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Syntheses and transformations of alicyclic β-aminohydroxamic acids

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A. INTRODUCTION AND AIMS

Hydroxamic acid moiety occurs in several pharmaceutically relevant natural and synthetic compounds. One of the most well-known is Desferrioxamine B which is a hydroxamate-type siderophore used in the treatment of iron-overload. Synthetic hydroxamic acids can be useful as well in several diseases e.g. ciclopirox is a topical antifungal drug, while vorinostat is found to be effective in cutaneous T-cell lymphoma. Due to the valuable and various biological properties the synthesis of hydroxamic acids got serious attention recently.

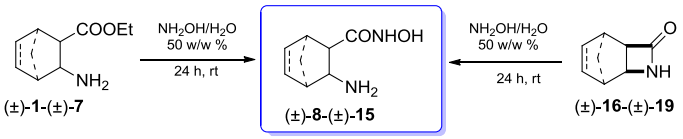
In view of the growing importance of hydroxamic acid derivatives, my PhD work had the major aim of developing simple route for the preparation of new alicyclic β-aminohydroxamic acids. We achieved the syntheses of new racemic and enatiomeric form of *cis*- and *trans*-2-aminocyclohexane-hydroxamic acids and *cis*- and *trans*-2-aminocyclohex-4-ene-hydroxamic acids and *diendo*- and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-hydroxamic acids and *diendo*- and *diexo*-3-aminobicyclo[2.2.1]heptane-2-hydroxamic acids starting from the appropriate esters or lactams. We also studied the diastereoselectivity of the domino ring-closure reaction of *diendo*- and *diexo*-2-aminonorbornenehydroxamic acids with oxocarboxylic acids, to examine the RDA reaction of the formed isoindolo-[2,1-*a*]quinazolinones and pyrrolo[1,2-a]quinazolines and to extend this methodology to obtain novel racemic and enantiomeric pyrrolo[1,2-*a*]pyrimidine and pyrimido[2,1-*a*]isoindole derivatives.

The stereochemistry of the synthesized racemic and enantiopure compounds was proved by NMR spectroscopy and X-ray crystallography. The enantiopurity of the final products were determined by and HPLC.

B. RESULTS AND DISCUSSION

I. Synthesis of new alicyclic β-aminohydroxamic acids

Simple and efficient routes have been developed for the preparation of new racemic and enantiomeric *cis*- and *trans*- cyclohexene-, cyclohexane-, *diendo*- and *diexo*- norbornene- and norbornane-β-aminohydroxamic acids. The racemic 2-aminohydroxamic acids (±)-**8**-(±)-**15** were successfully synthesized starting from appropriate esters (±)-**1**-(±)-**8** or lactams (±)-**16**-(±)-**19** treated with 3 equivalent of commercially available 50 w/w % aqueous hydroxylamine solution at room temperature (**Scheme 1**).



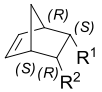
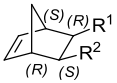
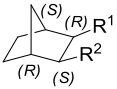
Scheme 1

The optically enriched hydroxamic acids (−)-**8**, (+)-**9**, (−)-**10**, (+)-**11**, (+)-**12**, (−)-**12**, (+)-**14**, (−)-**14**, (+)-**15** and (−)-**15** were also successfully prepared by the synthetic methods mentioned above, starting from enantiomeric amino esters. The starting amino ester enantiomers were synthesized from racemic ester by resolution via diastereomeric salt formation with commercially available resolution agents (mandelic acid, DBTA, DPTTA). The absolute configurations of ester enantiomers (−)-**1**, (−)-**2**, (−)-**3**, (−)-**4**, (+)-**6** and (−)-**6** were determined via comparing the measured optical rotations with literature data. For determination of the absolute configuration, ester base (+)-**5** was transformed into urea compound by reacting with (*S*)-(–)-α-methylbenzyl isocyanate and the crystalline product was examined by

X-ray crystallography. The *ee* values of the ester enantiomers were determined via HPLC and GC measurements. The diastereomeric salts were liberated to free ester bases and treated with 50 w/w % aqueous hydroxylamine solution and produced

enantiomerically enriched hydroxamic acids. Enantiomeric hydroxamic acids (+)-**13** and (−)-**13** were prepared from enantiomers of *diendo*-3-amino-N-hydroxybicyclo[2.2.1]hept-5-ene carboxamide (+)-**12** and (−)-**12** by catalytic (Pd/C) hydrogenation in Winci autoclave at 60 °C under 50 bar pressure. The structure of synthesized enantiomerically enriched esters and aminohydroxamic acids is summerized in **Table 1**.

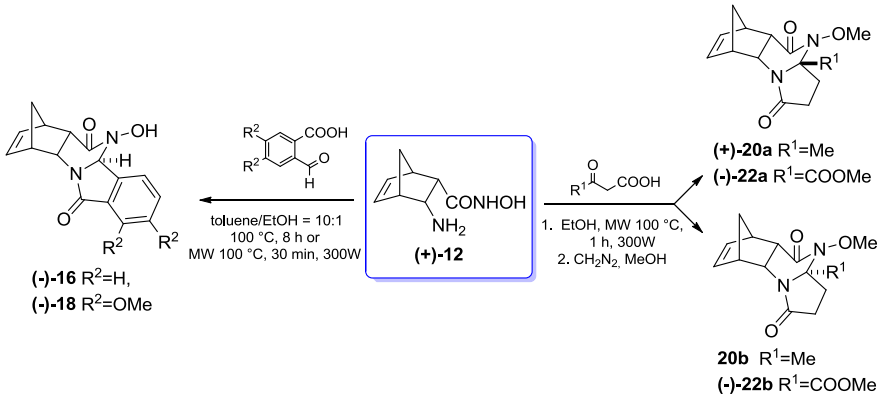
Table 1. Numbering and structure of enantiomeric esters and hydroxamic acids

Structure	**Ester** R^1= COOEt, R^2=NH_2	**Hydroxamic acids** R^1= COOEt, R^2=NH_2
	(−)-**1**	(−)-**8**
	(−)-**2**	(+)-**9**
	(−)-**3**	(−)-**10**
	(−)-**4**	(+)-**11**
	(−)-**5**	(+)-**12**
	-	(+)-**13**
	(−)-**6**	(+)-**14**
	(−)-**7**	(+)-**15**

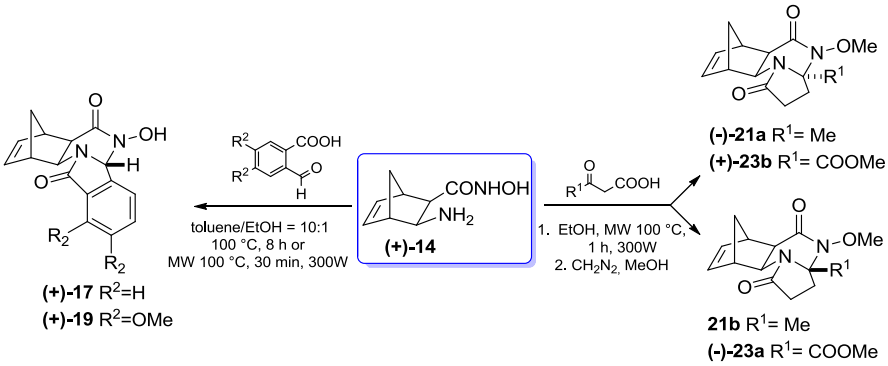
II. Domino reaction of *diendo*-and *diexo*-norbornene hydroxamic acids

For the study of the reactivity and selectivity of the domino ring-closure reaction of alicyclic hydroxamic acid with oxocarboxylic acids to form new isoindolo-[2,1-a]quinazolines and methanopyrrolo[1,2-*a*]quinazolines, *diendo*- and *diexo*-3-amino-*N*-hydroxybicyclo[2.2.1]hept-5-ene-carboxamide ((±)-**12** and (±)-**14**) were chosen as model compounds. The reactions were first carried out with racemic compounds then extended to enantiomeric hydroxamic acids as well.

2-Formylbenzoic acid or 6-formyl-2,3-dimethoxybenzoic acid along with *diendo*-hydroxamic acid (+)-**12** and *diexo*-hydroxamic acid (+)-**14** were heated at reflux in a mixture of ethanol and toluene in the presence of *p*-toluenesulfonic acid (*p*TsA) for 8 h. Alternatively, the reaction mixture was stirred at 100 °C for 30 min under microwave irradiation (max. 300 W). In all cases, the ^{1}H NMR spectra revealed the formation of the single epimers of isoindolo[2,1-*a*]quinazoline (−)-**16**, (+)-**17**, (−)-**18** and (+)-**19**. In similar conditions a ring closure reaction with levulinic acid and α-ketoglutaric acid resulted in two epimers of methanopyrrolo[2,1-*a*]quinazolines which could be easily separated by column chromatography after derivatization with diazomethane and produced pyrrolo[1,2-*a*]quinazolines (+)-**20a**, **20b**, (−)-**21a**, **21b**, (−)-**22a**, (−)-**22b**, (−)-**23a** and (+)-**23b** (**Schemes 2** and **3**). The stereoselectivity of the ring closures was detected by ^{1}H-NMR spectroscopy. Relative configurations of the newly built stereogenic centre elucidated via X-ray crystallography or 2D-NMR spectroscopy (depending on the characteristic NOE crosspeaks).



Scheme 2

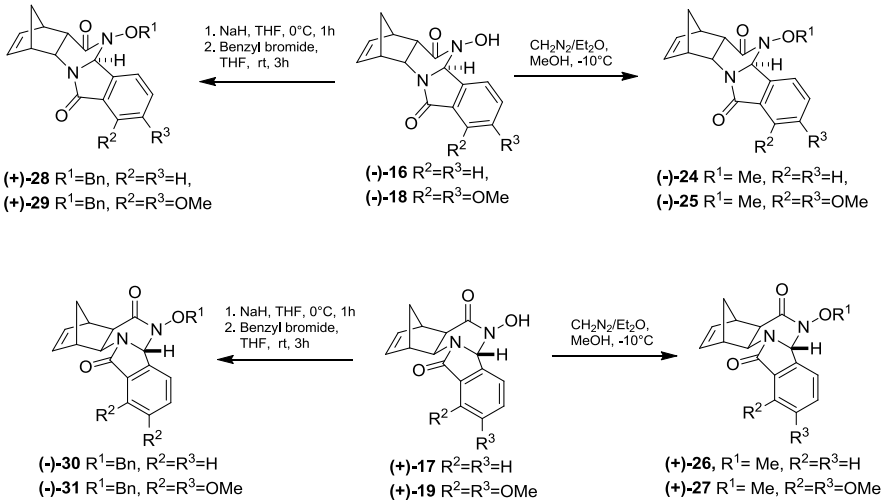


Scheme 3

III. Retro Diels–Alder reactions of cyclic compounds

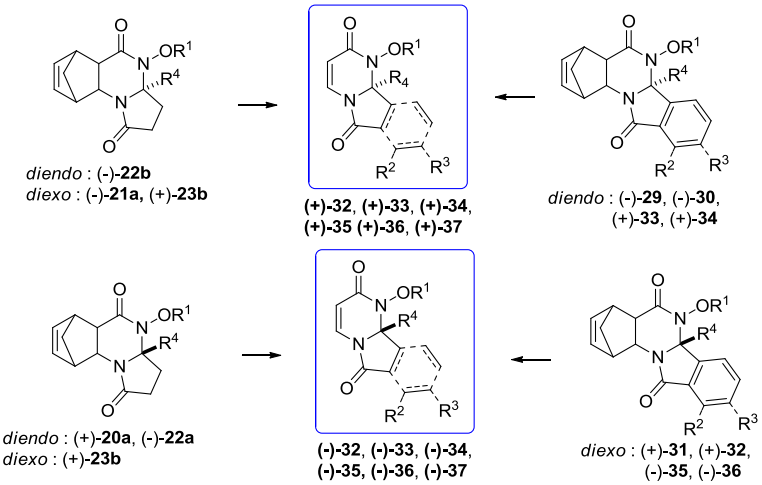
The RDA reactions were performed with racemic compounds then extended to enantiomeric derivatives. Various conditions for the retro Diels–Alder reaction of domino products (±)-**16**-(±)-**23** were applied such as heating melt phase or under microwave irradiation in different solvents (toluene, *N*,*N*-dimethylformamide, dioxane, 1,2-dichlorobenzene), but conversions were not complete.

In order to obtain more hydrophobic compounds, *O*-methyl (−)-**24**, (−)-**25**, (+)-**26** and (+)-**27** and *O*-benzyl (+)-**28**, (+)-**29**, (−)-**30** and (−)-**31** derivatives were synthesized from isoindolo[2,1-*a*]quinazolinones. Firstly (−)-**16**, (+)-**17**, (−)-**18** and (+)-**19** were dissolved in MeOH and next a solution of diazomethane in Et_2O was added dropwise and the reaction mixture was stirred for 20–30 min until no starting material could be observed by TLC. After evaporation the residues were purified by column chromatography. Products (−)-**24**, (−)-**25**, (+)-**26** and (+)-**27** were crystallized from *i*Pr_2O. Secondly (−)-**16**, (+)-**17**, (−)-**18** and (+)-**19** were dissolved in anhydrous THF then NaH in anhydrous THF were added to the solutions at 0 °C. Reaction mixtures were stirred for 2 hours at 0 °C. After that benzyl-bromide was added and stirred for 1 h at ambient temperature. When the reactions were complete, a few drops water were added to mixture to decompose the excess of NaH and solvents were evaporated. Ice-cold water was poured to the residues and followed that it were extracted with chloroform. After evaporation and purification *O*-benzyl products (+)-**28**, (+)-**29**, (−)-**30** and (−)-**31** were obtained as white crystals (**Scheme 4**).



Scheme 4

Cycloreversions of the synthesized *O*-methyl and *O*-benzyl derivatives were finally achieved heating by microwave irradiation in DCB. The crude products were purified by column chromatography eluted with EtOAc or EtOAc/ hexane = 2:1 to provide pyrimido[2,1-*a*]isoindoles (+)-**32**, (—)-**32**, (—)-**33**, (+)-**34**, (—)-**34**, (+)-**35** and (—)-**35** and pyrrolo[1,2-*a*]pyrimidines (+)-**36**, (—)-**36**, (+)-**37** and (—)-**37** as white crystals after evaporation or crystallization from iPr$_2$O with *ee* = 93-99% demonstrating that the starting compounds are excellent chiral sources (**Scheme 5**, **Table 2**). It is demonstrable, that the stereochemical information was efficiently transferred to the newly formed stereogenic centre through a traceless chirality transfer strategy. The configuration remains constant during RDA reaction, which allowed to define the absolute configuration of the final products. Simplicity, short reaction time, good yield, mild experimental conditions and easy work-up are the main advantages of our protocol.



Scheme 5

Table 2. Substituents of the pyrimido[2,1-*a*]isoindole **32-35** and pyrrolo-[1,2-*a*]pyrimidine **36** and **37** derivatives

	R^1	$R^2 = R^3$	R^4	*ee* %	Yield %
(+)-**32**	Me	H	H	95	27
(−)-**32**	Me	H	H	99	29
(+)-**33**	Me	OMe	H	98	20
(−)-**33**	Me	OMe	H	97	31
(+)-**34**	Bn	H	H	95	37
(−)-**34**	Bn	H	H	99	36
(+)-**35**	Bn	OMe	H	93	32
(−)-**35**	Bn	OMe	H	99	54
(+)-**36**	Me	_	COOMe	95	41
(−)-**36**	Me	_	COOMe	99	40
(+)-**37**	Me	_	Me	99	55
(−)-**37**	Me	_	Me	99	57

C. PUBLICATIONS

I. **Beáta Fekete**, Márta Palkó, István Mándity, Matti Haukka, Ferenc Fülöp:
A Domino Ring-Closure Followed by Retro-Diels–Alder Reaction for the Preparation of Pyrimido[2,1-*a*]isoindole Enantiomers
European Journal of Organic Chemistry **2016**, *21*, 3519–3527.
DOI: 10.1002/ejoc.201600434

IF: 2.882

II. **Beáta Fekete**, Márta Palkó, Matti Haukka, Ferenc Fülöp:
Synthesis of Pyrrolo[1,2-*a*]pyrimidine Enantiomers via Domino Ring-Closure followed by Retro Diels-Alder Protocol
Molecules **2017**, *22*, 1–13.
DOI: 10.3390/molecules22040613

IF: 3.098

III. Gyula Lajkó,Tímea Orosz, Nóra Grecsó, **Beáta Fekete**, Márta Palkó, Ferenc Fülöp,Wolfgang Lindner, Antal Péter, István Ilisz:
High-performance liquid chromatographic enantioseparation of cyclic *β*-aminohydroxamic acids on zwitterionic chiral stationary phases based on *Cinchona* alkaloids
Analytica Chimica Acta **2016**, 9*21*, 84–94.
DOI: 10.1016/j.aca.2016.03.044

IF: 4.513

IV. Attila Bajtai, **Beáta Fekete**, Márta Palkó, Ferenc Fülöp, Wolfgang Lindner, Michal Kohout, István Ilisz, Antal Péter
A comparative study for the liquid chromatographic enantioseparation of cyclic *β*-amino acids and the related cyclic *β*-aminohydroxamic acids on Cinchona alkaloid-based zwitterionic chiral stationary phases
Journal of Separation Science, **2018**, *41*, 1216−1223.
DOI: 10.1002/jssc.201701190

IF: 2.415

D. CONFERENCE LECTURES

V. **Fekete Beáta**:
Norbornénvázas aminohidroxámsavak szintézise és gyűrűzárási reakcióinak vizsgálata
„A Szegedi Ifjú Szerves Kémikusok Támogatásáért" Alapítvány tudományos előadóülése,
Szeged, 2014. május 7.

VI. **Fekete Beáta:**
Norbornénvázas aminohidroxámsavak domino gyűrűzárási reakcióinak vizsgálata,
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése,
Balatonszemes 2015. május 27-29.

VII. **Fekete Beáta:**
Pirimido[2,1-*a*]izoindolok és pirrolo[1,2-*a*]pirimidinek előállítása norbornénvázas béta-aminohidroxámsavak domino és RDA reakcióival
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium 2016.
Herceghalom 2016. szeptember 15-16.