Cite this: *RSC Adv.*, 2022, 12, 4187

Diastereoselective synthesis of new zwitterionic bicyclic lactams, scaffolds for construction of 2-substituted-4-hydroxy piperidine and its pipecolic acid derivatives†

Enrique Reyes-Bravo,^a Dino Gnecco,^a Jorge R. Juárez,^a María L. Orea,^a Sylvain Bernès,^b David M. Aparicio^{*a} and Joel L. Terán^{*a}

The synthesis of new chiral highly functionalized zwitterionic bicyclic lactams starting from acyclic β -enaminoesters derived from (*R*)-(-)-2-phenylglycinol is described. The key step involved an intramolecular non-classical Corey–Chaykovsky ring-closing reaction of the corresponding sulfonium salts derived from β -enaminoesters. This methodology permits the generation of two or three new stereogenic centers with high diastereoselectivity. The utility of these intermediates was demonstrated by the stereocontrolled total synthesis of *cis*-4-hydroxy-2-methyl piperidine and its corresponding pipecolic acid derivative.

Received 23rd December 2021
Accepted 21st January 2022

DOI: 10.1039/d1ra09298g

rsc.li/rsc-advances

Stereocontrolled synthesis of polysubstituted piperidines is a very important field in organic synthesis due to the great variety of piperidine-moiety-containing drugs, making it the most prevalent nitrogen heterocycle in approved drugs;¹ therefore, their synthesis has been the focus of considerable attention.

In this sense, chiral non-racemic bicyclic lactams derived from β -amino alcohols are commonly considered useful starting materials for preparing these substituted piperidine drugs.² One of the most effective methodologies for the synthesis of these bicyclic lactams is *via* an aza-annulation of β -enaminoesters³ derived from suitable β -amino alcohols.⁴

We recently reported the preparation of new cyclic zwitterionic intermediates *via* an intramolecular non-classical Corey–Chaykovsky ring-closing reaction. Their utility was demonstrated by the synthesis of stereoisomers of σ^1 -receptor agonists trozamicol⁵ or the synthesis of (+)- and (–)-Geissman–Waiss lactone (Scheme 1).⁶

Considering this precedent and highlighting the utility of cyclic zwitterionic intermediates, we present a new versatile methodology to access new chiral zwitterionic non-racemic bicyclic lactams starting from acyclic β -aminoesters derived

from (*R*)-(-)-2-phenylglycinol and its utility in the diastereoselective synthesis of 2-substituted-4-hydroxy piperidines.

We commence our finding by synthesizing a set of β -enaminoesters coming from (*R*)-(-)-2-phenylglycinol, which were prepared following the traditional methodologies, directly condensation of chiral amine with β -dicarbonyl compound⁷ or by addition to a corresponding alkyne.⁸ All enamino esters were obtained as an inseparable *E* : *Z* isomeric mixture and, these results are summarized below (Fig. 1).

With a set of chiral β -enaminoesters in hand, next these compounds were condensed with bromo acetyl bromide,⁹ affording the desirable *N*-acyl oxazolidine with the formation of a new stereogenic center at the hemiaminal position in good to excellent diastereomeric ratio. The stereochemistry at the new stereogenic center of the major diastereoisomer was determined from its X-ray diffraction analysis of *N*-acyl oxazolidine **10** as (2*R*),¹⁰ therefore we assumed that this is the

Scheme 1 Previous reports in the synthesis and utility of chiral cyclic zwitterionic intermediates.

^aCentro de Químico Instituto de Ciencias, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla, Edif. IC-9 Complejo de Ciencias C.U., 72570 Puebla, Mexico. E-mail: joel.teran@correo.buap.mx

^bInstituto de Física, Benemérita Universidad Autónoma de Puebla, 11F2(aka 110-B), Lab. 102, C.U., 72570 Puebla, Mexico

† Electronic supplementary information (ESI) available. CCDC 2125364–2125371. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra09298g

Fig. 1 β -Enamino esters derived from (*R*)-(-)-2-phenylglycinol.

Scheme 2 Synthesis of *N*-acyl oxazolidines. ^a Only the major diastereoisomer is shown. ^b *N*-acyl oxazolidines **12** and **14** were probed to be unstable therefore were employed without purification for the next reaction.

stereochemistry of the major diastereoisomer of each *N*-acyl oxazolidine (Scheme 2).

Then, the diastereomeric mixture of **8** was selected as a model for preparing the desired zwitterionic chiral bicyclic lactam. To this end, **8** was treated with dimethyl sulfide in DCM,¹¹ delivering the corresponding sulfonium salt which was immediately subjected to the intramolecular non-classical Corey–Chaykovsky ring-closing reaction to avoid its conversion to the undesired thioether derivative.

Firstly, sulfonium salt was treated with KOH (2 equiv.) in a mixture of CH₃CN : MeOH (9 : 1).⁶ Unfortunately, a mixture of expected zwitterion **22(a+b)** and undesired pyridine-2-one **22c**, was obtained. Therefore, screening experiments were performed. Gratifyingly, when the base was changed by K₂CO₃, the diastereomeric mixture of zwitterionic bicyclic lactams was exclusively obtained. ¹H-NMR analysis of the crude reaction revealed the presence of a diastereomeric mixture of bicyclic zwitterionic intermediates in a 73 : 27 *dr*. Two hemiaminal protons were assigned as a doublet of doublets at 5.40 ppm and 5.12 ppm with coupling constants *J* = 9.8, 5.3 Hz for the minor diastereoisomer and *J* = 11.4, 4.2 Hz for the major diastereoisomer. The assignment was confirmed by a ¹H–¹H COSY experiment (Table 1).

The absolute configuration at the hemiaminal position of the zwitterionic bicyclic diastereomeric mixture was

Table 1 Screening studies for nonclassical Corey–Chaykovsky ring-closing reaction^a

Entry	Base	Global yield [ratio 22(a+b) ^b : 22c]
1	KOH (2.0 equiv.)	95% [76 : 24]
2	KOH (1.0 equiv.)	83% [82 : 18]
3	K ₂ CO ₃ (1.2 equiv.)	97% [100 : 0]

^a All reactions were performed in CH₃CN : MeOH (9 : 1), for 4 hours at room temperature. ^b **22(a+b)** was obtained in a 73 : 27 *dr*.

determined by its X-ray diffraction analysis. A single crystal was found to include two independent molecules in the asymmetric unit of a triclinic cell (space group *P*1 with *Z'* = 2), one of which presenting a disorder on the chiral center C8a. Combining these features results in a mixture of diastereoisomers with a ratio refined to 77.5/22.5%,¹² close to that determined by NMR in solution, 73/27%. The determination of the absolute configuration in this crystal structure allowed the assignment for the major diastereoisomer **22a** as (8*aR*) and the minor diastereoisomer **22b** as (8*aS*) (Fig. 2).

Once the optimal reaction conditions were established, the scope of our synthetic proposal was investigated. Chiral zwitterionic bicyclic intermediates containing alkyl or aryl substituents at the hemiaminal position were obtained in excellent chemical and stereochemical yields. Furthermore, the absolute configuration at the hemiaminal position was determined as (8*aR*) for the major diastereoisomer from the X-ray diffraction analysis of zwitterions **23a** and **24a** (Scheme 3).¹² In the case of **24a**, orthorhombic single crystals feature three independent molecules in the asymmetric unit (space group *P*2₁2₁2₁, *Z'* = 3), however, all display the same conformation and stereochemistry.

To demonstrate the utility of these new chiral zwitterionic bicyclic compounds, the diastereoselective synthesis of 4-hydroxy piperidines was developed and **23a** was selected as

Fig. 2 X-ray structure of the diastereomeric mixture of chiral zwitterionic bicyclic intermediates **22(a+b)**.

Scheme 3 Intramolecular non-classical Corey–Chaykovsky ring-closing reaction for the synthesis of chiral zwitterionic bicyclic intermediates.

a model, therefore this compound was subjected to a desulfurization process to access the corresponding oxazolo[3,2-*a*]pyridine-5,7(6*H*)-dione **29**. Catalytic hydrogenation was first attempted under various heterogeneous hydrogenation conditions. The use of Pd–C or RANEY®–Ni as a catalyst in acidic or neutral conditions led the oxazolo[3,2-*a*]pyridine-5,7(6*H*)-dione **29** in low chemical yield. The best result was obtained when reductive desulfurization was conducted using Zn (15 equiv.) in acetic acid, affording the compound **29** in 98% chemical yield

(Table 2, entry 8). In addition, compound **29** provided suitable crystals for X-ray crystallographic analysis confirming the presence of an oxazolo[3,2-*a*]pyridine-5,7(6*H*)-dione core and enabling the determination of the absolute configuration at the hemiaminal position as (8*aR*),¹² as in the starting material **23a**.

Next, compound **29** was subjected to ketone reduction with NaBH₄ (10 equiv.) in MeOH. The NMR spectrum of the crude reaction showed the presence of a diastereomeric mixture of 7-hydroxy oxazolo[3,2-*a*]pyridin-5-one **32(a+b)** in an 87 : 13 diastereomeric ratio. Once the diastereomeric mixture was separated, the major diastereoisomer **32a** crystallized, determining the new stereogenic center bearing the hydroxy group as (7*R*).¹² The asymmetric unit of **32a** contains two independent molecules (space group *P*₂₁, *Z'* = 2), both with the same geometry. The diastereoselectivity observed could be explained by the addition of the hydride reagent from the less hindered face, opposite to the methyl group (Scheme 4). After, reduction of the amide and hemiaminal functions of alcohol **32a** was performed with BH₃·DMS reagent, affording the 2,4-*cis*-2-methyl-4-hydroxy

Scheme 4 Synthesis of (2*S*,4*S*)-2-methylpiperidin-4-ol **35** and hydrochloride salt of (2*R*,4*R*,6*S*)-4-hydroxy-6-methylpiperidine-2-carboxylic acid **38**.¹⁴

Table 2 Screening experiments for desulfurization of zwitterion **23a**^a

Entry	Catalyst (mol%)	Solvent	Temp	Time	Product	Yield (%)
1	Pd/C (10% mol)	EtOH	rt	16 h	29	Traces
2	Pd/C (10% mol)	EtOH	Reflux	16 h	29	Traces
3	Pd/C (10% mol)	EtOH	Reflux	4 h	29 : 30 : 31	38 : 40 : 13
4	RANEY®–Ni	THF : H ₂ O (8 : 2)	rt	8 h	29	6
5	RANEY®–Ni	Acetone	rt	14 h	29	19
6	RANEY®–Ni	EtOH	–10 °C to rt	8 h	29	13
7	RANEY®–Ni	Toluene	Reflux	8 h	31	38
8	Zn (15 equiv.)	AcOH	rt	7 days	29	98

^a Ammonium formate was used as a hydrogen source.

piperidine **33a** as a major diastereoisomer for which the absolute configuration was unambiguously established by X-ray analysis.¹² Indeed, the methyl and hydroxyl substituents are arranged *cis* in the piperidine ring.

Finally, complete synthesis of *cis*-4-hydroxy-2-methyl piperidine was accomplished by a simple debenzoylation *N*-Boc protection reaction, followed by an acidic treatment to get **35** in quantitative yield. On the other hand, the synthesis of pipecolic acid derivative **38** was obtained through a 3-steps sequence reaction starting from intermediate **34**, which involved silyl protection of the hydroxyl function followed by a diastereoselective deprotonation-electrophilic quenching endocyclic carbonylation process to access at the pipecolic acid analog **38**. The absolute stereochemistry was assigned *via* the X-ray diffraction analysis of the corresponding hydrochloride salt. This compound crystallizes as a monohydrate, and the configuration (*2R, 4R, 6S*)¹² is consistent with the refinement of a Flack parameter, $x = 0.06(5)$ ¹³ (Scheme 4).

Conclusions

In summary, we have developed a new concise high diastereoselective strategy route to access new zwitterionic bicyclic oxazolo intermediates starting from chiral β -enaminoesters derived from (*R*)-(-)-2-phenylglycinol. In addition, the utility of these new intermediates was also demonstrated in a short diastereoselective synthesis of (*2S,4S*)-2-methylpiperidin-4-ol and hydrochloride salt of (*2R,4R,6S*)-4-hydroxy-6-methylpiperidine-2-carboxylic acid. Applying this methodology to the synthesis of more complex pipecolic acids products is currently underway in our laboratory, and the results of these efforts will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to CONACyT (Project A1-S-13280 and 268178) and VIEP-BUAP (Project 100148077-VIEP2021) for financial support. ERB thanks to CONACyT for the scholarship (658611). We thank A. L. García-Torres for HRMS spectrometry analyses.

Notes and references

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- 2 L. F. Roa, D. Gnecco, A. Galindo and J. L. Terán, *Tetrahedron: Asymmetry*, 2004, **15**, 3393; L. F. Roa, D. Gnecco, A. Galindo, J. L. Terán and S. Bernès, *Tetrahedron: Asymmetry*, 2004, **15**, 847; V. Semak, C. Escolano, C. Arróniz, J. Bosch and M. Amat, *Tetrahedron: Asymmetry*, 2010, **21**, 2542; M. Amat, C. Escolano, N. Llor, M. Huguet, M. Pérez and J. Bosch, *Tetrahedron: Asymmetry*, 2003, **14**, 1679; M. Amat, M. Cantó, N. Llor and J. Bosch, *Chem. Commun.*, 2002, 526; M. D. Groaning and A. I. Meyers, *Tetrahedron*, 2000, **56**, 9843.
- 3 C. Cavé, V. Daley and J. d'Angelo, *Tetrahedron: Asymmetry*, 1995, **6**, 79; H. M. C. Ferraz, E. O. Oliveira, M. E. Payret-Arrua and C. A. Brandt, *J. Org. Chem.*, 1995, **60**, 7357; C. J. Valduga, H. S. Braibante and E. F. J. Braibante, *J. Heterocycl. Chem.*, 1998, **35**, 189; A. Amougay, O. Letsh and J. P. Pete, *Tetrahedron*, 1996, **52**, 2405; C. Cimarelli and G. Palmieri, *J. Org. Chem.*, 1996, **61**, 5557; S. Ali and A. T. Khan, *Tetrahedron Lett.*, 2013, **54**, 436.
- 4 P. W. Hickmott and G. Sheppard, *J. Chem. Soc. C*, 1971, 1358; P. W. Hickmott and G. Sheppard, *J. Chem. Soc. C*, 1971, 2112; C. Agami, L. Dechoux and S. Hebbe, *Tetrahedron Lett.*, 2003, **44**, 5311; C. Agami, L. Dechoux, C. Ménard and S. Hebbe, *J. Org. Chem.*, 2002, **67**, 7573; C. Agami, L. Dechoux, S. Hebbe and C. Ménard, *Tetrahedron*, 2004, **60**, 5433.
- 5 R. López-González, A. Zarate, D. M. Aparicio, A. Mendoza, D. Gnecco, J. R. Juárez, N. Romero-Ceronio, L. Orea and J. L. Terán, *Tetrahedron Lett.*, 2016, **57**, 1683.
- 6 R. López-González, D. Gnecco, J. R. Juárez, V. Gómez-Calvario, S. Bernès, D. M. Aparicio and J. L. Terán, *Tetrahedron Lett.*, 2020, **61**, 151697.
- 7 D. F. Martin, G. A. Janusonis and B. B. Martín, *J. Am. Chem. Soc.*, 1961, **83**, 73; B. Rechsteiner, F. Teixier-Boullet and J. Hamelin, *Tetrahedron Lett.*, 1993, **34**, 5071; A. Arcadi, G. Bianchi, S. Di Giuseppe and F. Marinelli, *Green Chem.*, 2003, **5**, 64; A. R. Khosropour, M. Khodaei and M. Kookhazadeh, *Tetrahedron Lett.*, 2004, **45**, 1725; Z. H. Zhang, L. Yin and Y. M. Want, *Adv. Synth. Catal.*, 2006, **348**, 184; R. Dalpozzo, A. Deino, M. Nardi, B. Russo and A. Procopio, *Synthesis*, 2006, 1127; J. Lin and L. F. Shang, *Monatsh. Chem.*, 2007, **138**, 77; F. Epofano, S. Genovese and M. Curini, *Tetrahedron Lett.*, 2007, **48**, 2717.
- 8 B. J. Turunen and G. I. Georg, *J. Am. Chem. Soc.*, 2006, **128**, 8702; N. Panda and R. Mothkuri, *J. Org. Chem.*, 2012, **77**, 9407; H. Pilotzi, D. Gnecco, M. L. Orea, J. R. Juárez, D. M. Aparicio and J. L. Terán, *Heterocycles*, 2018, **96**, 895.
- 9 D. M. Aparicio, D. Gnecco, J. R. Juárez, M. L. Orea, N. Waksman, R. Salazar, M. Flores-Alamo and J. L. Terán, *Tetrahedron*, 2012, **68**, 10252.
- 10 CCDC: 2125364 (**10**), contain the ESI crystallographic data for this paper.†
- 11 D. M. Aparicio, J. L. Terán, D. Gnecco, A. Galindo, J. R. Juárez, M. L. Orea and A. Mendoza, *Tetrahedron: Asymmetry*, 2009, **20**, 2764.
- 12 CCDC: 2125365 (**22(a+b)**), 2125366 (**23a**), 2125367 (**24a**), 2125368 (**29**), 2125369 (**32a**), 2125370 (**33a**), 2125371 (**38**) contain the ESI†
- 13 H. D. Flack and G. Bernardinelli, *Acta Crystallogr. Sect. A*, 1999, **55**, 908.
- 14 In this article, Authors reported the corresponding pipecolic acid enantiomer: L. S. Fowler, L. H. Thomas, D. Ellis and A. Sutherland, *Chem. Commun.*, 2011, **47**, 6569.