–7.39 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 21.4, 52.7, 58.1, 76.3, 100.3, 125.8, 127.8, 128.9, 134.3, 139.1, 151.6, 161.6, 174.8.