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Chiral cyclic zwitterionic bipyridinium-4-olates for the diastereoselective synthesis of (*R*,*S*)- and (*S*,*R*)-trozamicol

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ABSTRACT

A series of new chiral enantiopure cyclic zwitterionic bipyridinium-4-olates compounds were prepared in four steps starting from the corresponding primary chiral amine. With these intermediates, a convenient methodology has been developed for the synthesis of *cis*-3-piperidinyl-4-hydroxypiperidines. Specifically, the utility of this chiral zwitterionic type intermediate has been demonstrated by the synthesis of (*R*,*S*)- and (*S*,*R*)-trozamicol.

Introduction

Piperidine ring are important structure which are immerse in a wide broad of important compounds. More specifically, 3-amino-4-hydroxypiperidines are one of the important architectures because it appears in several natural products, or pharmacologically active compounds.[1] In these sense, the (*R*,*R*)-trozamicol (a 3-amino-4-hydroxypiperidine) and its analogues present a σ_1 receptor binding affinities.[2] The σ_1 receptors are considered as a therapeutic target for the treatment of depression,[3] anxiety,[4] schizophrenia[5] and Alzheimer's disease.[6] Therefore, a continuous interest exists in the development of new methodologies for asymmetric synthesis of this six-membered azaheterocycle (Fig. 1).[2,7]

Surprisingly the synthesis of (*R*,*S*)- and (*S*,*R*)-trozamicol stereoisomers has not been explored. These strongly suggest that these isomers could also possess interesting pharmacological properties.

3-Amino-4-substituted piperidines commonly are prepared through a regio- and stereoselective hetero nucleophilic addition to a piperidinylaziridine,[8] or via epoxide ring-opening of 3,4-epoxypiperidines with an appropriate nucleophile to afford a regioisomeric opening mixture of *trans*-vicinal aminoalcohol under different reaction conditions with a view to study the reactivity and regioselectivity.[9]

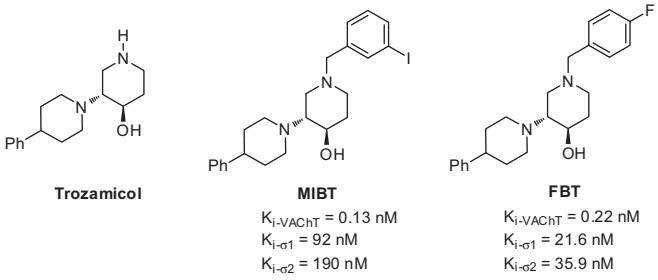

Figure 1. Trozamicol and analogues those are potent for σ_1 receptors.

On the other hand, it is well known that pyridinium zwitterions are usually very reactive species, which should be kept at low temperatures and in an inert atmosphere. The majority of these zwitterions are synthesized by first preparing the pyridinium salt, followed by the elimination of an acid in the reaction with a base.[10]

Since pyridinium salts derived from α-halogenocarbonyl compounds are easily deprotonated to give pyridinium zwitterions, which are prone to be high potential synthons and undergo versatile reactions,[11] we envisioned that our previously methodology to the synthesis of cyclic zwitterionic piperidine compounds[12] could

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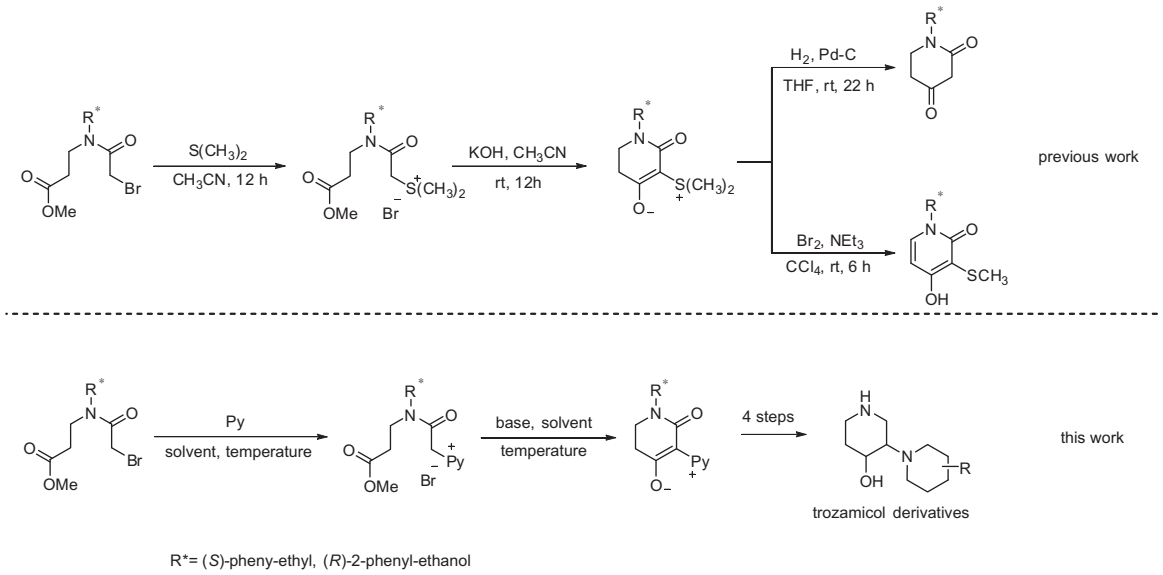
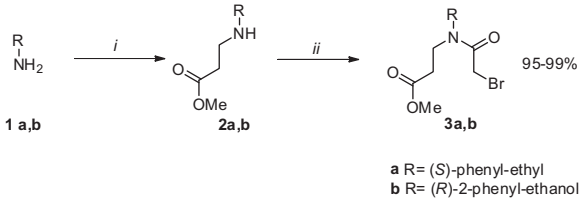


Scheme 1. Previous studies and this work.



Scheme 2. Reagents and conditions: (i) methyl acrylate (1.2 equiv), methanol, reflux, 3 h, 95–98% yield. (ii) Bromoacetyl bromide (1.2 equiv), for **3a**: K_2CO_3 (2 equiv), DCM/H_2O 1:1, 0 °C, 1 h; for **3b**: NEt_3 (1 equiv), DCM, 0 °C, 1 min.

be applied to the synthesis of chiral zwitterionic bipyridinium-olates that could be used on the preparation of trozamicol and its derivatives (Scheme 1).

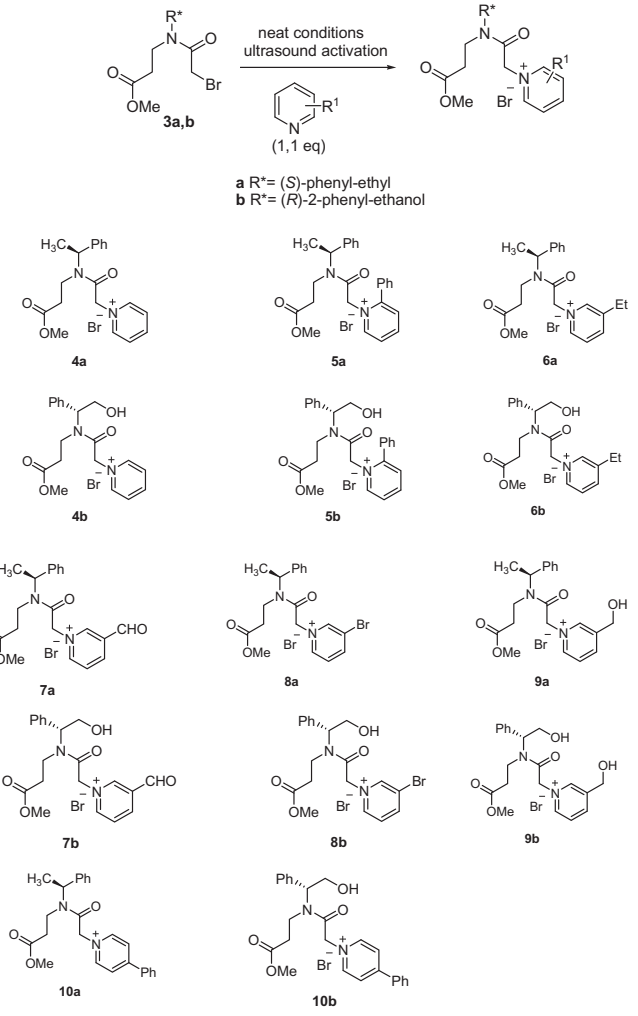
Results and discussion

Chiral bromoacyl amides were prepared as follow. Firstly the corresponding chiral amine was condensed with methyl acrylate allowing the formation of aminoester **2a**,**b**; then, the resulting aminoester was reacted with bromoacetyl bromide to afford the desired bromoacyl amide **3a**,**b** (Scheme 2).

Next, diverse pyridines were condensed with **3a**,**b**. Best results were obtained when the reaction was carried out under ultrasonic activation and neat conditions. The desired pyridinium salt was obtained as a dynamic rotameric mixture in quantitative yields (Scheme 3).

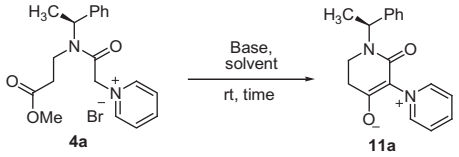
We then turned our attention to the intramolecular cyclization. To this end, pyridinium salt **4a** was treated with diverse bases. The best result was obtained when **4a** was treated with KOH (6 equiv) in MeOH, allowing the formation of the desired cyclic zwitterion **11a** in *quasi* quantitative yield in a few minutes (Table 1).[13]

Encouraged by the above finding, we attempted to synthesize more functionalized zwitterion intermediates derived from substituted pyridine compounds. Pleasingly, a broad range of 2-, 3- and 4-substituted pyridinium salts gave the expected cyclic intermediates in good chemical yields. However, pyridinium salt derived



Scheme 3. Synthesis of several pyridinium salts.

Table 1
Intramolecular cyclization of pyridinium salt **4a**

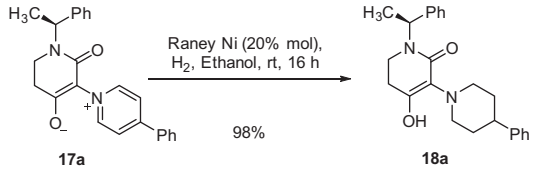


Entry	Solvent	Base	Time (h)	Yield (%)
1	CH_3CN	KOH[a]	16 h	80
2	MeOH	NaOMe[a]	1 h	50
3	MeOH	KOH[a]	1 h	98
4	MeOH	KOH (6 equiv)	10 min	98

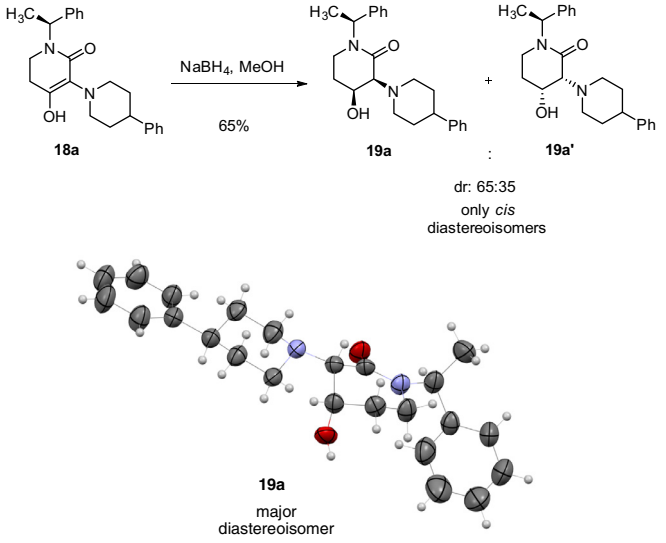
[a] 2 equiv of the base were used.

Table 2
Chiral cyclic zwitterionic derivatives obtained from intramolecular cyclization of pyridinium salts

11a 97% 10 min	**12a + 12a'** 100%, 10min dr= 60:40	**13a** 100%, 1h
11b 83%, 1h	**12b** traces 2h	**13b + 13b'** 97%, 16h dr =73:27
14a + 14a' 56%, 10 min, dr = 83:16	**15a + 15a'** 80%, 10 min, dr= 85:15	**16a** 93%, 10min
14b + 14b' 57%, 10 min	**15b + 15b'** 99%, 10 min, dr 85:15	**16b** 99%, 10 min
17a 98%, 1h	**17b** 85%, 1h	



Scheme 4. Reduction of zwitterionic compound **17a**.



Scheme 5. Diastereoselective reduction of compound **18a**.

from 2-phenylpyridine and (*R*)-(−)-2-phenylglycinol gave the desired cyclic zwitterionic compound **12b** in traces and the corresponding oxazepanone compound as a major product (not show on Table 2). This result could be attributed to the more favourable intramolecular transesterification reaction.

Interestingly, cyclic zwitterions **12(a+a′)** and **14(a+a′)** were obtained as an inseparable atropisomeric mixture, while zwitterions **12b**, **13b**, **14a**, **15a** and **15b** were obtained as a separable atropisomeric mixture in a 2:1 diastereomeric ratio. It is important to mention that zwitterion **13a**, **16a** and **16b** were obtained as a sole atropisomer in a high chemical yield. All zwitterions were isolated in its betaine form (Table 2).

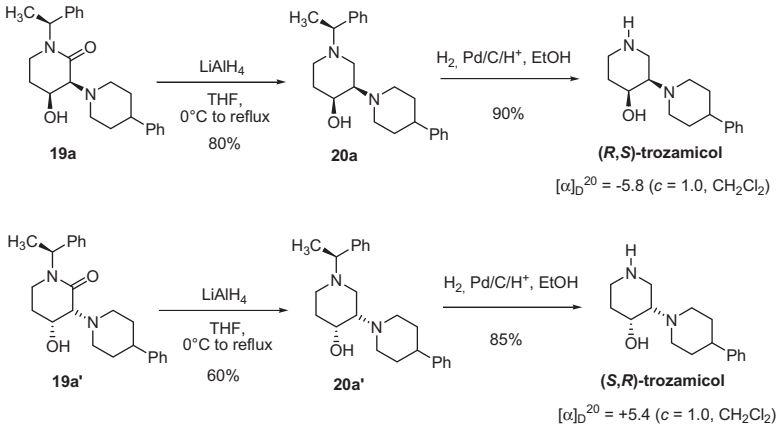
Continuing with our research aimed to apply these intermediates to the synthesis of trozamicol, we oriented our attention to the reduction of the aromatic pyridinium ring. To this end, zwitterion **17a** was submitted to different catalytic hydrogenation conditions including Pd/C (20% mol), PtO_2 (20% mol), etc. Excellent yield was obtained when the hydrogenation was carried out with Raney Ni catalyst in EtOH at room temperature. The confirmation of the reducing compound **18a** was corroborated from the NMR spectrum of the crude reaction which shows the characteristic piperidine ring signals around 1.5–3.2 ppm (see Supplementary material) (Scheme 4).

Thereafter, the enol function of compound **18a** was reduced with $NaBH_4$ to afford exclusively the *cis* diastereomeric mixture of the corresponding vicinal aminoalcohols **19(a+a′)**, which were easily separated by chromatographic purification. Fortunately, major diastereoisomer **19a** crystallized, enabling the unequivocal configuration at C-3 and C-4 as (*S*,*S*) respectively by X-ray diffraction analysis[14] (Scheme 5).

Then, the amide function was reduced with $LiAlH_4$[15] to afford the desired piperidine compound. Finally, the corresponding piperidine was subject to hydrogenolysis process delivering the (*R*,*S*)- and (*S*,*R*)-trozamicol[16] (Scheme 6).

Conclusion

In summary, we proved that chiral non-racemic zwitterionic bipyridinium-4-olates are valuable starting material for the preparation of trozamicol derivatives, and represent a novel methodology to regiospecific synthesis of *cis*-3-piperidinyl-4-hydroxy piperidine intermediates. This new, versatile, and scalable access



Scheme 6. Synthesis of (−)-(*R*,*S*)-trozamicol and (+)-(*S*,*R*)-trozamicol.

to trozamicol derivatives opens the route to the pharmacological investigation of these promising compounds as well as the design of analogues.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.029.

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13. The formation of a cyclic zwitterion compound was confirmed by the ^{1}H NMR spectrum **9a**, wherein the benzylic C–H$_\alpha$ resonates at δ = 5.97 ppm.
14. Crystal structure was deposited at the Cambridge Crystallographic Data Centre. Deposit number: CCDC 1451876.
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16. (−)-(*R*,*S*)-Trozamicol yield 90%, colorless oil. $[\alpha]_D^{20}$ = −5.8 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (dddd, *J* = 2.75, 5.05, 10.26, 12.6 Hz, 1H), 1.69 (dd, *J* = 3.8, 12.2 Hz, 1H), 1.74 (dd, *J* = 3.8, 12.3 Hz, 1H), 1.86 (m, 2H), 1.98 (ddd, *J* = 2.65, 5.5, 14.1 Hz, 1H), 2.09 (td, *J* = 2.3, 11.8 Hz, 1H), 2.23 (td, *J* = 2.45, 11.5 Hz, 1H), 2.28 (ddd. *J* = 2.75, 4.7, 11.1 Hz, 1H). 2.54 (tt, *J* = 3.7, 12.2 Hz, 1H), 2.73 (ddd, *J* = 1.2, 4.6, 12.0 Hz, 1H), 2.77 (t, *J* = 11.3 Hz, 1H), 2.89 (td, *J* = 2.75, 12.4 Hz, 1H), 3.06 (m, 2H), 3.29 (m, 1H), 4.14 (br, 1H), 7.19–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 33.6, 33.7, 40.0, 42.6, 44.3, 49.4, 51.0, 62.9, 63.4, 126.2, 126.8, 128.4, 146.1 HRMS (FAB): Calcd for $C_{16}H_{24}N_2O$: 260.1889. Found: 260.1888. (+)-(*S*,*R*)-trozamicol. Yield 85%, colorless oil. $[\alpha]_D^{20}$ = +5.4 (*c* = 1.0, CH_2Cl_2).