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Diastereoselective synthesis of lortalamine analogs

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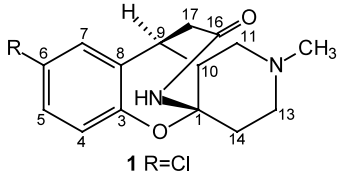
Abstract—(*R*)-(+)-1-(1-Naphthyl)ethylamine was found to be a more effective chiral auxiliary in the asymmetric synthesis of lortalamine analogs than (*S*)-(−)-α-methylbenzylamine. Chiral, non-racemic ketones **6** and **7** were prepared and transformed into pairs of diastereomeric intermediates of final lortalamine analogs. For one of them, the stereochemistry on the heterocyclic part was established on the basis of X-ray crystallography. Enantiomerically pure (+)-*des*-chloro-lortalamine **2** was finally obtained.

1. Introduction

Benzopyranopyridino- and pyrimidino-derivatives exhibit a wide variety of pharmacological activity, including antipyretic, anti-inflammatory, analgesic, gastroprotective and antiplatelet activities.[1] Additionally, several 2-aryl-4-oxobenzopyrano[2,3-*d*]pyrimidines have been shown to exhibit in vivo antitumor properties.[2] Moreover, several examples of neurochemical action have been reported in this group of compounds.[3] Among them, the tetracyclic compound, (1*R**,9*R**,10*S**)-6-chloro-12-methyl-2-oxa-12,15-diazatetracyclo-[7.5.3.$0^{1,10}$.$0^{3,8}$]heptadeca-3,5,7-trien-16-one) was developed and introduced as a relatively safe antidepressant and antipsychotic drug (lortalamine **1**, LM 1404).[4] Interestingly, lortalamine **1** is sold as a racemate. There are no reports available on either enantioselective synthesis, or resolution of racemic mixtures of these types of derivatives.



1 R=Cl

2 R=H

2. Results and discussion

Having been engaged in the asymmetric synthesis of compounds of pharmacological interest, we recently turned our attention to the possibility of the stereoselective construction of the lortalamine system. We first selected a *des*-chloro analog **2** as our model synthetic target. It is known that racemic compound **2** can be prepared from ethyl coumarin-3-carboxylate **3** and 1-methyl-4-piperidone in a two-step procedure.[4] We observed that when the chiral, non-racemic *N*-[(*S*)-α-methylbenzyl]-4-piperidone **6**[5] was used for this reaction, an intermediate β-keto ester **8**[6] as a relatively unstable and inseparable diastereomeric mixture was initially formed (Scheme 1). The structure of **8** remained unclear for us until we were able to obtain a monocrystal of **10**[7] that was suitable for X-ray crystallographic analysis. Surprisingly, we found that in this crystal, that belongs to the common non-centrosymmetric space group $P2_1$, both diastereomeric molecules were present in the unit cell (Fig. 1).[7] Subsequent acid hydrolysis and decarboxylation of **8** brought about the formation of isomers **14a**[8] and **14b**[9] in a ratio of 48:52, respectively.

In each of the series (**8**–**13**) both isomers could easily be separated by column chromatography on silica gel but a single-crystal X-ray analysis could be performed only for diastereomer **15a**.[10] This allowed the assignment of (1*S*,9*S*,10*R*) stereochemistry at the heterocyclic part of the molecule (Fig. 2). In the case of pure diastereomer

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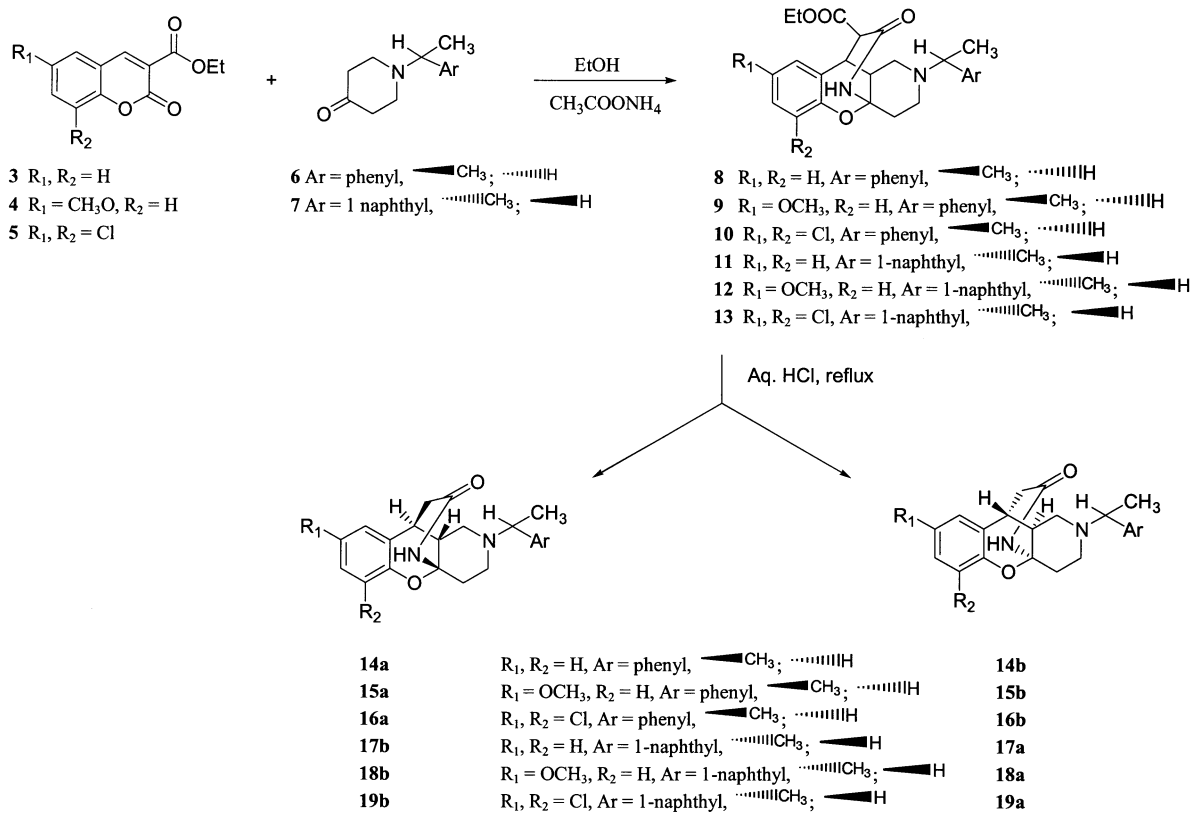

3 $R_1, R_2 = H$
4 $R_1 = CH_3O, R_2 = H$
5 $R_1, R_2 = Cl$

6 Ar = phenyl, CH$_3$; H
7 Ar = 1 naphthyl, CH$_3$; H

8 $R_1, R_2 = H$, Ar = phenyl, CH$_3$; H
9 $R_1 = OCH_3, R_2 = H$, Ar = phenyl, CH$_3$; H
10 $R_1, R_2 = Cl$, Ar = phenyl, CH$_3$; H
11 $R_1, R_2 = H$, Ar = 1-naphthyl, CH$_3$; H
12 $R_1 = OCH_3, R_2 = H$, Ar = 1-naphthyl, CH$_3$; H
13 $R_1, R_2 = Cl$, Ar = 1-naphthyl, CH$_3$; H

14a	$R_1, R_2 = H$, Ar = phenyl, CH$_3$; H	**14b**
15a	$R_1 = OCH_3, R_2 = H$, Ar = phenyl, CH$_3$; H	**15b**
16a	$R_1, R_2 = Cl$, Ar = phenyl, CH$_3$; H	**16b**
17b	$R_1, R_2 = H$, Ar = 1-naphthyl, CH$_3$; H	**17a**
18b	$R_1 = OCH_3, R_2 = H$, Ar = 1-naphthyl, CH$_3$; H	**18a**
19b	$R_1, R_2 = Cl$, Ar = 1-naphthyl, CH$_3$; H	**19a**

Scheme 1.

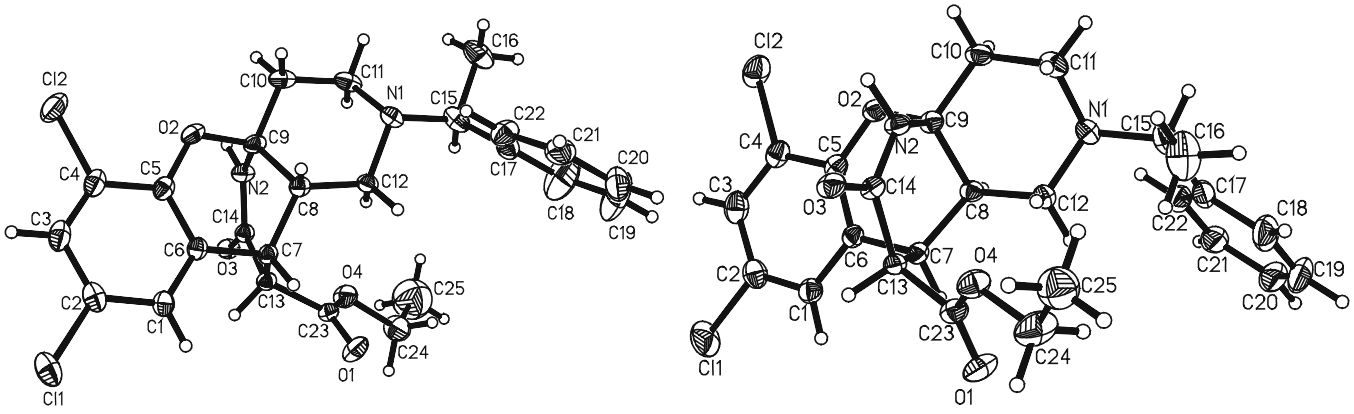

Figure 1. ORTEP diagram of compound **10**. Two diastereomers are present in the unit cell.

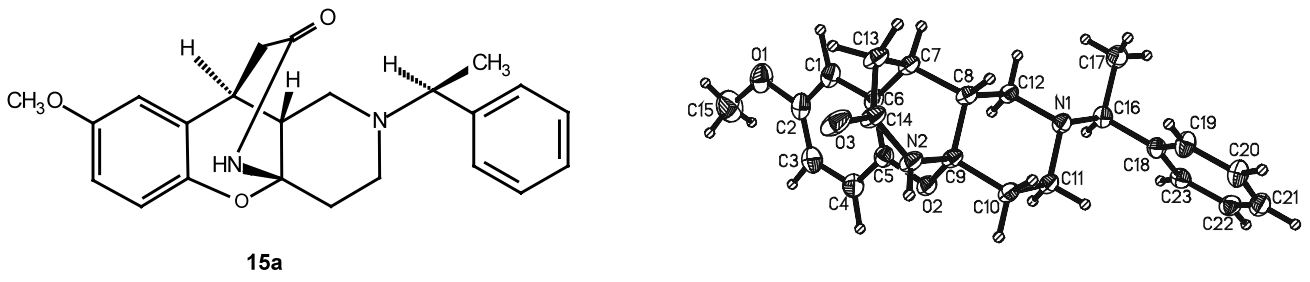

Figure 2. X-Ray crystal structure of **15a**.

Table 1. Diastereoselectivity of lortalamine analogs formation[13]

Entry	Diastereomers	Yield (%)	Selectivity
1	**14a**[a]:**14b**[a]	89	48:52
2	**15a**:**15b**	91	62:38
3	**16a**:**16b**	78	40:60
4	**17a**:**17b**	92	29:71
5	**18a**:**18b**	95	23:77
6	**19a**:**19b**	77	84:16

[a] **a**, less polar; **b**, more polar diastereomer on silica plate.

14a, the chiral auxiliary was subsequently removed by hydrogenolysis over Pd/C and the secondary amine thus formed was subsequently *N*-methylated using formaldehyde–sodium borohydride to afford (+)-**2** in enantiomerically pure form.

We observed that whereas the modification of the coumarin component affected the diastereomeric ratio slightly (Table 1, entries 1–3), a more profound influence on the stereoselectivity could be noticed when a more sterically demanding amine was applied as the chiral auxiliary. Thus, when ketone **7** derived from (*R*)-(+)-1-(1-naphthyl)ethylamine[5] was used, we observed an increase of the selectivity to around 23:77 or even 84:16 (Table 1, entries 4–6).

The preliminary results described above show that popular chiral, non-racemic 1-arylethyl amines may also serve as good chiral inductors in the diastereoselective synthesis of benzopyranopyridine derivatives.

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6. **Typical preparation of β-keto ester 8**: A mixture of *N*-[(*S*)-α-methylbenzyl]-4-piperidone **6** (0.70 g, 3.4 mmol), ethyl coumarin-3-carboxylate **3** (0.75 g, 3.4 mmol) and ammonium acetate (1.32 g, 17.2 mmol) in anhydrous ethanol (7 ml) was stirred for 90 h at room temperature. Alcohol was removed under reduced pressure and after addition of water (20 ml), the mixture was extracted with chloroform. Column chromatography on 230/400 mesh silica gel (chloroform/methanol 99:1) and recrystallization (ethanol/ether) gave **8** as white crystals (89% yield). $[\alpha]_D^{20}=-10.5$ (*c* 1.4, $CHCl_3$); mp 172–178°C; ^{13}C NMR (125 MHz, $CDCl_3$, most of the signals are doubled): δ 168.48, 168.43, 167.26, 150.64, 129.80, 129.76, 129.54, 129.29, 129.18, 128.58, 128.46, 127.36, 127.23, 124.98, 122.03, 121.87, 120.63, 117.52, 117.28, 83.34, 64.00, 63.77, 62.21, 61.36, 61.32, 53.57, 53.54, 51.10, 51.01, 50.50, 48.51, 47.43, 46.21, 37.28, 36.92, 35.61, 35.43, 18.69, 13.79; EI 70 eV *m*/*z* (%): 420 (65), 405 (80), 374 (20), 347 (45), 315 (35), 289 (25), 200 (50), 184 (25), 105 (100).
7. **X-Ray intensity data for 10 and 15a**: Measurements were completed at $T=293$ K on a Kuma KM4CCD κ-axis diffractometer with Mo Kα radiation ($\lambda=0.71073$ Å). 2120 frames were collected at 0.9° intervals with a counting time of 5 s for **15a** (656 frames and 0.7° for **10**, respectively). The data were corrected for Lorentz and polarization effects. No absorption corrections were applied. The structures were solved by direct methods from SHELXS[11] and refined using SHELXL software.[12] Crystal data for compound **10**: $C_{25}H_{24}Cl_2N_2O_4$, $M=487.36$, monoclinic space group $P2_1$; $a=12.910(3)$, $b=14.020(3)$, $c=12.920(3)$ Å, $\beta=91.00(3)°$, $V=2338.1(8)$ Å^3, $Z=4$ and $D_{calcd}=1.384$ Mg/m^3. Colorless crystal, μ (Mo Kα) $=0.313$ mm^{-1}, $F(000)=1016$, 4727 reflections collected. Least squares on F^2 (all reflections), $R=0.0633$, $wR_2=0.1795$ (observed).
8. **Selected data for 14a**: $[\alpha]_D^{20}=+31.6$ (*c* 2.05, $CHCl_3$); mp 156–157°C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30–6.78 (9H, m), 6.51 (1H, s), 3.41 (2H, ABq, $J=13.5$), 2.90 (2H, br d, $J=5.5$ Hz), 2.79–2.70 (2H, m), 2.60 and 2.56 (1H, two s), 2.36–2.32 (2H, m), 1.98–1.95 (1H, m), 1.92–1.86 (2H, m), 1.80 (1H, br s), 1.28 (3H, d, $J=6.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 171.22, 149.87, 144.58, 129.14, 128.63, 128.33, 127.31, 126.92, 123.28, 121.72, 117.32, 81.45, 64.06, 48.73, 47.46, 42.26, 38.04, 36.53, 32.83, 19.00; EI 70 eV 8 kV *m*/*z* (%): 348 (75), 333 (100), 243 (50), 271 (8), 200 (18), 105 (62), 91 (10), 77 (12); IR (KBr, cm^{-1}) 3450, 3200, 2800, 1680, 1580.
9. **Selected data for 14b**: $[\alpha]_D^{23}=-27$ (*c* 2.0, $CHCl_3$); mp 218–220°C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29–6.78 (9H, m), 6.56 (1H, s), 3.44 (2H, ABq, $J=5.5$), 2.76–2.70 (2H, m), 2.60–2.51 (2H, m), 2.39–2.24 (2H, m), 2.11 (1H, d, $J=13.5$ Hz), 2.00 (1H, br s), 1.80–1.75 (1H, t, $J=11.5$ Hz), 1.33 (3H, d, $=5.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 171.18, 149.82, 129.15, 128.59, 128.40, 127.29, 126.97, 123.24, 121.70, 117.29, 81.37, 64.45, 51.14, 45.35, 42.20, 37.90, 36.53, 32.58, 20.01; EI 70 eV 8 kV *m*/*z* (%): 348 (85), 333 (100), 243 (60), 271 (10), 200 (25), 105 (65), 91 (10); IR (KBr, cm^{-1}) 3400, 3200, 3000–2700, 1510.
10. **Crystal data for compound 15a**: $C_{23}H_{26}N_2O_3$, $M=378.46$, monoclinic space group $C2$, $a=31.122(6)$, $b=9.761(2)$, $c=7.8290(16)$ Å, $\beta=97.19(3)°$, $V=2359.6(8)$ Å^3, $Z=4$ and $D_{calcd}=1.065$ Mg/m^3. Clear colorless crystal, μ (Mo Kα) $=0.071$ mm^{-1}, $F(000)=808$, 21246 reflections collected, 5754 [R(int) $=0.0310$], 5072 observed [$I>2\sigma(I)$]. Least squares on F^2 (all reflections), $R=0.0584$, $wR_2=0.1556$ (observed).
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13. HPLC analyses were performed on a Knauer (model 64) apparatus, using 4×250 mm (5 μm) Li-Chrosorb Si-60 silica column with gradient ratio of dichloromethane/methanol.