Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c9ob02084e

Stereoselective Michael additions on α-aminoacrylates as the key step to an L-Oic analogue bearing a quaternary stereocenter†

Federico Maria Cecchinelli,[a] Giuseppe Celentano,[a] Alessandra Puglisi [b] and Nicoletta Gaggero *[a]

Received 25th September 2019,
Accepted 13th December 2019

DOI: 10.1039/c9ob02084e

rsc.li/obc

A novel, highly stereoselective route for pharmaceutically relevant octahydroindole-2-carboxylates bearing a quaternary stereocenter has been developed. The key chiral intermediates 3 have been prepared in good yields and enantiomeric excesses up to 98%. A broad substrate range has been tolerated under the reaction conditions.

Peptides present high potentiality for the development of new drugs.[1,2] However, the major disadvantages of practical application in medicine of bioactive peptides are low bioavailability, poor metabolic stability and intrinsic flexibility. Thus, the active sequence must be constrained in a defined conformation, in order to achieve the desired activity and selectivity. Proline residues, due to their unique conformational properties and limited ability to establish hydrogen bonds, do not occur in regular α-helices or β-sheet structures. Rather, they play a specific structural role as N-terminal caps to α-helices, as helix termination signals, or as corner residues in β-turn sequences. Most notably, however, prolines are key players in many biologically essential processes, such as protein folding, signal transduction, protein–protein recognition, or receptor–ligand binding of Pro-containing peptides.[3] The peculiar conformational features of proline have made it a major target for potential molecular engineering modifications, since its inner constitutional restrictions aid limiting low energy accessible conformations, helping biasing the conformational freedom of the peptide in which this residue is included. In the search for more potent and selective drugs, the design of constrained analogues of chemical leads has been a classical approach. To reach this goal a first method consists in introducing a second cycle on the parent structure to reduce its conformational mobility and adjust the substituent's orientation. A particularly attractive proline analogue is octahydroindole-2-carboxylic acid (Oic). The fused bicyclic structure of Oic secures conformational rigidity and increased lipophilicity as compared with proline.[4] The most studied stereoisomer of Oic is the one with (2*S*,3a*S*,7a*S*) absolute configuration, known as L-Oic (Fig. 1), which is also the only commercially available stereoisomer. The methodologies for the preparation of enantiopure L-Oic take advantage both from stereoselective synthesis and chemical, chromatographic and enzymatic resolutions.[5] Derivatives containing the L-Oic scaffold have numerous pharmacological proprieties. Among the more relevant applications, it has been used in several bradykinin B2 receptor antagonists and prolyl oligopeptidase (POP) inhibitors. L-Oic is also a key intermediate in the synthesis of angiotensin-converting enzyme (ACE) inhibitors for the treatment of hypertension, *e.g.* Perindopril.

The lack of synthetic procedures for the synthesis of the other Oic stereoisomers has hampered the investigations on their pharmacological properties to date.

Another method to reduce conformational flexibility aims at building quaternary centers to afford C-branched derivatives featuring an additional substituent.[6] Molecules containing quaternary stereocenters play a key role and many biologically active molecules occurring in nature share this structural feature. The construction of quaternary stereocenters *via* chemical synthesis is extremely challenging. Until now, within the top 200 drug in US only 12 contain a tetrasubstituted stereocenter (6%) and none of them has been built by chemi-

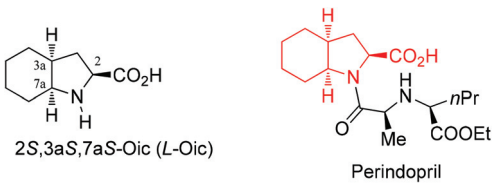
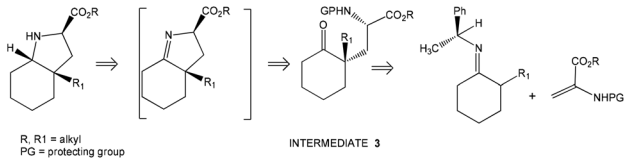


Fig. 1 (L)-Oic and (L)-Oic scaffold containing Perindopril.

[a]*Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, via Venezian 21, 20133-Milano, Italy. E-mail: nicoletta.gaggero@unimi.it*

[b]*Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19-20133, Milano*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ob02084e



Scheme 1 Retrosynthetic strategy.

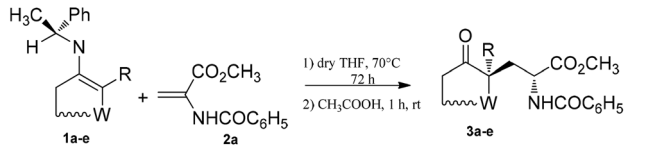
cal synthesis but results from derivatization of natural substrates already bearing the tetrasubstituted stereocenter in the correct absolute configuration.[7] Cativiela has reported the synthesis of an Oic analogue bearing a quaternary stereocenter in the α-position to the carboxylic group.[8] Recently, a stereoselective Lewis base (LB)-catalyzed dual umpolung domino Michael reaction between cyclohexadienones and alkynyl esters has been developed. Triphenylphosphine (PPh_3), as a LB catalyst, afforded the hydroindole-2-carboxylate scaffold as a single diastereoisomer in moderate yield. The intermediate could be easily transformed to a (2*R*,3a*S*,7a*S*)-methyl 7a-methyloctahydroindole-2-carboxylate.[9]

The aim of our work has been the synthesis of a proline derivative which contains both the octahydroindolic constrained bicyclic scaffold and a quaternary stereocenter at the 3a position of the fused bicyclic skeleton. We envisaged the possibility of stereoselectively access highly functionalized propanoates **3** as the key intermediates of our synthetic route. The following deprotection of the amino functionality, its intramolecular cyclization to the corresponding imine, followed by hydrogenation of the C=N bond would lead to an Oic derivative bearing a quaternary stereocenter in 3a position (Scheme 1).

The synthesis of the enantiomerically enriched *N*-protected 3-(1-substituted-2-oxocyclohexyl)-2-amino propanoates **3** was performed *via* the stereoselective alkylation of racemic 2-monosubstituted cycloalkanones, first reported by d'Angelo *et al.*[10] This methodology has emerged as a powerful tool for the stereoselective construction of quaternary carbon atoms with excellent enantiomeric excesses. It involves a Michael-type addition of electrophilic olefins and chiral ketimines derived from enantiopure α-phenylethylamine reacting in their secondary enamine tautomeric forms at the most substituted α-carbon atom. When α-substituted Michael acceptors are used, a largely prevailing diastereoisomer is obtained, thereby allowing the simultaneous, complete stereo-control of both new stereocenters formed.[11–15] Notheworthy, a patent by Sanofi-Aventis reported an application of the d'Angelo strategy to prepare another ACE inhibitor known as Ramipril.[16]

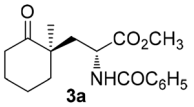
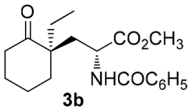
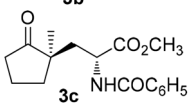
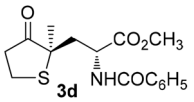
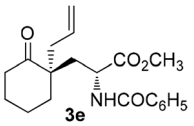
The first attempt has been performed at neutral conditions between the crude ketimine **(*S*)-1a** obtained by the condensation of 2-methylcyclohexanone and (*S*)-α-phenylethylamine‡ with the potentially competent electrophile, methyl 2-benzamido acrylate[17] **2a** for 72 h in THF at 66 °C in presence of hydroquinone (few mg) to prevent acrylate§ polymerization under the reaction conditions (scheme in Table 1).

Table 1 Michael addition between chiral imines **1a–1e** and methyl 2-benzamido acrylate **2a**



1a, R = Me, W = $(CH_2)_2$
1b, R = Et, W = $(CH_2)_2$
1c, R = Me, W = CH_2
1d, R = Me, W = S
1e, R = CH_2-CH=CH_2, W = $(CH_2)_2$

3a R = Me, W = $(CH_2)_2$
3b R = Et, W = $(CH_2)_2$
3c R = Me, W = CH_2
3d R = Me, W = S
3e R = CH_2-CH=CH_2, W = $(CH_2)_2$

Entry	Ketimine	Michael adduct	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1a**	 **3a**	90	>98 : 2	95
2	**1b**	 **3b**	90	95 : 5	98
3	**1c**	 **3c**	95	>98 : 2	98
4	**1d**	 **3d**	93	>98 : 2	98
5	**1e**	 **3e**	80	85 : 15	96

[a] Isolated yield after chromatographic purification. [b] Determined by ^{1}H-NMR on the crude. [c] Determined by HPLC on chiral stationary phase.

With this optimal result in our hands, the reaction scope has been investigated on a series of 2-substituted cyclanones with five or six carbon atoms (Table 1, entries 1–5). The reac-

‡ The condensation of the cyclanones with optically pure or racemic α-phenylethylamine was typically performed in refluxing toluene for 24 h in the presence of 4 Å molecular sieves. The conversion was evaluated by ^{1}H-NMR and the imine was used without further purification.

§ Acrylates can be stored at −18° C without degradation for about one month.

¶ It was possible to quantitatively recover the optically pure (*S*)-α-phenylethylamine after neutralization of the aqueous medium and extraction after hydrolysis of crude Michael adduct.

‖ The attempt to carry out the Michael reaction under organocatalytic conditions according to the procedure of Carter *et al.*[19] gave poor yield and incomplete diastereoselection probably due to the presence of two groups with similar steric and electronic features in the α position of acrylate.

tion proved to be very efficient, leading to high yields and enantiomeric excess over a broad substrate range. Sulfur functionalized 2-methyltetrahydrothiophen-3-one afforded the corresponding adduct in excellent yield and ee (Table 1, entry 4). 3-Allylcyclohexanone led to the corresponding product in 80% yield and 96% ee (Table 1, entry 5). In the examined cases, one single diastereoisomer was detected, except with 2-ethylcyclohexanone (Table 1, entry 2) and 2-allylcyclohexanone (Table 1, entry 5) where measurable amounts of a second diastereoisomer were detected.

We then examined the reaction's tolerance to the acrylate coupling partner in view of further synthetic elaboration of the product. *N*-Boc and *N*-Cbz protected methyl 2-aminoacrylates were unreactive with the ketimine of 2-methyl cyclohexanone (***S*)-1a**, under the usual experimental conditions, also for longer reaction times.

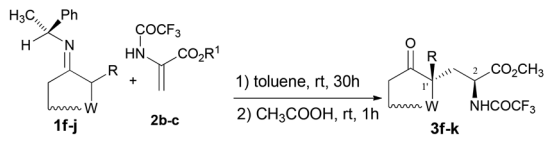
On the other hand, methyl 2-(2,2,2-trifluoroacetamido) acrylate **2b** smoothly reacted with **(*R*)-1f** affording the Michael adduct **3f** in 80% yield and 94% ee after 30 h in toluene at room temperature (Table 2, entry 1). Indeed, the use of **2b** appears as a significant improvement if compared with **2a**, allowing to carry out the reactions at room temperature for a shorter time, affording the corresponding products in high yields and enantiomeric excesses. Hence, a new set of experiments was explored employing **2b** with the ketimines derived from different 2-substituted cyclanones (Table 2, entries 2–5). Also in this new series of experiments the length of the alkyl chain in α position to the carbonyl group of five or six membered cyclanones did not modify the outcome of the reaction (Table 2, entries 1, 5 and 2, 3). The more sterically demanding methylthio substituent was well tolerated (Table 2, entry 4). Moreover, under these milder conditions, in all cases only one diastereoisomer was obtained. At last, benzyl 2-(2,2,2-trifluoroacetamido) acrylate **2c** was synthesized and tested using **(*S*)-1a** as nucleophilic partner according to the new conditions, affording **3k** in 90% yield and 96% ee (Table 2, entry 6).

Having demonstrated the feasibility of the methodology for the stereoselective synthesis of propanoates **3**, we attempted to synthesize an Oic analogue by further modification of adduct **3f**. The overall synthesis is illustrated in Scheme 2. Michael adduct **3f** was subjected to acidic hydrolysis (stoichiometric *p*-toluenesulfonic acid, PTSA, 65 °C, methanol, 24 h) followed by hydrogenation reaction. We preferred acidic removal of trifluoroacetyl group with respect to basic hydrolysis to prevent the possibility of racemization of the stereocenter in a position to the protected amino group. Moreover, this methodology preserved the methylester. The deprotection step directly afforded imine **4** after intramolecular *in situ* condensation of the free amino group with the carbonyl functionality. Hydrogenation of the crude reaction mixture using 10% palladium–carbon as a catalyst, at 40 °C, for 24 hours, under 15 bar of H_2 in a Parr® system quantitatively afforded bicycle **5** as *p*-toluene sulfonate salt. A first attempt of performing hydrogenolysis of compound **4** at room temperature and atmospheric pressure required much longer reaction time (72 h).

In order to evaluate the enantiomeric excess of the final product we converted amine **5** into its 2-bromo-benzenesulfonic amide **6**. HPLC on chiral stationary phase revealed an enantiomeric excess ≥98%.

It is worth mentioning that the use of *para*-toluenesulfonic acid and methanol as the solvent in the deprotection step is more convenient if compared to the aqueous hydrolysis with hydrochloric acid at 100 °C necessary for the benzamide func-

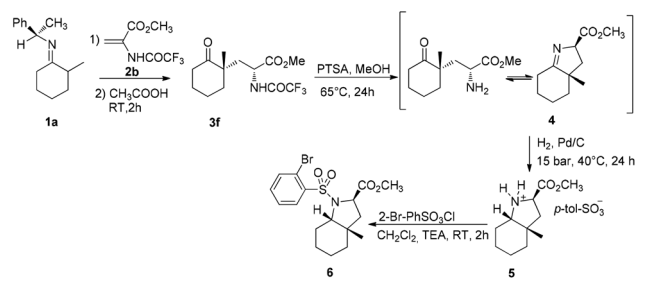
Table 2 Michael reactions using 2-(2,2,2-trifluoroacetamido) acrylates **2b–2c**



1f, R = Me, W = $(CH_2)_2$ **2b**, R^1 = CH_3 **3f**, R = CH_3, W = $(CH_2)_2$, R^1 = CH_3
1g, R = Et, W = $(CH_2)_2$ **2c**, R^1 = Bn **3g**, R = C_2H_5, W = $(CH_2)_2$, R^1 = CH_3
1h, R = Me, W = CH_2 **3h**, R = CH_3, W = CH_2, R^1 = CH_3
1i, R = S-Me, W = $(CH_2)_2$ **3i**, R = S-CH_3, W = $(CH_2)_2$, R^1 = CH_3
1j, R = CH_2-CH=CH_2, W = $(CH_2)_2$ **3j**, R = CH_2-CH=CH_2, W = $(CH_2)_2$, R^1 = CH_3
3k R = CH_3, W = $(CH_2)_2$, R^1 = Bn

Entry	Ketimine	Acrylate	Michael adduct	Yield[a] (%)	ee[b] (%)
1	**1f**	**2b**	**3f**	80	94
2	**1g**	**2b**	**3g**	68	97
3	**1h**	**2b**	**3h**	52	94
4	**1i**	**2b**	**3i**	80	97
5	**1j**	**2b**	**3j**	75	97
6[c]	**1a**	**2c**	**3k**	90	96

[a] Isolated yield after chromatographic purification. [b] Determined by HPLC on chiral stationary phase. [c] (*S*)-Phenylethylamine was used.



Scheme 2 Synthetic sequence for the preparation of 2(*R*),3a(*S*),7a(*S*)-**5**.

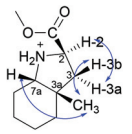


Fig. 2 Some selected NOE correlations for **5**.

tionality hydrolysis of **3a**.** It allowed milder reaction conditions and the possibility of performing the hydrogenation step on a crude material in methanol avoiding a partial hydrolysis of the ester moiety, which affords a mixture of **5** and the product with the free carboxylic acid. Moreover, the presence of *para*-toluenesulfonic acid in the crude mixture, allowed to isolate compound **5** as its sulfonate salt by precipitation after concentrating the solution. Compound **5** was obtained after a 4-step reaction sequence with one chromatography purification only, in 40% yield.

The relative stereochemistry of **5** was determined by analysis of NOESY spectroscopic data, assuming the absolute configuration of **3f** as determined by d'Angelo experiments (Fig. 2).[11–15] A nOe correlation between methyl 3a and H-7a and a nOe correlation between methyl 3a and H-3b are suggestive of their close spatial proximity, indicating that they are located on the same side of the ring. The spectrum shows the absence of a measurable nOe correlation between methyl 3a and protons H-3a and H-2.

We also observed other nOe correlations: between H-2 and H-3a, between H-3b and H-7a and between O–CH_3 and H-3b. These correlations confirmed the *trans* relationship between H-2 and methyl 7a on the octahydroindole skeleton.[18]

Conclusions

In conclusion, the method described in this work offers a novel, concise, efficient and broadly applicable synthesis of bicyclic derivatives of proline in excellent optical purity and high chemical yields. With respect to the methods reported in the literature, this route has the advantage of a great versatility as regards both the nature of the substituents on the quaternary stereocenter and the fused ring size by an appropriate choice of the starting ketone. Moreover, the procedure is operationally simple, the reactions are carried out at moderate temperature, neutral conditions and only the Michael adduct **3** needs isolation and chromatographic purification, all the other intermediates being used *in situ*. Although the cheap, commercially available, optically pure PEA needs to be used in stoichiometric amount, it can be recovered and recycled in subsequent reactions. With this methodology it is possible to prepare both the enantiomers of the final product, since both (*R*) and (*S*) α-phenylethylamine are commercially available at modest price.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 K. Fosgerau and T. Hoffmann, *Drug Discovery Today*, 2015, **20**, 122–128.
2 J. L. Lau and M. K. Dunn, *Bioorg. Med. Chem.*, 2018, **26**, 2700–2707.
3 G. Tuchscherer and M. Mutter, *Chimia*, 2001, **55**, 306–313.
4 V. Kubyshkin and N. Budisa, *Org. Biomol. Chem.*, 2017, **15**, 619–627.
5 F. J. Sayago, P. Laborda, M. I. Calaza, A. I. Jiménez and C. Cativiela, *Eur. J. Org. Chem.*, 2011, 2011–2028.
6 J. Blesl, M. Trobe, F. Anderl, R. Breinbauer, G. A. Strohmeier and K. Fesko, *ChemCatChem*, 2018, **10**, 3453–3458.
7 M. Bartholow, *Pharmatimes*, 2012, 48–51.
8 F. J. Sayago, P. Laborda, M. I. Calaza, A. I. Jiménez and C. Cativiela, *Tetrahedron*, 2008, **64**, 84–91.
9 K. Kishi, S. Takizawa and H. Sasai, *ACS Catal.*, 2018, **8**, 5228–5232.
10 M. Pfau, G. Revial, A. Guingant and J. d'Angelo, *J. Am. Chem. Soc.*, 1985, **107**, 273–274.
11 J. d'Angelo, C. Cavé, D. Desmaele, A. Gassama, C. Thominiaux and C. Riche, *Heterocycles*, 1998, **47**, 725–746.
12 C. Cavé, D. Desmaele, J. d'Angelo, C. Riche and A. Chiaroni, *J. Org. Chem.*, 1996, **61**, 4361–4368.
13 I. Jabin, G. Revial, A. Tomas, P. Lemoine and M. Pfau, *Tetrahedron: Asymmetry*, 1995, **6**, 1795–1812.
14 J. d'Angelo, D. Desmaele, F. Dumas and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459–505.
15 D. Desmaele, S. Delarue-Cochin, C. Cavè, J. d'Angelo and G. Morgant, *Org. Lett.*, 2004, **14**, 2421–2424.
16 G. Kretzschmar, J. Oehme and K. Rossen, *PCT Int. Appl*, WO2015189108A12015151217, 2015.
17 J. G. Pierce, D. Kasi, M. Fushimi, A. Cuzzupe and P. Wipf, *J. Org. Chem.*, 2008, **73**, 7807–7810.
18 For proton assignement see ESI.†
19 J. Y. Kang and R. G. Carter, *Org. Lett.*, 2012, **14**, 3178–3181.

The hydrolysis/cyclization reaction of **3a has been performed in HCl 6N, at 100 °C for 24 h.

