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First enantioselective synthesis of the antitumour alkaloid (+)-crispine A and determination of its enantiomeric purity by ^{1}H NMR

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Abstract—A simple enantioselective synthesis of the pyrrolo[2,1-*a*]isoquinoline alkaloid (+)-crispine A, based on the use of an asymmetric transfer hydrogenation as the key step, is described. The enantiomeric excesses of the obtained alkaloid samples were determined from ^{1}H NMR spectra recorded in the presence of (+)-(*R*)-*t*-butylphenylphosphinothioic acid as a chiral solvating agent.

1. Introduction

Carduus crispus Linn. (welted thistle) belongs to a large family of popular invasive plants occurring mainly in Asia and Europe on wasteland or grounds not properly cared for. Despite its relatively bad reputation, this handsome plant serves simultaneously as an excellent food for cattle and horses and also as a source of valuable pharmacological ingredients. Since ancient times, it has widely been applied in folk medicine for the treatment of bronchits, stenocardia, gastroenteritis and rheumatism.[1] Several individual components have recently been isolated from this plant and fully characterized, including a new flavone glycoside and related compounds.[2] Important cytotoxic activity against SKOV3, KB and HeLa human cancer lines was detected for crispine A **1**, a novel isoquinoline alkaloid that was isolated from *C. crispus* by Zhao et al.[1] Another component of this plant, crispine B **2**, showed a profound antitumour activity on human ovarian neoplasm cells (Fig. 1).[2]

Very recently, a short and direct total synthesis of racemic crispine A **1** by the use of a novel protocol for pyrrole construction was proposed by Knölker and Agarwal.[3]

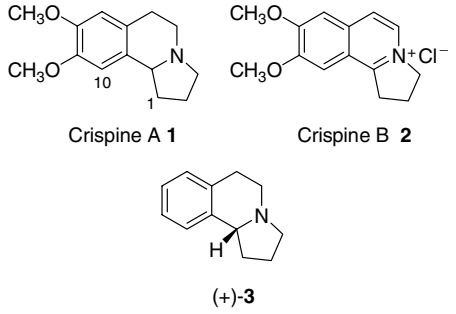

Figure 1. The chemical structures of compounds **1**–**3**.

2. Results and discussion

Several synthetic strategies for the preparation of pyrrolo[2,1-*a*]isoquinoline core of crispine A **1** have already been reported[4–10] including an elegant stereoselective route to (+)-**3** from L-malic or L-tartaric acid.[6,11]

Due to a growing demand for the development of simple synthetic procedures of high atom economy and low environmental impact, we decided to introduce the

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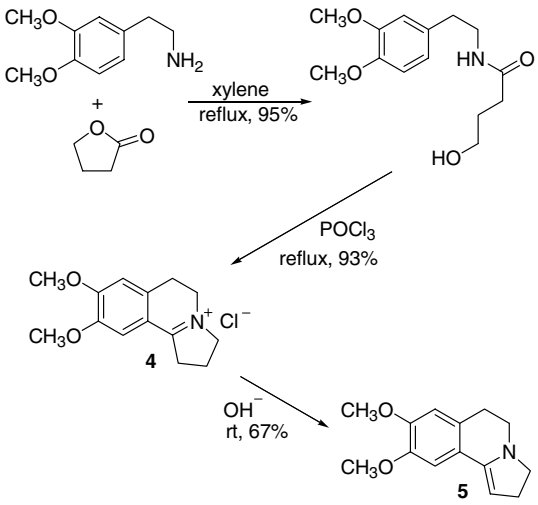

Scheme 1. Preparation of compounds **4** and **5**.

chirality on the last step of the synthetic sequence leading to crispine A **1**, preferably via a catalytic method. For this purpose we utilized the iminium salt **4** as a prochiral substrate. The salt **4** was readily available by a slightly modified known procedure[12] from γ-butyrolactone and homoveratrylamine (Scheme 1). Moreover, salt **4** can be converted to enamine **5**[12] having different solubility properties allowing solvent variation during an optimization of the final catalytic asymmetric reduction step.

In preliminary experiments, compounds **4** or **5** were initially subjected to treatment with sodium borohydride modified by chiral acids.[13] We have already applied this important procedure getting fair-to-good results in our experiments[14] but disappointingly, in the case of compounds **4** and **5** this approach brought about unacceptable results (<20% ee), despite solvent and temperature variations. On the other hand, the asymmetric transfer hydrogenation method[15] afforded the desired alkaloid with much better enantiomeric excess. We observed that the reduction of compound **4** or **5** could be realized with a 5:2 formic acid–triethylamine mixture in acetonitrile containing a chiral Ru complex pre-formed from various ligands (amines **6**–**9**, Fig. 2).[16]

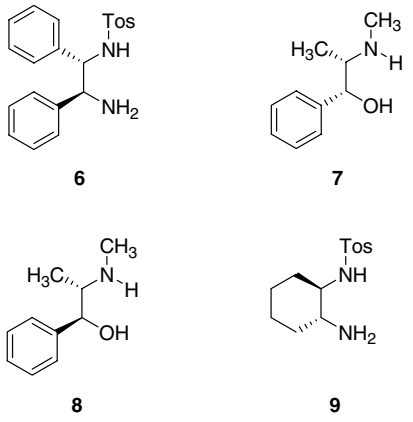

Figure 2. The structures of ligands **6**–**9**.

The highest chemical yield and enantiomeric excess were observed in experiments in which the amine **6** was used as a chiral ligand and the reaction was carried at 0 °C (Table 1).[17]

Table 1. Chemical yields and enantiomeric excesses of crispine A **1** samples

Entry	Substrate	Ligand	*T* (°C)	Yield (%)	Configuration	ee (%)
1	**4**	**6**	22	95	(+)-(*R*)	77
2	**4**	**6**	0	96	(+)-(*R*)	92
3	**4**	**7**	22	87	(+)-(*R*)	3
4	**4**	**8**	22	81	(+)-(*R*)	5
5	**4**	**9**	22	91	(−)-(*S*)	71
6	**5**	**6**	0	90	(+)-(*R*)	>99

The isolated (+)-(*R*)-**1** revealed the same spectroscopic data (NMR and MS) as those reported for the natural product.[1] It seems highly probable that the absolute configuration of (+)-**1** is the same as established for (+)-**3** by Lee and Park.[6] To confirm this hypothesis we are currently trying to get a single crystal suitable for crystallographic measurements. We experienced also some uncertainty connected with the determination of the enantiomeric excess of the synthetic sample of (+)-(**1**).[18] Having had difficulties in obtaining a baseline separation of enantiomers of (±)-**1** on chiral HPLC (with 2,4-DNPG and cyclodextrin-coated columns), we decided to utilize an NMR technique based on chiral additives. Among several known solvating agents, (−)-(*S*)- and (+)-(*R*)-*t*-butylphenylphosphinothioic acid **10** (Fig. 3) were shown to be very useful in the determination of the enantiomeric excess of various classes of non-racemic compounds.[19–21]

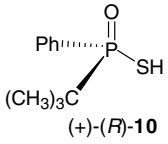

Figure 3. The structure of (+)-(*R*)-**10**.

The application of this thioacid for the samples of crispine A **1** obtained in our experiments gave the ^{1}H NMR spectra in which the magnetic nonequivalence, due to the formation of diastereoisomeric solvates, was visible for all groups of protons, especially for the aromatic and OMe protons. The best diagnostic value proved to be the absorption of the aromatic proton at C(10), which appeared in the ^{1}H NMR spectrum of racemic crispine A **1** as a singlet at δ 6.569 ppm and in the presence of (+)-(*R*)-**10** as two well separated singlets at 6.234 and 6.392 ppm ($\Delta\delta = 0.16$ ppm, see (a) in Fig. 4). Since in the ^{1}H NMR spectrum of (+)-(**1**) $\{[\alpha]_D^{23} = +100.4$ (*c* 1, $CHCl_3)\}$, measured in the presence of (+)-(*R*)-**10** (see c), only one singlet of aromatic proton at C(10) was observed, we can conclude that the product is enantiomerically pure within the detection limits of ^{1}H NMR.

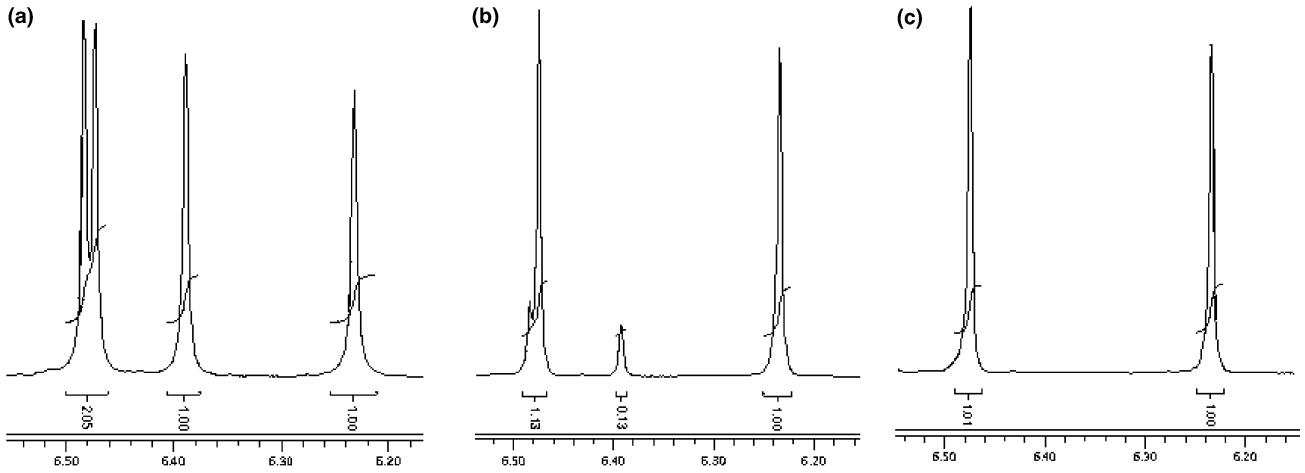

Figure 4. ^{1}H NMR spectra (aromatic region) of (a) the racemic crispine A **1**; (b) enriched in (+)-**1** enantiomer, $[\alpha]_D^{23} = +77.3$ (*c* 1, $CHCl_3$) (Table 1, entry 1); (c) (+)-**1**, $[\alpha]_D^{23} = +100.4$ (*c* 1, $CHCl_3$) (Table 1, entry 6) measured in the presence of (+)-(*R*)-**10**.

Therefore, the Ru-catalyzed asymmetric transfer hydrogenation has again proven its extremely high efficiency in the enantioselective synthesis of heterocyclic compounds, allowing us to prepare crispine A in essentially enantiopure form.

Acknowledgements

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16. According to the procedure given in Roszkowski, P.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Lis, T.; Czarnocki, Z. *J. Mol. Catal. A: Chem.* **2005**, *232*, 143–149.
17. *Typical procedure*: The catalyst was pre-formed from $[RuCl_2(C_6H_6)]_2$ (6 mg, 24 μmol) and (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-toluoylsulfonyl)ethylenediamine **6** (7.3 mg, 20 μmol) in 4 mL CH_3CN. To a solution of enamine **5** (100 mg, 0.43 mmol) in CH_3CN (10 mL) a 5:2 formic acid–triethylamine mixture (2.5mL) was introduced at 0 °C followed by the addition of the pre-formed catalyst. The mixture was then stirred at 0 °C for 10 h and then was made basic by addition of aqueous Na_2CO_3 solution and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using 10:1 chloroform–methanol as a solvent system to afford 90.8 mg (90% yield) of compound (+)-(*R*)-**1** as a slowly solidified colourless oil; $[\alpha]_D^{23} = +100.4$ (*c* 1, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (m, 1H), 1.85 (m, 1H), 1.92 (m, 1H), 2.32 (m, 1H), 2.55 (q, 1H), 2.63 (m, 1H), 2.73 (m, 1H), 3.01 (m, 1H), 3.07 (m, 1H), 3.18 (m, 1H), 3.41 (t, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 6.57 (s, 1H), 6.61 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.21, 28.03, 30.45, 48.33, 53.13, 55.86, 55.97, 62.94, 108.81, 111.29, 126.18, 130.93, 147.18, 147.30. ESMS (positive ion mode) $m/z =$ 234.1 (M^++1).
18. For (+)-**1**, $[\alpha]_D^{23} = +100.4$ (*c* 1, $CHCl_3$), lit.[1] for natural (+)-**1** $[\alpha]_D = +91$ (MeOH). In our case a persistent turbidity of the MeOH solution was obtained.
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