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Enantioselective route to ferrugine and its methyl analogue via aldol deoxygenation

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ABSTRACT

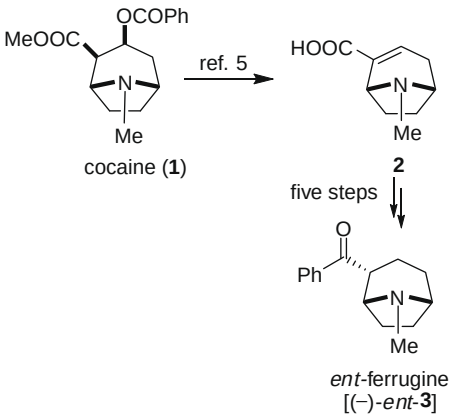
A simple enantioselective approach to ferrugine (2α-benzoyltropane) and its methyl analogue (2-acetyltropane) is reported. The four-step sequence uses an enantioselective aldol reaction of tropinone with benzaldehyde or acetaldehyde, combined with an aldol deoxygenation via tosylhydrazone reduction and oxidation of the side-chain hydroxy group. The final products, ferrugine and its methyl analogue, are prepared in 35% and 23% overall yields, respectively. Both enantiomers of the products (ee 90–99%) are accessible via the same route using either enantiomer of *N*,*N*-bis(1-phenylethyl)amine hydrochloride as the chiral reagent.

Tropane alkaloids are a group of structurally related natural products, with examples including cocaine, atropine and baogontenng A, many of which are known for their potent biological activity.[1] Ferrugine is one of the alkaloids isolated from the extracts of the Australian arboreal species *Darlingiana ferruginea*.[2] Ferrugine and its close relative, ferruginine, are nicotinic receptor antagonists, being potentially useful in the treatment of Alzheimer's disease.[3]

Unlike ferruginine, which has been the target of many syntheses,[4] ferrugine has attracted little attention. To the best of our knowledge, only two approaches to ferrugine have been reported. The first synthesis served as confirmation of the assigned structure of the newly isolated alkaloid.[4e] Bick's synthesis adopted the chiral pool approach, utilizing (−)-cocaine (**1**) as the starting material and anhydroecgonine[5] **2** as an intermediate. As a result, the synthesis gave the unnatural enantiomer, (−)-*ent*-ferrugine (Scheme 1). Preparation of the natural isomer via such a route is not possible.

Very recently, a new route to racemic ferrugine, using cyclohept-4-enecarboxylic acid as starting material (Scheme 2), was reported.[6] The sequence of nine synthetic steps including Curtius rearrangement, LAH reduction of an amide, formation of an acid chloride with triphosgene, light-induced radical cyclization and a Chugaev-like thermal elimination followed by PhLi or MeLi addition gave (±)-ferrugine (**3**) or its methyl analogue **6** in 11.8% and 13.6% overall yields, respectively (Scheme 2).

Herein, we report a new, expedient synthetic approach to ferrugine and its methyl analogue that allows for the preparation of all the three forms: racemic and either enantiomeric form, via the same reaction sequence. The simple, four-step synthesis employs selective introduction of the acyl group to the tropane skeleton using, as the key transformation, the proven enantioselective aldol reaction of tropinone, combined with a novel aldol deoxygenation. Synthesis of functionalized tropanes can, in principle, be based on either of the three strategies: (i) manipulation of the available functionalized tropane derivatives (e.g., a chiral pool approach using natural cocaine), (ii) assembling the tropane nucleus from suitably functionalized building blocks and (iii) functionalization and further transformation of the tropane skeleton. The third strategy is the most versatile and conceptually simple. It allows for the preparation of either enantiomer and has already been used to access various tropane derivatives successfully.[7] Consequently, the simplest way to construct ferrugine and similar structures would



Scheme 1. Bick's synthesis of *ent*-ferrugine (*ent*-**3**).

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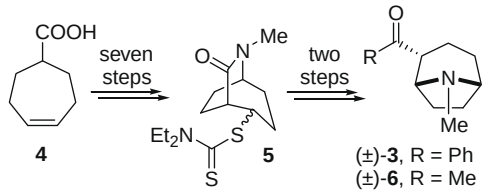
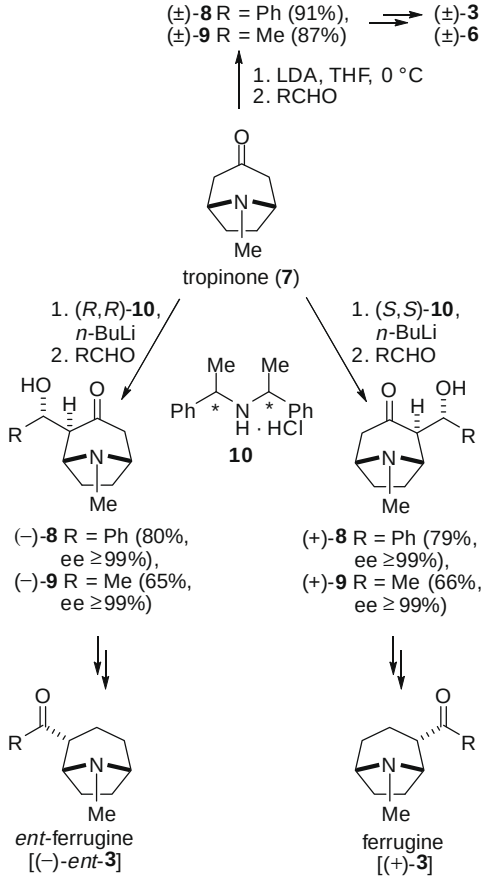


Scheme 2. Synthesis of (±)-ferrugine (**3**) via thermal elimination of a diethyldithiocarbamate.

be via installation of an acyl group at C-2 of the tropane skeleton. Plans based on direct tropinone acylation, although theoretically feasible, were hard to achieve in practice owing to the problems with chemoselective deoxygenation of one of the carbonyls of the resulting 1,3-diketone or their synthetic equivalents. We envisaged, however, an aldol reaction, followed by functional group manipulation, might be a better and synthetically equivalent transformation sequence. This could be realized provided that the sensitive aldol product (prone to retroaldolization, dehydration and isomerization) was stable under the subsequent reaction conditions and could be deoxygenated. To the best of our knowledge such an approach to enantioselective acylation of the tropane scaffold has not been studied.

Consequently, starting from tropinone, which is a relatively cheap and readily available scaffold, suitable for enantioselective deprotonation,[8] and using as the key transformation, a highly stereoselective aldol reaction (α-deprotonation with LDA or a chiral lithium amide, followed by reaction with benzaldehyde or acetaldehyde), the known product **8** and its novel methyl analogue **9** were prepared in virtually diastereomerically pure form (Scheme 3). To obtain the ferrugine structure, the keto group of the aldol products needs to be removed, and the secondary hydroxy group oxidized to a carbonyl. Finding suitable and mild enough conditions for these transformations was the main challenge of our approach. Based on our experience with the stability of tropinone aldols, a suitable method for removal of the carbonyl group could be via reduction of an intermediate tosylhydrazone. The first obstacle was the conversion of the aldol products into tosylhydrazones **11** and **12**. The use of typical literature procedures proved unsuccessful: refluxing in MeOH or EtOH with *p*-toluenesulfonyl hydrazide; with 3 Å molecular sieves and *p*-toluenesulfonic acid,[9] or reaction in benzene with $BF_3{\cdot}Et_2O$.[10] Under these conditions, the aldols decomposed giving none of the desired products. Finally, the reaction promoted by titanium(IV) isopropanolate, which was previously used for the syntheses of imines,[11] gave good results. Investigation of the reaction at room temperature in three different solvents (Table 1, Scheme 4) indicated absolute EtOH as the medium of choice.

Hydrazones **11** and **12** were synthesized under the optimized reaction conditions in 82% and 62% yield, respectively. Work-up of the titanium-promoted reaction was complicated by copious amounts of titanium hydroxides that were difficult to be separated. The crude tosylhydrazones were eventually purified by fast dry-column flash chromatography or crystallization from ethanol. Attempts to oxidize the hydroxy group at this stage with DMP,[12] PDC, $SO_3{\cdot}Py$,[13] Swern oxidation[14] or IBX[15] gave negligible

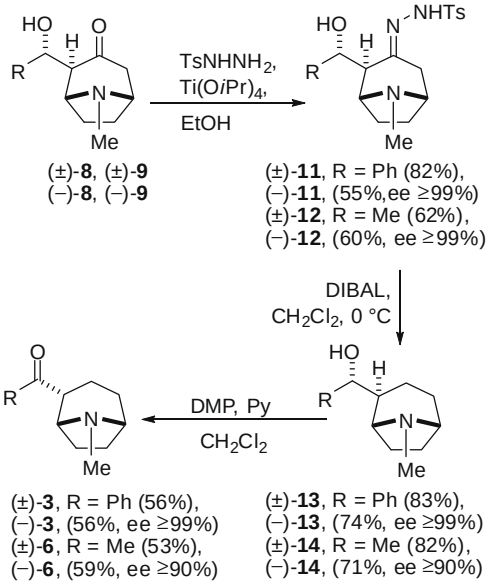


Scheme 3. The aldol reaction of tropinone (**7**) as the key step in the synthesis of ferrugine and its methyl analogue.

Table 1
Studies on the preparation of tosylhydrazone **11**

Entry	Reagent and solvent	Conversion of **8** into products[a] (%)	Isolated yield of **11**[b] (%)
1	MeOH	—	—
2	abs EtOH	86	15
3	$BF_3{\cdot}Et_2O$	—	—
4	$Ti(Oi\text{-}Pr)_4$, AcOEt	80	20
5	$Ti(Oi\text{-}Pr)_4$, abs EtOH	100	82

[a] Calculated from the ^1H NMR spectra of crude reaction mixtures.
[b] Product purified by chromatography on silica gel using CH_2Cl_2 saturated with NH_3 as eluent.



Scheme 4. Synthesis of (±)-ferrugine (**3**) and *ent*-**3** by aldol deoxygenation.

amounts of the desired product. It is thought that the oxidation may be hindered either by hydrogen bond formation between the hydroxy group and the nitrogen atom of the tosylhydrazone group or by steric congestion in the structure. Therefore, reductive deoxygenation of the tosylhydrazone group was investigated at this stage. The use of $NaBH_4$ in absolute ethanol[16] or in DMF with and without heating, as well as LAH,[17] failed to give the desired product. However, reduction with $NaBH_4$ in a mixture of acetic acid and MeOH gave the expected product **13** in 55% yield. A better result was achieved using DIBAL-H.[18]

When this reaction was carried out at 0 °C for 72 h the product was obtained in 83% yield after purification on deactivated silica gel (elution with dichloromethane saturated with NH_3). Representative results on tosylhydrazone reductions are shown in Table 2. Applying the optimized reduction method to the methyl analogue **12** provided *exo*-2-(1-hydroxyethyl)tropane **14** in 82% yield. The final step was oxidation of the side-chain hydroxy group. Attempted Swern oxidation gave poor results, but the use of typical Dess–Martin oxidation (in dry dichloromethane with pyridine at rt for 22 h) provided ferrugine **3** and the methyl analogue **6** (Scheme 4), in 56% and 53% yields, respectively, after chromatography. Analytical data was in agreement with those reported in the literature.[4e,6] Having devised a synthetic route to racemic ferrugine the enantioselective synthesis of either enantiomer was realized using the commercially available hydrochloride of chiral amine **10** (Scheme 3). Thus (−)-*exo*-2-(1-hydroxybenzyl)tropinone (−)-**8** was prepared using (*R*,*R*)-*N*,*N*-bis(1-phenylethyl)amine hydrochloride[8a] and two equivalents of *n*-butyllithium. Following the literature procedure,[8a] the aldol product (−)-**8** was isolated by precipitation and crystallization in 80% yield and with an ee ⩾ 99%. The tosylhydrazone (−)-**11** was obtained in the next step in 55% yield and with an ee ⩾ 99%.[19] Reduction of (−)-**11** with DIBAL-H gave the chiral alcohol (−)-**13** in 74% yield (ee ⩾ 99%) and oxidation of the hydroxy group gave *ent*-ferrugine [(−)-**3**] in 56% yield. Measurement of the enantiomeric excess of the final product by ^{1}H NMR in the presence of (+)-TFAE proved the high enantiomeric purity, ee ⩾ 99%. However, the optical rotations of the synthesized product measured at two different concentrations ($[\alpha]_D$ −100, *c* 1, $CHCl_3$ and $[\alpha]_D$ −29, *c* 0.3, $CHCl_3$) did not compare well with the literature value for natural ferrugine ($[\alpha]_D$ +55, $CHCl_3$),[4e] however, the concentration at which the optical rotation of the natural product was recorded was not given.[20] The natural enantiomer of ferrugine was also obtained via the same reaction sequence using (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amine hydrochloride (*S*,*S*-**10**) for the tropinone deprotonation. The enantiomers of the methyl analogues were equally accessible from enantiomers of aldols **9** (Scheme 4). The acetyl tropane **6** was, however, present admixed with a small amount of its *exo* diastereomer (2β-acetyltropane, ca. 15%).

In summary, we have developed a simple, four-step, route to 2-acyl tropanes based on aldol deoxygenation via tosylhydrazone reduction. The method was used for the first enantioselective synthesis of ferrugine and its methyl analogue (2-acetyltropane) using enantioselective deprotonation and the aldol reaction of tropinone. Thus, by using our approach, the racemate or either enantiomer of the 2-acyltropane derivative can be synthesized with high enantiomeric purity (⩾90–99%) using LDA or the commercially available chiral reagents, (*R*,*R*)- or (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amine hydrochloride.[21] The natural enantiomer of ferrugine, which is not available using Bick's chiral pool strategy[4e] starting from (−)-cocaine, was synthesized for the first time.

Table 2
Selected results on the deoxygenative reduction of the tosylhydrazone group in **11**

Entry	Reaction conditions	Yield (%)
1	$NaBH_4$, EtOH, 35 °C	—
2	$NaBH_4$, DMF, 80 °C	—
3	$NaBH_4$, MeOH, AcOH, 80 °C	55
4	LAH, THF, rt	—
5	LAH, THF, reflux	33[a]
6	DIBAL, CH_2Cl_2, 0 °C	83
7	NaH, PhH	—

[a] Calculated from the ^{1}H NMR spectra of crude reaction mixtures.

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19. All enantiomeric excesses were measured by ^{1}H NMR in the presence of (+)-2,2,2-trifluoro-1-(9-anthranyl)ethanol, (+)-TFAE.
20. The substantial difference in the values recorded at *c* = 1 and *c* = 0.3 clearly showed that the specific rotation of (−)-ferrugine is dependent on concentration and that the literature value must have been taken at a concentration between 0.3 and 1.0.
21. *All new compounds gave satisfactory analytical data*: (−)-2α-Benzoyltropane, [(−)-*ent*-ferrugine], (−)-**3**. Purification using preparative thin layer chromatography (PTLC) (5% MeOH/CH_2Cl_2+NH_3) gave a yellow oil (0.110 g, 56%). R_f = 0.5 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.98–7.92 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.43 (m, 2H), 3.82–3.76 (m, 1H), 3.35 (d, *J* = 6.0 Hz, 1H), 3.20–3.15 (m, 1H), 2.35 (s, 3H), 2.05–1.69 (m, 5H), 1.62–1.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 201.5, 136.3, 132.8, 128.6, 128.4, 63.6, 61.1, 47.7, 40.3, 29.8, 26.0, 22.7, 18.5; ν_{max} ($CHCl_3$) 1675 (C=O) cm^{-1} HRMS (EI): M^+, found 229.1460, $C_{15}H_{19}NO$ requires 229.1467; ee ⩾ 99%;$[\alpha]_D^{20}$ −100 (*c* 1, $CHCl_3$), −29 (*c* 0.3, $CHCl_3$); lit.[4e] data for (+)-enantiomer $[\alpha]_D^{19}$ +55, ($CHCl_3$).