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Approaches to the enantioselective synthesis of ferrugine and its analogues

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ABSTRACT

A four-step synthetic route, to ferrugine (2α-benzoyltropane), its methyl analogue (2-acetyltropane) and their *N*-benzyl analogues is reported. The reaction sequence uses tropinone or *N*-benzylnortropinone aldols as key intermediates. Reduction of aldol derived *N*-tosylhydrazones and oxidation of the side chain hydroxyl group followed by spontaneous diastereomer equilibration provides the final products. Relative configuration of the *exo*,*anti* *N*-methyl and *N*-benzyl aldols was retained during *N*-tosylhydrazone formation. The relative stereochemistry of *N*-tosylhydrazones was assigned by single crystal diffraction. The final products, ferrugine and its methyl analogue, were synthesized in enantiomerically pure form via asymmetric deprotonation of tropinone using chiral lithium amide/lithium chloride aggregate prepared in situ from (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amine hydrochloride.

1. Introduction

Ferrugine is a tropane alkaloid isolated from the extracts of the Australian arboreal species *Darlingiana ferruginea*.[1] Other tropane alkaloids, many of which are known for their potent biological activity[2] include cocaine, atropine and baogonteng A. Tropanes like ferrugine (**1**, Fig. 1) and closely related, ferruginine (**2**) are nicotinic receptor antagonists, potentially useful in the treatment of Alzheimer's disease.[3]

Fig. 1. Structures of natural ferrugine and ferruginine.

Unlike ferruginine, which has been synthesized by several approaches[4–9] ferrugine has been accessed synthetically only in two ways: (i) by Bick et al.[10] via anhydroecgonine obtained from cocaine, (ii) by Grainger et al. via thermal elimination of diethyldithiocarbamate as the key reaction.[11] Bick's synthesis relied on the chiral pool approach, employing (−)-cocaine (**6**) as starting material to get the enantiomerically pure key intermediate anhydroecgonine (**5**),[12,13] and its ester hydrogenation of which followed by reaction with diphenylcadmium gave (−)-*ent*-ferrugine. The synthesis being not very effective nonetheless provided confirmation of structure and absolute configuration of natural (+)-ferrugine. The chiral pool approach using cocaine can give the unnatural enantiomer, (−)-*ent*-ferrugine only (Scheme 1). The more recent route by Grainger et al., leads to racemic ferrugine, via a sequence of nine synthetic transformations,[11] which cannot be easily carried out in an asymmetric fashion. In principle, combination of the Bick route with the known preparation of enantiomerically enriched anhydroecgonine methyl ester (**4**, R=Me) obtained via enantioselective deprotonation of tropinone[14–17] may constitute an enantioselective approach giving either enantiomeric form of ferrugine (Scheme 1).

N-Benzyl analogue of ferrugine **10** or 2-acetyl *N*-benzylnortropane could be formally synthesized enantioselectively using a combination of Node's[18,19] enzymatic (PLE catalyzed) dealkoxycarbonylation of dicarboxylates **7** combined with the Bick route (Scheme 2). Any method used for synthesis of ferruginine (**2**)[4]

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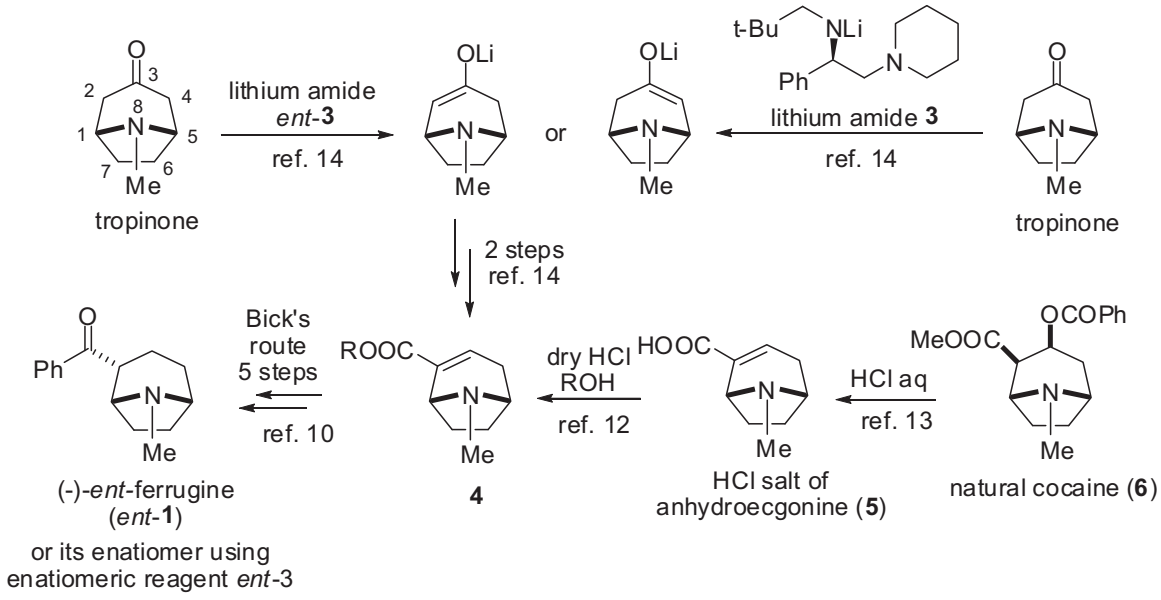
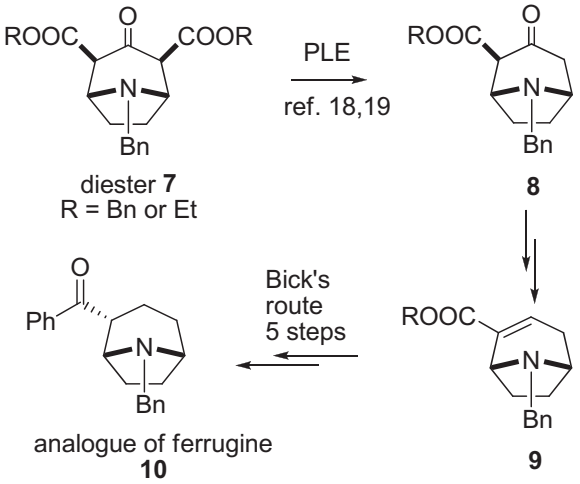


Scheme 1. Formal enantiselective synthesis of ferrugine based on Bick's approach and asymmetric deprotonation of tropinone.

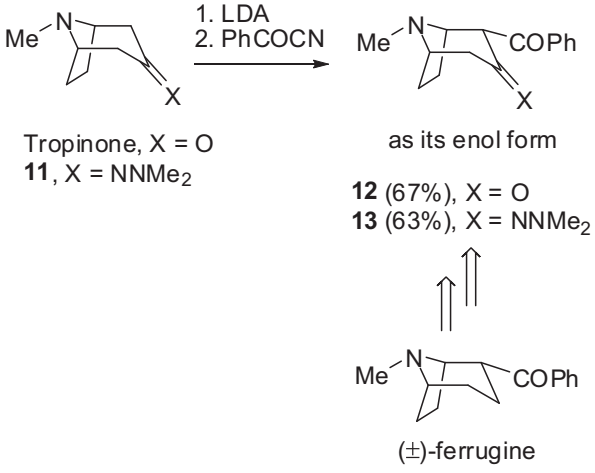
(e.g., synthesis by Aggarwal,[5] Husson,[6] Rapaport,[7] or Rigby[8]) could in principle also be adopted by adding alkene hydrogenation for synthesis of acetyl analogous of ferrugine. However, all such approaches would be excessively lengthy and would give minimal yield of the target molecule. In a preliminary communication we have demonstrated viability of a short route to either enantiomer of ferrugine via enantioselective aldol reaction.[20] Herein we wish to report our full study on possible approaches to the synthesis of ferrugine and its *N*-benzyl and acetyl analogues via a short synthetic sequence.



Scheme 2. Formal enantiselective synthesis of ferrugine based on Bick's approach and enzymatic (PLE) dealkoxycarbonylation.

2. Results and discussion

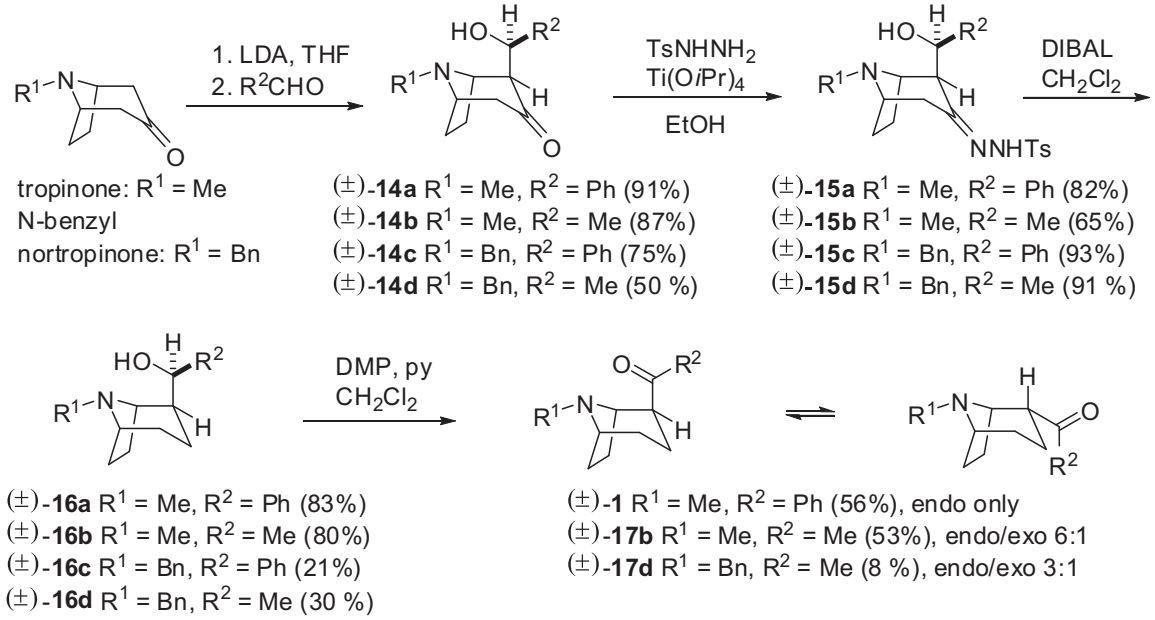
The asymmetric deprotonation of C_s symmetrical molecules,[21,22] e.g., tropinone is a powerful, proven, methodology for the synthesis of enantiomerically pure compounds including tropane derivatives.[14,23] Because deprotonation followed by acylation is the simplest method for stereoselective introducing of acyl group on tropane scaffold[24,25] we have turned our attention to benzoylation of tropinone at the C-2 position. The reaction turned out to be most effective with benzoyl cyanide as acyl donor (Scheme 3). Using benzoyl chloride gave besides **12**, several other products with predominance of an enone formed by a ring opening reaction known with chloroformates.[26]



Scheme 3. Approaches to ferrugine via direct C-acylation of tropane scaffold.

The actual challenge was however, the selective removal of the C-3 carbonyl in the resulting 1,3-diketone **12**. Disappointingly no method for regioselective conversion of the cyclic ketone carbonyl into a leaving group could be found. Efforts to use synthetic ketone equivalents: e.g., use of tropinone *N*,*N*-dimethylhydrazone (**11**) differentiated the two carbonyls effectively. Masking one of the carbonyls gave opportunity for functional group manipulation leading to the desired removal of the C-3 carbonyl. Nonetheless the attempts to reduce and eliminate the masked carbonyl in **13** (side chain protection, reduction to amine or hydrazine, N-acylation, followed by elimination of formed amide or hydrazide) were fruitless. Therefore we turned our attention to deoxygenation of tropinone aldols in hope of using the

known enantioselective aldol reactions as the method for introduction of the C-2 side chain in ferrugine and in its analogues. Tropinone and *N*-benzylnortropinone aldols could be prepared by known and adopted procedures in both racemic and optically pure forms. The racemic tropinone aldol **14a** and the unknown analogue **14b** as well as their *N*-benzyl counterparts **14c** and **14d** were prepared in nearly diastereomerically pure forms (≥95% of the *exo*,*anti* diastereoisomer; Scheme 4). The relative stereochemistry of the *N*-benzyl aldols **14c**,**d** was inferred from the NMR data to be *exo*,*anti* in analogy to the known aldol **14a**. The *exo*,*anti* configuration in **14c** was later also confirmed by X-ray structure analysis.[27] Based on our experience, reduction of tosylhydrazones was judged to be the most suitable method for removal of the carbonyl group in the aldols. In our plan the final transformation—side chain hydroxyl oxidation—was to remove the side chain stereocenter making the strategy insensitive to aldol isomerization. Consequently we could proceed with the deoxygenation of the carbonyl group even if the tosylhydrazone intermediates were obtained as diastereomeric mixtures. This must have been taken into account because of the known propensity of tropinone aldols to isomerization and, the recently observed, higher stability of the *exo*,*syn* over the *exo*,*anti* isomers.[28] Effective transformation of such aldols to hydrazones was somewhat challenging. Unfortunately reactivity of the carbonyl in the aldols was apparently sterically hindered by the *exo* side chain and the bicyclic tropane skeleton. In addition reactions of such aldols containing amine functionality are often complicated by easy retroaldolization, dehydration or isomerization. Formation of tosylhydrazones was found satisfactory only if promoted by titanium(IV) isopropoxide, a reagent successfully used for the preparation of imines from hindered ketones.[29] Despite good conversion (>80% by NMR) the tosylhydrazone products were hard to isolate in good yields (<25%). Optimization of the reaction medium (abs EtOH) and workup (removal of copious amounts of titanium hydroxides) allowed for isolation of the hydrazones **15** in satisfactory purities as single diastereomers. Chromatographic purification or crystallization (ethanol) gave hydrazones ready for the next step. Hydrazones **15a,b** were obtained in good yields 82% and 65% (Scheme 4). Although the relative stereochemistry of the tosylhydrazones formed should not affect the overall outcome of the planned synthetic sequence (Scheme 4), because of removal of one stereocenter and configurational lability of the C-2 stereocenter of the final products under basic conditions (presence of amine in the molecule itself), the question whether the relative configuration remained unchanged in the tosylhydrazones formed was intriguing. As no NMR data for this type of compound was available the only reliable method at hand was single crystal X-ray diffraction. Crystal structures of two representative tosylhydrazones of tropinone (**15a**) and *N*-benzylnortropinone (**15c**) aldols are shown in Figs. 2 and 3. As can be seen, the hydrazones



Scheme 4. Synthesis of racemic ferrugine and its *N*-benzyl and C-2 acetyl analogues.

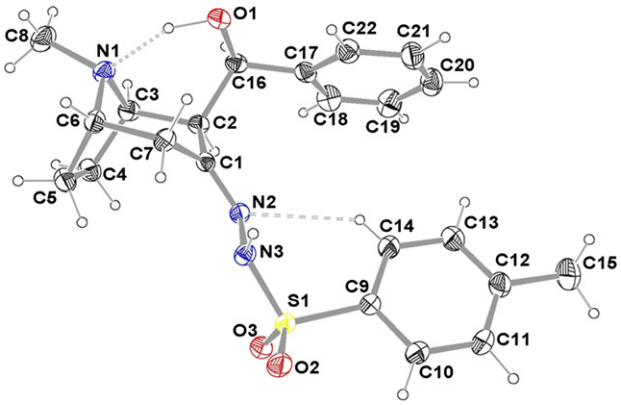


Fig. 2. X-ray structure of *N*-tosylhydrazone of *exo*-2-(1′-hydroxybenzyl)tropane (**15a**). Geometry of intramolecular H-bonds: O1—H1O 0.93(2), O1···N1 2.760(2), H1O···N1 1.90(2) Å, O1—H1O···N1 154(2)° and C(14)—H(14) 0.88(3), C(14)···N(2) 3.169(3), H(14)···N(2) 2.52(3) Å, angle C(14)—H(14)···N(2) 131(2)°. Displacement ellipsoids are drawn at 30% probability level, atoms numbering arbitrary.

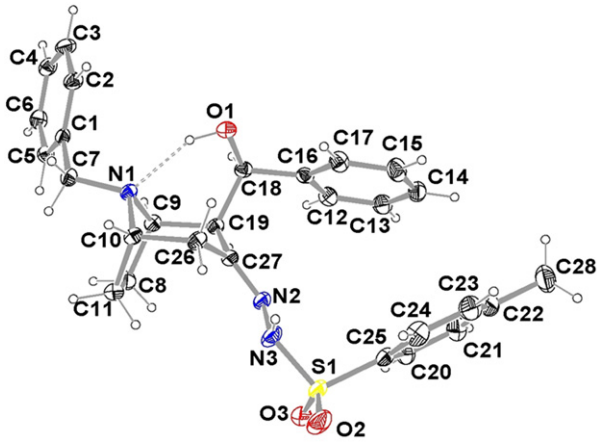
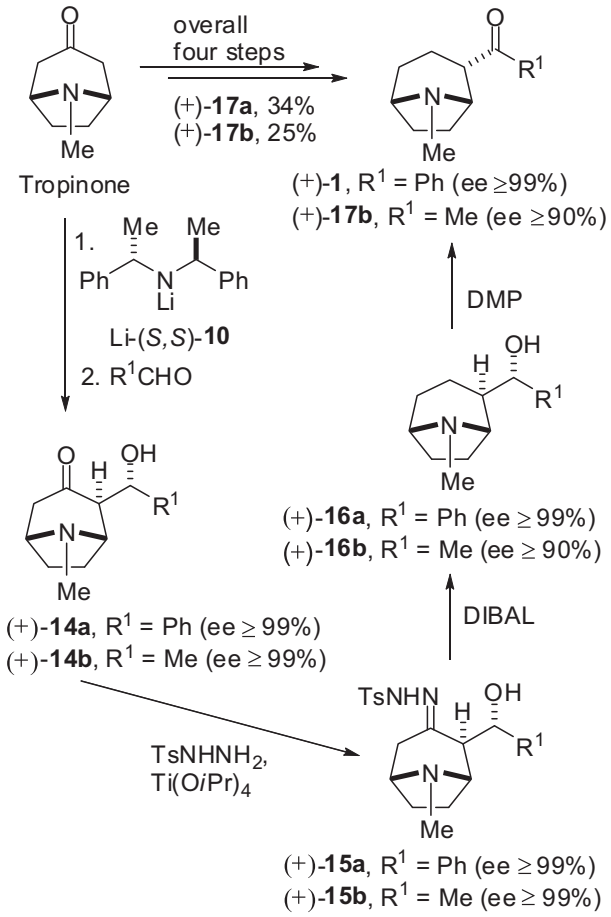


Fig. 3. X-ray structure of *N*-tosylhydrazone of *exo*-2-(1′-hydroxybenzyl)-*N*-benzylnortropinone (**15c**). Geometry of intramolecular H-bond: O1–H1O 1.07(3), O1···N1 2.628(2), H1O···N1 1.62(3) Å, angle O1–H1O···N1 154(3)°. Displacement ellipsoids are drawn at 30% probability level, atoms numbering arbitrary.

retained the relative configuration of the *exo*,*anti* aldols. Their molecular structure is dominated by intramolecular hydrogen bonds between side chain hydroxyl and the ring nitrogen atom, which exist even if other strong acceptors are present (tosyl oxygens, hydrazone moiety). In compound **15a** another relatively strong intramolecular H-bond is observed between C14 proton and N2 nitrogen of the hydrazone group of geometry shown in Fig. 2. Hydrazone proton in compound **15c** is involved in intermolecular hydrogen bond of geometry N3–H3N 0.95(2), N3···O1 [0.5−*x*, *y*−0.5, 0.5−*z*] 2.764(2), H3N···O1 1.83(2), N3–H3N···O1 167(2).

The optimal tosylhydrazone removal method, found for **15a**, was reduction with DIBAL-H in dichloromethane.[30] Other reagents, e.g.,: $NaBH_4$ in a mixture of acetic acid with MeOH, $NaBH_4$ in abs ethanol,[31] $NaBH_4$ in DMF, and LAH,[32] gave inferior results (0–55% yield). It appeared that success of the DIBAL-H reduction depended on purity of the tosylhydrazone substrates. When crystallized or carefully chromatographed and dry substrates were used the reduction gave good yields (80–83%) of the *N*-methyl derivatives **16a**,**b**. However, the *N*-benzyl products **16c**,**d** were obtained in markedly worse yields (21–30%). At this stage of the synthesis the *N*-benzyl analogues began to cause problems, which could not be overcome entirely. In our hands, the yields for the *N*-benzyl products in the reduction step and the following oxidation step (vide infra) remained evidently lower than for the *N*-methyl derivatives (Scheme 4). Oxidation of the side chain hydroxyl was the last step. The presence of the tertiary amine in the target molecule narrows the choice of potential oxidants. Use of the classic Swern oxidation, or its modifications (SO_3·Py), gave disappointing results. Treatment of **16a** with Dess–Martin periodinane[33,34] under typical conditions (dry DCM, pyridine, rt) unfailingly provided the product of oxidation in 56% yield (after meticulous purification by PTLC). Gratifyingly NMR data of the product fully agreed with literature data reported for ferrugine **1** isolated from a plant material.[1,10,11] We envisaged that the presence of the carbonyl in the side chain would render the hydrogen at the C-2 (α to ketone carbonyl) sufficiently acidic to enolize in the presence of amine and spontaneously equilibrate the mixture of possible *exo* and *endo* isomers of the oxidation product **1** (Scheme 4). Inspection of NMR spectra of the oxidation product indicated the presence of virtually one isomer (*endo*) as described for ferrugine. Clearly for 2-benzoyl tropane (**1**) the thermodynamic equilibrium, as was expected, is strongly shifted toward the *endo* form. The acetyl analogue of ferrugine (2-acetyltropane, **17b**) was obtained by the same procedure in 53% yield but as a mixture of two isomers. In this case the acetyl group preference of the *endo* over the *exo* configuration was much less definite and was inferred from NMR spectra to be ca. 6:1. This agreed with observations by Grainger.[11] Disappointingly oxidation of the *N*-benzyl analogues **16c**,**d** followed by chromatographic isolation gave the desired product **17d** in 8% yield (Scheme 4). The ratio of *endo*/*exo* isomers found by NMR was ca. 3:1 (64:36 by GC–MS). The product of oxidation of **16c** was identified by GC–MS in chromatographically purified fraction but could not be isolated in pure form. Explanation of encountered problems with the *N*-benzyl analogues and possible solutions calls for further studies.

Because yields of the two last steps in the syntheses of the *N*-benzyl derivatives remained below our expectations we constrained applications of the enantioselective variant to the *N*-methyl derivatives (Scheme 5). Following the literature procedure,[14] the aldol product (+)-**14a** was prepared in very good yield and ee using (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amine ((*S*,*S*)-**10**) hydrochloride and 2 equiv of *n*-butyllithium. Adopting the procedure for reaction with acetaldehyde gave the aldol (+)-**14b** admixed with its diastereomer. Crystallization of crude aldols gave diastereomerically pure products (+)-**14a** and (+)-**14b** with 99% ee, and in 80% and 65% yields. The optically pure (ee ≥99%) tosylhydrazones (+)-**15a** and (+)-**15b** were prepared in 55% and 60% yields, respectively. Following step gave the chiral alcohols (+)-**16a** in 74% yield (ee ≥99%) and (+)-**16b** in 70% yield (ee ≥90%). Finally, oxidation concomitant with spontaneous *exo*/*endo* isomerization provided (+)-ferrugine ((+)-**1**) in 56% yield as well as its acetyl analogue **17b** as a mixture of *exo*/*endo* isomers (2α-acetyltropane/2β-acetyltropane, ca. 85:15). Enantiomeric excess measured by ^{1}H



Scheme 5. Enantioselective synthesis of ferrugine and its acetyl analogue (absolute configurations as shown).

NMR was ≥99% for (+)-ferrugine and ≥90% for the major diastereomer of the acetyltropane **17b**. The absolute configuration of synthesized ferrugine was a result of propensity for selective removal of one the enantiotopic protons in tropinone molecule by enantiomeric form of the chiral amide used in the aldol reaction step. The absolute configuration of ferrugine **1** agreed with known sense of enantioselection for chiral amide Li-(*S*,*S*)-**10** in reaction with tropinone[14] and with correlation of absolute configuration of (−)-cocaine with ferrugine by Bick's synthesis.[10]

3. Conclusions

We showed that enantioselective deprotonation combined with deoxygenation of the aldol carbonyl group can be an expedient strategy for synthesizing C-2 acyl tropanes. The same simple, four-step, route depending on lithium amide bases used, allows to prepare racemic form, or either enantiomer of the acyltropane at will. The practicability of the approach was demonstrated by the synthesis of natural ferrugine and its methyl analogue (2-acetyltropane) with high enantiomeric purity (≥90–99%) using convenient chiral amine hydrochloride as the chiral reagent. However, limitations of this approach are problems with reduction of tosylhydrazones and oxidation of the side chain alcohols in case of the *N*-benzylnortropane derivatives. Nonetheless, these problems may be overcome by further study.

4. Experimental section

4.1. General methods

Thin-layer chromatography (TLC) was performed on pre-coated plates (Merck, silica gel 60, F_{254}) unless indicted otherwise. The spots were detected using UV light (254 nm), and phosphomolybdic acid followed by charring. Infrared (IR) spectra of compounds were recorded on a Nicolet Magna-IR 550 FTIR Series II Spectrometer ($CHCl_3$). Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker AVANCE II 400 spectrometer in $CDCl_3$ at ambient temperature. Chemical shifts are reported in parts per million downfield of tetramethylsilane. Specific rotation was measured with Optical Activity AA-10R or Perkin Elmer 141 Automatic Polarimeter. Reagents were purchased from Aldrich. The chiral amine **10** is available commercially in both enantiomeric forms (e.g., Aldrich, (−)-bis[(*S*)-1-phenylethyl]amine). Tropinone and aldehydes were purified by standard techniques.[35] *N*-benzylnortropinone was prepared as described.[36] All enantiomeric excesses were measured by ^1H NMR in the presence of (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE).

Crystallographic data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer with CuKα radiation (λ=01.54178 Å). The structures were solved by direct methods and refined using SHELXS97[37] and SHELXL97[37] programs. All non-H atoms were refined anisotropically; all H-atoms bonded to carbon atoms were placed on geometrically calculated positions and refined using a riding model. The hydroxyl H-atoms in both structures were located from $\Delta\rho$ maps and refined isotropically.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 873342 and 873341, respectively, for compounds **15a**, and **15c**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

4.2. General procedure for the preparation of benzoyl tropanes 12 and 13

A solution of *n*-buthyllithium in hexane (2.33 M, 1.2 equiv) was added dropwise to a cooled (0 °C) solution of diisopropylamine (1.2 equiv) in THF (10 mL for 3.0 mmol of ketone or hydrazone). The mixture was stirred for 30 min, then tropinone (at −78 °C) or *N*,*N*-dimethylhydrazone of tropinone (at 0 °C) was added (1 equiv) in THF (3 mL for 3.0 mmol of ketone or hydrazone). After stirring for 1–4 h at the same temperature, benzoyl cyanide (1.15 equiv) was added at −78 °C. After stirring for 15 min the reaction was quenched with aq solution of K_2CO_3 (40%, 5 mL), warmed up to rt, and extracted with DCM (3×15 mL). The crude extracts of **12** were additionally washed with aq $AgNO_3$ (5%, 2×10 mL) followed by aq ammonia solution (10%, 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give the crude product. Purification by dry-column flash chromatography on silica gel (0–15% MeOH/DCM) gave products as oils.

*4.2.1. 2-Benzoyl-8-methyl-8-azabicyclo[3.2.1]octan-3-on (**12**) as predominating enol form 2-benzoyl-8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-ol.*[24] Yield: 0.489 g, 67%; R_f=0.65 (10% MeOH/DCM). ^1H NMR ($CDCl_3$): enol form (≥90%): 16.42 (br s, 1H), 7.62–7.41 (m, 5H), 3.85 (d, *J*=5.7 Hz, 1H), 3.45 (t, *J*=6.0 Hz, 1H), 2.93 (ddd, J_1=19.2 Hz, J_2=5.5 Hz, J_3=1.9 Hz, 1H), 2.38–2.00 (m, 2H), 2.34 (s, 3H), 2.23 (d, *J*=19.2 Hz, 1H), 2.07–1.98 (m, 1H), 1.76–1.67 (m, 1H); ^{13}C NMR ($CDCl_3$): 195.1, 181.2, 134.9, 130.4, 128.5, 128.1, 112.4, 59.4, 57.8, 40.1, 36.7, 33.7, 29.0.

*4.2.2. 2-Benzoyl-3-(2′,2′-Dimethylhydrazono)-8-methyl-8-azabicyclo [3.2.1]octane (**13**) as enol form.* Yield: 0.539 g, 63%; R_f=0.61 (20% MeOH/DCM). ^1H NMR ($CDCl_3$): enol form (≥98%) 12.06 (br s, 1H), 7.35–7.27 (m, 5H), 3.78 (d, *J*=5.1 Hz, 1H), 3.45 (t, *J*=5.6 Hz, 1H), 3.06 (dd, J_1=18.9 Hz, J_2=5.1 Hz, 1H), 2.55 (s, 6H), 2.50 (s, 1H), 2.35 (s, 3H), 2.15–2.25 (m, 2H), 1.99–1.90 (m, 1H), 1.62–1.55 (m, 1H); ^{13}C NMR ($CDCl_3$): 191.7, 160.7, 141.3, 128.7, 128.0 (2C), 126.5 (2C), 102.6, 60.5, 57.9, 48.3 (2C), 36.6, 34.1, 32.1, 28.3; ν_{max} ($CHCl_3$): 2961, 2461, 1574, 1534, 1306 cm^{-1}. HRMS (EI): M^+, found 285.1837, $C_{17}H_{23}N_3O$ requires 285.1841.

4.3. General procedure for the preparation of aldols (±)-14a–d (LDA deprotonation of ketone)

A solution of *n*-buthyllithium in hexane (2.33 M, 1.2 equiv) was added dropwise to a cooled (0 °C) solution of diisopropylamine (1.2 equiv) in THF (10–25 mL). The mixture was stirred for 30 min, then cooled to −78 °C and a solution of ketone (1 equiv) in THF (5–10 mL) was added dropwise. After stirring for 2 h, aldehyde (1.15 equiv) was added and the mixture was stirred for another 10–40 min. The reaction was quenched with NH_4Cl_{aq} (20 mL), allowed to warm up to rt and extracted with DCM (3×30 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give the crude product. Precipitation or crystallization from mixed solvent system hexane/dichloromethane gave the major aldol isomer *exo*,*anti* as white solid.

4.4. General procedure for preparation of enantiomerically enriched aldols (+)-14a,b

A solution of *n*-buthyllithium in hexane (2.33 M, 2.4 equiv) was added dropwise to a cooled (0 °C) solution of (*R*,*R*)-bis(1-phenylethyl)amine hydrochloride (1.2 equiv) in THF (10 mL). The mixture was stirred for 45 min, then cooled to −78 °C and a solution of ketone (1 equiv) in THF (6 mL) was added dropwise. After stirring for 2 h, aldehyde (1.15 equiv) was added and the mixture was stirred for another 10–40 min. The reaction was quenched

with NH_4Cl_{aq} (20 mL), allowed to warm up to rt, and extracted with DCM (3×30 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give the crude product and chiral amine mixture. The product was taken up in small portion of warm dichloromethane and the resulting solution was diluted slowly with hexane to precipitate the solid product. The chiral amine remained in supernatant and was saved for recovery.

*4.4.1. (+)-(1S,2R,1′S,5R)-2-(1′-Hydroxybenzyl)-tropinone ((+)-**14a**).*[24] To solution of chiral lithium amide (12 mmol) was added a solution of tropinone (0.696 g, 5 mmol, 1 equiv) in THF (6 mL). After 2 h, benzaldehyde (0.59 mL, 5.75 mmol, 1.15 equiv) was added, and the mixture was stirred for another 10 min. Then the experiment was performed as described in general procedure. Crystallization from hexane/dichloromethane gave aldol **14a** (0.981 g, 80%) as white crystals, mp = 129–131 °C. ^{1}H NMR ($CDCl_3$): 7.70 (br s, 1H), 7.37–7.22 (m, 5H), 5.23 (d, J=3.0 Hz, 1H), 3.65–3.56 (m, 1H), 3.54–3.44 (m, 1H), 2.86 (ddd, J=2.0, 5.0, 15.5 Hz, 1H), 2.47 (s, 3H), 2.45–2.39 (m, 1H), 2.36 (t, J=2.0 Hz, 1H), 2.33–2.12 (m, 2H), 1.73–1.46 (m, 2H); ee ≥99%; $[\alpha]_D^{20}$ +21 (*c* 1.2, MeOH), Ref.24 $[\alpha]_D^{20}$ +23 (*c* 0.0173, $CHCl_3$), Ref.14 $[\alpha]_D^{20}$ +19.7 (*c* 1.2, MeOH).

*4.4.2. (±)-exo,anti-2-(1′-Hydroxyethyl)tropinone (**14b**).* To solution of LDA (36 mmol) was added a solution of tropinone (4.176 g, 30 mmol, 1 equiv) in THF (10 mL). After 2 h, freshly distilled acetaldehyde (2 mL, 35 mmol, 1.15 equiv) in THF (2 mL) was added, and the mixture was stirred for another 40 min. Then the reaction was worked up as described in general procedure. Crystallization gave aldol **14b** (4.765 g, 87%) as a white crystals, mp = 99–104 °C. R_f=0.78 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): 7.13 (br s, 1H), 4.16 (dq, J=2.0, 6.5 Hz, 1H), 3.46–3.35 (m, 2H), 2.70 (ddd, J=1.5, 5.0, 16.0 Hz, 1H), 2.39 (s, 3H), 2.35–2.03 (m, 4H), 1.68–1.43 (m, 2H), 1.08 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): 209.6, 70.7, 67.8, 62.9, 61.5, 51.5, 40.7, 26.4, 26.3, 21.0; ν_{max} ($CHCl_3$): 3150 (–OH), 1705 (C=O) cm^{-1}. *m*/*z* 183 (M^+, 3), 110 (72), 96 (78), 83 (79), 82 (100), 81 (85), 55 (72), 42 (71), 40 (94); HRMS (EI): M^+, found 183.2480, $C_{10}H_{17}NO_2$ requires 183.2475.

*4.4.3. (+)-(1S,2R,1′R,5R)-2-(1′-Hydroxyethyl)-tropinone ((+)-**14b**).* To solution of chiral lithium amide (7.2 mmol) was added a solution of tropinone (0.418 g, 3.0 mmol, 1 equiv) in THF (6 mL). After 2 h, freshly distilled acetaldehyde (0.2 mL, 3.5 mmol, 1.15 equiv) in THF (0.2 mL) was added, and the mixture was stirred for another 40 min. Then the experiment was performed as described in general procedure. The crude product was obtained as a mixture of diastereoisomers (0.544 g, 99%). Crystallization gave the major isomer (0.365 g, 65%) as white crystals, mp 102–105 °C. ee ≥99%; $[\alpha]_D^{20}$ +47 (*c* 1, MeOH).

*4.4.4. (±)-exo,anti-2-(1′-Hydroxybenzyl)-N-benzylnortropinone (**14c**).* To solution of LDA (7.2 mmol) was added a solution of *N*-benzylnortropinone (1.292 g, 6 mmol, 1 equiv) in THF (7 mL). After 2 h, benzaldehyde (0.70 mL, 6.9 mmol, 1.15 equiv) was added, and the mixture was stirred for another 10 min. Then the reaction was worked up as described in general procedure. Crystallization gave aldol **14c** (1.454 g, 75%) as white crystals, mp = 99–104 °C. R_f=0.77 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): 7.43–7.21 (m, 10H), 5.11 (d, J=3 Hz, 1H), 3.73–3.65 (m, 3H), 3.58–3.57 (m, 1H), 2.82 (ddd, J_1=1.5 Hz, J_2=4.5 Hz, J_3=6 Hz, 1H), 2.45–2.44 (m, 1H), 2.36–2.32 (m, 3H), 1.70–1.66 (m, 2H); ^{13}C NMR ($CDCl_3$): 208.3, 141.6, 137.6, 129.0, 128.7, 128.0, 127.7, 127.2, 125.5, 76.4, 65.1, 64.5, 58.9, 57.0, 51.5, 26.8, 26.3; ν_{max} ($CHCl_3$): 3173 (–OH), 1712 (C=O) cm^{-1}, HRMS (EI): M^+, found 321,1722, $C_{21}H_{23}NO_2$ requires 321.1729.

*4.4.5. (±)-exo,anti-2-(1′-Hydroxyethyl)-N-benzylnortropinone (**14d**).* To solution of LDA (12 mmol) was added a solution of *N*-benzylnortropinone (2.153 g, 10 mmol, 1 equiv) in THF (10 mL). After 2 h, freshly distilled acetaldehyde (0.60 mL, 11.5 mmol, 1.15 equiv) in THF (1 mL) was added, and the mixture was stirred for another 40 min. Then the reaction was worked up as described in general procedure. Crystallization gave aldol **14d** (1.290 g, 50%) as a white crystals, mp = 107–112 °C. R_f=0.8 (10% MeOH/DCM). ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.34 (m, 5H), 6.94 (br s, 1H), 4.05 (dq, J_1=2.0 Hz, J_2=6.5 Hz, 1H), 3.64 (d, J=3.2 Hz, 2H), 3.58–3.51 (m, 2H), 2.66 (ddd, J_1=3.8 Hz, J_2=5.0 Hz, J_3=16.0 Hz, 1H), 2.36–2.34 (m, 1H), 2.28–2.26 (m, 2H), 2.11 (d, J=1.9 Hz, 1H), 1.70–1.60 (m, 2H), 1.09 (d, J=6.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 209.8, 137.5, 128.9, 128.7, 127.7, 70.4, 65.5, 62.9, 58.5, 56.9, 51.5, 26.8, 26.4, 20.8. IR ($CHCl_3$): 3193 (–OH), 1708 (C=O) cm^{-1}; HRMS (EI): M^+, found 259.1568, $C_{16}H_{21}NO_2$ requires 259.1572.

4.5. General procedure for the preparation of tosylhydrazones 15a–d

To a solution of titanium(IV) isopropoxide (1 equiv) in abs EtOH (5–18 mL) was added *p*-toluenesulfonyl hydrazide (1 equiv) and corresponding aldol **14a–d** (1 equiv). After stirring at rt for 120 h was added $NaCl_{aq}$ (5–10 mL). The mixture was filtrated through pad of Celite and washed with DCM (4×10 mL). The aqueous layer was extracted with DCM (3×25 mL). The combine extracts were dried over $MgSO_4$ and concentrated. Purification through dry-column flash chromatography (0–20% MeOH/DCM+NH_3) gave the product.

*4.5.1. (±)-N′-Tosylhydrazone exo-2-(1′-hydroxybenzyl)tropane (**15a**).* To a solution of titanium(IV) isopropoxide (2.94 mL, 10 mmol, 1 equiv) in EtOH (18 mL) was added *p*-toluenesulfonyl hydrazide (1.563 g, 10 mmol, 1 equiv) and *exo*,*anti*-2-(1′-hydroxybenzyl)tropinone aldol **14a** (2.454 g, 10 mmol, 1 equiv). Then the reaction was carried out as described in general procedure to give the product (3.412 g, 82%), mp 156–160 °C. R_f=0.6 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): 7.54–7.50 (m, 2H), 7.21–7.16 (m, 2H), 7.11–7.07 (m, 2H), 7.07–6.97 (m, 3H), 5.05 (d, J=4.0 Hz, 1H), 3.39–3.34 (m, 1H), 3.33–3.28 (m, 1H), 2.59–2.52 (m, 1H), 2.45 (s, 3H), 2.44–2.39 (m, 2H), 2.30 (s, 3H), 2.14–1.97 (m, 2H), 1.62–1.53 (m, 1H), 1.45–1.36 (m, 1H); ^{13}C NMR ($CDCl_3$): 156.8, 143.5, 141.8, 135.2, 129.6, 127.7, 127.6, 126.7, 126.0, 77.3, 67.0, 60.8, 56.7, 40.8, 36.0, 26.3, 25.7, 21.6. ν_{max} (KBr) 3500 (–OH), 1599 (C=N), 1165, 1335 (SO_2) cm^{-1}; *m*/*z* 152 (100), 106 (37), 105 (38), 95 (37), 94 (32), 91 (53), 82 (64), 77 (46%); HRMS (EI): M^++H, found 414.1857, $C_{22}H_{28}N_3O_3S$ requires 414.1852.

Crystal data for (*rac*)-**15a**: monoclinic, space group $P2_1/n$; a=9.8531(2), b=10.3665(2), c=21.3902(4) Å, β=102.183(1)°, V=2135.64(7) Å^3, Z=4, D_{calcd}=1.286 mg m^{-3}, F(000)=880, crystal dimensions 0.29×0.27×0.07 mm, radiation CuKα (λ=1.54178 Å). 16,168 reflections were collected in the range of $-11\leq h\leq 11$, $-11\leq k\leq 12$, $-24\leq l\leq 25$; of these 3734 were independent, R(int)= 0.0398. The structure was solved and refined using 2999 reflections with $I>2\sigma$. Final R and R_w were 0.0421and 0.1160, respectively.

*4.5.2. (+)-N′-Tosylhydrazone of (+)-(1S,2R,1′S,5R)-2-(1′-hydroxybenzyl)tropinone ((+)-**15a**).* To a solution of titanium(IV) isopropoxide (0.77 mL, 2.6 mmol, 1 equiv) in EtOH (11 mL) was added *p*-toluenesulfonyl hydrazide (0.406 g, 2.6 mmol, 1 equiv) and (+)-**14a** (0.648 g, 2.6 mmol, 1 equiv). Then the reaction was carried out as described in general procedure to give the product (0.591 g, 55%) as an oil ee ≥99%; $[\alpha]_D^{20}$ +78 (*c* 1, MeOH).

*4.5.3. (±)-N′-Tosylhydrazone of exo-2-(1′-hydroxyethyl)tropinone (**15b**).* To a solution of titanium(IV) (0.47 mL, 1.6 mmol, 1 equiv) in EtOH (5 mL) was added *p*-toluenesulfonyl hydrazide (0.250 g, 1.6 mmol, 1 equiv) and **14b** (0.290 g, 1.6 mmol, 1 equiv). Then the

reaction was carried out as described in general procedure to give the product (6.934 g, 62%), mp 158–161 °C. R_f=0.5 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): 7.90–7.23 (m, 2H), 7.39–7.20 (m, 2H), 4.10–3.93 (m, 1H), 3.40–3.18 (m, 2H), 2.62–2.47 (m, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 2.25–2.19 (m, 1H), 2.13–1.98 (m, 3H), 1.67–1.30 (m, 3H), 0.56 (d, J=6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): 154.5, 143.8, 135.1, 129.3, 128.2, 71.7, 68.0, 60.5, 54.4, 40.6, 36.3, 26.1, 25.5, 20.2, 19.1; ν_{max} (KBr) 3215 (−OH), 1600 (C=N), 1338, 1167 (SO_2) cm^{-1}; m/z 351 (M^+,1) 196 (59), 152 (63), 122 (42), 94 (45), 92 (52), 91 (87), 82 (100), 42 (50%); HRMS (EI): M^++H, found 352.1704, $C_{17}H_{26}N_3O_3S$ requires 352.1695.

*4.5.4. (+)-N′-Tosylhydrazone of (+)-(1S,2R,1′R,5R)-2-(1′-hydroxyethyl)tropinone ((+)-**15b**).* To a solution of titanium(IV) isopropoxide (0.47 mL, 1.6 mmol, 1 equiv) in EtOH (5 mL) was added *p*-toluenesulfonyl hydrazide (0.250 g, 1.6 mmol, 1 equiv) and (+)-**14b** (0.290 g, 1.6 mmol, 1 equiv). Then the reaction was carried out as described in general procedure to give the product as an oil (7.512 g, 65%), ee ≥99%; $[\alpha]_D^{20}$ +61 (*c* 1, MeOH).

*4.5.5. (±)-N′-Tosylhydrazone of exo-2-(1′-hydroxybenzyl)-N-benzylnortropinone (**15c**).* To a solution of titanium(IV) isopropoxide (0.79 mL, 2.65 mmol, 1 equiv) in EtOH (24 mL) was added *p*-toluenesulfonyl hydrazide (0.494 g, 2.65 mmol, 1 equiv) and **14c** (0.853 g, 2.65 mmol, 1 equiv). Then the reaction was carried out as described in general procedure to give the product (1.131 g, 93%), mp 156–160 °C. R_f=0.86 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): 7.37–7.34 (m, 4H), 7.33–7.27 (m, 5H), 7.19–7.00 (m, 5H), 4.92 (d, J=4.0 Hz, 1H), 3.92–3.45 (m, 2H), 3.42–3.34 (m, 2H), 2.57–2.54 (m, 1H), 2.43–2.39 (m, 6H), 2.12–1.93 (m, 3H), 1.64–1.58 (m, 1H), 1.44–1.39 (m, 1H); ^{13}C NMR ($CDCl_3$): 157.1, 143.4, 141.6, 137.9, 135.2, 129.5, 129.4, 128.9, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 127.2, 126.7, 126.0, 76.8, 64.7, 58.0, 57.1, 56.9, 36.1, 26.3, 26.2, 21.5; ν_{max} ($CHCl_3$) 3304 (−OH), 1600 (C=N), 1165, 1333 (SO_2) cm^{-1}; HRMS (ESI): M^++Na, found 512.1973, $C_{28}H_{31}N_3O_3SNa$ requires 512.1984.

Crystal data for (*rac*)-**15c**: monoclinic, space group $P2_1/c$, a=24.6542(5), b=5.8232(1), c=17.1721(4) Å, β=91.3090(1)°, V=2464.69(9) Å^3, Z=4, D_{calcd}=1.319 mg m^{-3}, F(000)=1040, crystal dimensions 0.80×0.47×0.45 mm, radiation CuKα (λ=1.54178 Å). 26,658 reflections were collected in the range of $-29\le h\le 29$, $-5\le k\le 6$, $-19\le l\le 20$; of these 4363 were independent, R(int)=0.0393. The structure was solved and refined using 4035 reflections with $I>2\sigma$. Final R and R_w were 0.0361 and 0.0938, respectively.

*4.5.6. (±)-N′-Tosylhydrazone of exo,anti-2-(1′-hydroxyethyl)-N-benzylnortropinone (**15d**).* To a solution of titanium(IV) isopropoxide (1.45 mL, 4.9 mmol) in EtOH (18 mL) was added *p*-toluenesulfonyl hydrazide (0.912 g, 4.9 mmol) and **14d** (1.271 g, 4.9 mmol). Then the reaction was carried out as described in general procedure to give the product (1.906 g, 91%), mp 149–155 °C. R_f=0.76 (10% MeOH/DCM); ^{1}H NMR (200 MHz, $CDCl_3$): 7.79–7.77 (m, 2H), 7.29–7.22 (m, 7H), 3.89 (dq, J_1=6.0 Hz, J_2=12.5 Hz, 1H), 3.51 (s, 2H), 3.43–3.37 (m, 1H), 3.35–3.32 (m, 1H), 2.49–2.39 (m, 3H), 2.37 (s, 3H), 2.31–2.26 (m, 1H), 2.10–2.06 (m, 3H), 1.65–1.60 (m, 1H), 1.48–1.42 (m, 1H), 0.53 (d, J=6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 155.3, 143.8, 137.1, 135.0, 129.8, 129.4, 128.9, 128.6, 128.1, 128.0, 127.6, 71.6, 65.6, 57.7, 57.0, 54.6, 36.3, 26.4, 26.0, 21.5, 21.4, 19.9. IR ($CHCl_3$): 3216 (−OH), 1599 (C=N) 1336, 1166 (−SO_2) cm^{-1}. HRMS (ESI): M^++Na, found 450.1836, $C_{23}H_{29}N_3O_3SNa$ requires 450.1830.

4.6. General procedure for the reductive removal of tosylhydrazone group

To a cooled solution (0 °C) of corresponding tosylhydrazone **15a**–**d** (1 equiv) in dry DCM (10–24 mL), was added a solution of diisobutylaluminum hydride in hexane (1 M, 3 equiv). After stirring for 24 h, another portion of DIBAL was added (1 M, 2–3 equiv). After 72 h, the reaction was quenched with water (20 mL), allowed to warm to rt and extracted with DCM (3×15 mL). The combined extracts were dried over $MgSO_4$ and concentrated.

*4.6.1. (±)-exo-2-(1′-Hydroxybenzyl)tropane (**16a**).* To a solution of **15a** (0.414 g, 1.00 mmol, 1 equiv) in DCM (20 mL), was added a solution of DIBAL in hexane (1 M, 5.0 mL, 5.0 mmol, 5 equiv). Then the reaction was carried out as described in general procedure to give the crude product. Purification by dry-column flash chromatography on silica gel (0–10% MeOH/DCM+NH_3) gave colorless oil (0.192 g, 83%). R_f=0.4 (10% MeOH/DCM); ^{1}H NMR ($CDCl_3$): 7.42–7.16 (m, 5H), 5.23 (d, J=2.5 Hz, 1H), 3.54–3.45 (m, 1H), 3.32–3.21 (m, 1H), 2.33 (s, 3H), 2.28–1.95 (m, 3H), 1.70–1.53 (m, 3H), 1.44–1.18 (m, 3H); ^{13}C NMR ($CDCl_3$): 144.2, 127.8, 126.4, 125.7, 78.2, 68.2, 62.2, 44.9, 41.1, 31.2, 26.4, 24.6, 14.3. ν_{max} (KBr) 3670 (−OH) cm^{-1}; m/z 231 (M^+, 12), 125 (21), 96 (64), 84 (51), 83 (33), 82 (100), 57 (46), 42 (38%); HRMS (EI): M^+, found 231.1618, $C_{15}H_{21}NO$ requires 231.1623.

*4.6.2. (+)-(1S,2R,1′S,5S)-2-(1′-Hydroxybenzyl)-tropane ((+)-**16a**).* To a solution of (+)-**15a** (0.530 g, 1.28 mmol, 1 equiv) in DCM (24 mL), was added a solution of DIBAL in hexane (1 M, 6.5 mL, 6.5 mmol, 5 equiv). Then the experiment was performed as described in general procedure. Purification by dry-column flash chromatography (0–10% MeOH/DCM+NH_3) gave a colorless oil (0.220 g, 74%). ee ≥99%; $[\alpha]_D^{20}$ +35 (*c* 1, MeOH).

*4.6.3. (±)-exo-2-(1′-Hydroxyethyl)tropane (**16b**).* To a solution of **15b** (0.699 g, 2 mmol, 1 equiv) in DCM (15 mL), was added a solution of DIBAL in hexane (1 M, 12 mL, 12 mmol, 6 equiv). Then the reaction was carried out as described in general procedure to give the crude product. Purification by column chromatography on neutral aluminum oxide (0–5% MeOH/DCM) gave colorless oil (0.271 g, 80%). R_f=0.24 (5% MeOH/DCM+NH_3); ^{1}H NMR ($CDCl_3$): 4.16 (dd, J=1.5, 6.5 Hz, 1H), 3.26–3.11 (m, 2H), 2.40–2.27 (m, 1H), 2.22 (s, 3H), 2.16–1.81 (m, 3H), 1.74–1.15 (m, 4H), 1.14 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): 72.3, 68.5, 61.8, 44.0, 41.2, 31.6, 26.0, 24.6, 20.8, 14.0; ν_{max} (KBr) 3670 (−OH) cm^{-1}; m/z 169 (M^+, 25) 97 (17), 96 (88), 94 (16), 84 (23), 83 (28), 57 (49), 42 (40%); HRMS (EI): M^+, found 169.2643. $C_{15}H_{21}NO$ requires 169.2640.

*4.6.4. (+)-(1S,2R,1′R,5S)-2-(1′-Hydroxyethyl)-tropane ((+)-**16b**).* To a solution of (+)-**15b** (0.699 g, 2 mmol, 1 equiv) in DCM (15 mL), was added a solution of DIBAL in hexane (1 M, 12 mL, 12 mmol, 6 equiv). Then the experiment was performed as described in general procedure. Purification by column chromatography on neutral aluminum oxide (0–5% MeOH/DCM) gave a colorless oil (0.240 g, 71%). ee ≥90%; $[\alpha]_D^{20}$ +48 (*c* 1, MeOH).

*4.6.5. (±)-exo-2-(1′-Hydroxybenzyl)-N-benzylnortropane (**16c**).* To a solution of **15c** (1.903 g, 4.16 mmol, 1 equiv) in DCM (10 mL), was added a solution of DIBAL in hexane (1 M, 25 mL, 25 mmol, 6 equiv). Then the experiment was performed as described in general procedure. Purification by dry-column flash chromatography on neutral aluminum oxide (0–50% AcOEt/hexane) gave yellow oil (0.267 g, 21%). R_f=0.77 (10% MeOH/DCM); ^{1}H NMR ($CDCl_3$): 7.43–7.39 (m, 10H), 5.14 (d, 1H), 3.60–3.49 (m, 4H), 2.30–2.09 (m, 2H), 1.69–1.62 (m, 2H), 1.38–1.33 (m, 2H), 0.99–0.97 (m, 3H); ^{13}C NMR ($CDCl_3$): 144.0, 138.1, 128.9, 128.4, 127.7, 127.2, 126.2, 125.6, 72.0, 66.4, 59.2, 57.7, 45.1, 31.6, 27.0, 24.8, 14.8. ν_{max} ($CHCl_3$) 3387 (−OH) cm^{-1}; HRMS (EI): M^+, found 307.1947, $C_{21}H_{25}NO$ requires 307.1936.

*4.6.6. (±)-exo-2-(1′-Hydroxyethyl)-N-benzylnortropane (**16d**).* To a solution of **15d** (1.864 g, 4.36 mmol, 1 equiv) in DCM (18 mL), was

added a solution of DIBAL in hexane (1 M, 26.16 mL, 26.16 mmol, 6 equiv). Then the reaction was carried out as described in general procedure to give the crude product. Purification by dry-column flash chromatography on neutral aluminum oxide (0–10% MeOH/DCM) gave yellow oil (0.321 g, 30%). R_f=0.47 (10% MeOH/DCM); ^{1}H NMR ($CDCl_3$): 7.33–7.32 (m, 5H), 4.10 (dq, J_1=1.1 Hz, J_2=6.3 Hz, 1H), 3.52 (d, J=12.8 Hz, 1H), 3.42 (d, J=12.8 Hz, 1H), 3.36–3.31 (m, 1H), 3.25–3.21 (m, 1H), 2.22–2.02 (m, 2H), 2.00–1.90 (m, 1H), 1.74–1.65 (m, 3H), 1.54–1.49 (m, 1H), 1.38–1.32 (m, 1H), 1.25–1.24 (m, 1H), 1.13 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): 138.2, 128.9, 128.5, 127.2, 72.4, 67.1, 59.2, 57.8, 44.2, 31.7, 26.9, 24.9, 20.9, 14.8; IR ($CHCl_3$): 3179 (−OH) cm^{-1}; MS (EI): 245 (M^+, 19), 200 (11), 172 (25), 158 (49), 104 (8), 91 (100), 65 (13), 41 (10); HRMS (EI): M^+, found 245.1771, $C_{16}H_{23}NO$ requires 245.1780.

4.7. General procedure for oxidation of alcohols 16

To a solution of corresponding alcohol **16a**–**d** (1 equiv) in dry DCM (2–4 mL) was added pyridine (3 equiv) and Dess–Martin periodinane (2 equiv). After stirring for 22 h at rt KOH (2 M, 5 mL) was added and the reaction mixture extracted DCM (3×15 mL). The combined organic layers were washed with a mixture of KOH (2 M, 15 mL) and $Na_2S_2O_3$ (20%, 15 mL), dried over $MgSO_4$ and concentrated.

*4.7.1. (±)-endo-2-Benzoyltropane [(±)-ferrugine] (**1**).*[10,11] To a solution of **16a** (0.347 g, 1.5 mmol, 1 equiv) in DCM (2 mL) was added pyridine (0.37 mL, 4.5 mmol, 3 equiv) and DMP (1.273 g, 3 mmol, 2 equiv). Then the reaction was carried out as described in general procedure to give the crude product. Purification by dry-column flash chromatography (0–0.5% MeOH/DCM+NH_3) followed by PTLC (silica gel, 5% MeOH/DCM+NH_3) gave yellow oil (0.192 g, 56%). R_f=0.5 (10% MeOH/DCM); R_f=0.5 (10% MeOH/DCM); ^{1}H NMR ($CDCl_3$): 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 ($CDCl_3$): 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.

*4.7.2. (+)-endo-2-Benzoyltropane, (+)-ferrugine ((+)-**1**).* To a solution of (+)-**16a** (0.200 g, 0.86 mmol, 1 equiv) in DCM (2 mL), was added pyridine (0.21 mL, 2.58 mmol, 3 equiv) and DMP (0.745 g, 1.76 mmol, 2 equiv). Then the experiment was performed as described in general procedure. Purification using PTLC (silica gel, 5% MeOH/DCM+NH_3) gave a yellow oil (0.110 g, 56%); ee ≥99%; $[\alpha]_D^{20}$ +100 (*c* 1, $CHCl_3$), +29 (*c* 0.3, $CHCl_3$); Ref.10 $[\alpha]_D^{19}$ +55 ($CHCl_3$).

*4.7.3. (±)-2-Acetyltropane (**17b**).*[11] To a solution of **16b** (0.188 g, 1.11 mmol, 1 equiv) in DCM (4 mL), was added pyridine (0.27 mL, 3.33 mmol, 3 equiv) and DMP (0.945 g, 2.22 mmol, 2 equiv). Then the experiment was performed as described in general procedure. Purification using PTLC (silica gel, 5% MeOH/DCM+NH_3) gave yellow oil (0.098 g, 53%). R_f=0.5 (10% MeOH/DCM); *endo*/*exo* (α/β) ca. 6:1 ratio, ^{1}H NMR ($CDCl_3$): (*endo* isomer) 3.42 (dd, J=2.0, 6.5 Hz, 1H), 3.18–3.10 (m, 1H), 2.84 (ddd, J=2.5, 6.0, 11.5 Hz, 1H), 2.32 (s, 3H), 2.11 (s, 3H), 2.05–1.84 (m, 2H), 1.83–1.73 (m, 1H), 1.71–1.58 (m, 2H), 1.55–1.40 (m, 3H); ^{13}C NMR ($CDCl_3$): 209.7, 65.4, 61.0, 53.1, 50.6, 29.7, 28.4, 25.7, 23.2, 18.0; *m*/*z* 167 (44), 123 (49), 122 (88), 108 (45), 94 (100), 91 (45), 57 (58), 44 (42), 42 (77%); ν_{max} ($CHCl_3$) 1705 (C=O) cm^{-1}.

*4.7.4. (+)-2-Acetyltropane ((+)-**17b**).* To a solution of (+)-**16b** (0.101 g, 0.60 mmol, 1 equiv) in DCM (4 mL), was added pyridine (0.15 mL, 1.80 mmol, 3 equiv) and DMP (0.511 g, 1.20 mmol, 2 equiv). Then the experiment was performed as described in general procedure. Purification by column chromatography on neutral aluminum oxide (0–2% MeOH/DCM) gave a yellowish oil (0.059 g, 59%) mixture of two diastereoisomers *endo*/*exo* (α/β) in ca. 6:1 ratio (ee of the major isomer ≥90%).

*4.7.5. (±)-2-Acetyl-N-benzylnortropane (**17d**).*[38] To a solution of **16d** (0.294 g, 1.20 mmol) in DCM (4 mL), was added pyridine (0.30 mL, 3.60 mmol) and DMP (1.022 g, 2.40 mmol). Then the experiment was performed as described in general procedure. Purification by column chromatography on neutral aluminum oxide (0–2% MeOH/DCM) gave a yellowish oil (0.023 g, 8%) mixture of two diastereoisomers *endo*/*exo* (α/β) ca. 3:1 ratio. R_f=0.6 (10% MeOH/DCM); GC–MS: t_R=46.03 min, *m*/*z* 243 (M^+, 55), 200 (35), 172 (52), 159 (31), 158 (88), 104 (23), 91 (100), 43 (28); t_R=46.37 min, *m*/*z* 243 (M^+, 38), 200 (23), 172 (33), 159 (18), 158 (53), 104 (15), 91 (100), 43 (22); ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) 7.45–7.37 (m, 2H), 7.35–7.21 (m, 3H), 3.63 (s, 2H, CH_2Ph *endo* isomer), 3.52–3.46 (m, 1H), 3.43 (12.5%, d, J=13.0 Hz, C*H*Ph *exo* isomer), 3.33 (12.5%, d, J=13.0 Hz, C*H*Ph *exo* isomer), 3.24–3.17 (m, 1H), 2.98–2.86 (m, 1H), 2.07 (75% s, 3H, *endo*-CH_3), 2.30–1.20 (m, 8H), 1.88 (25% s, 3H, *exo*-CH_3); ^{13}C NMR ($CDCl_3$): (mixture of diastereoisomers) 210.0, 209.0, 139.8, 129.1, 128.6, 128.3, 128.1, 126.99, 126.97, 126.94, 61.28, 60.5, 58.9, 58.4, 56.5, 54.7, 53.3, 30.4, 29.84, 28.4, 27.4, 26.4, 26.2, 25.8, 23.8, 18.6, 16.7.

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