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The Pseudotransannular Ring Opening of 1-Aminocyclohept-4-ene-derived Epoxides in the Synthesis of Tropane Alkaloids: Total Synthesis of (±)-Ferrugine

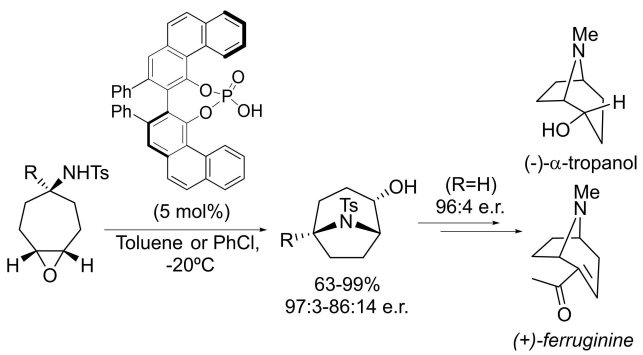
Sandra Rodriguez,[a] Uxue Uria,*[a] Efraim Reyes,[a] Liher Prieto,[a] Marta Rodríguez-Rodríguez,[a] Tomás Tejero,[b] Pedro Merino,*[c] and Jose L. Vicario*[a]

We have optimized a synthetic approach to (±)-Ferrugine in 8 steps starting from 5-aminocyclohept-1-ene and using the Brønsted acid-catalyzed pseudotransannular ring-opening of the epoxide derived from this cycloheptene as the key step for the construction of the 8-azabicyclo[3.2.1]octane central core. While attempting the enantioselective synthesis of this natural product from enantiopure 2-hydroxy-8-azabicyclo[3.2.1]octane we have found that this compound shows a pronounced tendency to racemize *via* an achiral symmetric aziridinium intermediate. This racemization side process has been studied in detail using both experimental and computational methods.

Introduction

Tropane alkaloids constitute a family of natural products that show a wide variety of interesting biological activities,[1] associated with their affinity towards nicotinic and muscarinic acetylcholine receptors located both at the central and the autonomous nervous system and therefore directly related to diseases such as asthma, Alzheimer's disease, chronic obstructive pulmonary disease, Parkinson disease, and depression. In fact, several members of this family of alkaloid-derived drugs have also been labeled as essential medicines by the World Health Organization.[2] Despite the intensive efforts displayed to develop efficient synthetic approaches to tropane alkaloids,[3] the mass production of these compounds through chemical synthesis is still not economically viable, mainly due to the challenging installation of the fixed stereocentres present in the central 8-azabicyclo[3.2.1]octane scaffold that is common to all members of this family. As a consequence, still many of the tropane alkaloids administered as drugs such as tropine or scopolamine are currently produced through extraction from natural sources obtained by intensive cultivation. This agriculture-based production can turn into supply shortages and therefore, the development of efficient synthetic approaches for the stereocontrolled construction of tropane alkaloids is still of maximum interest.

Recently, we reported an efficient approach towards the enantioselective synthesis of the tropane core through Brønsted acid-catalyzed pseudotransannular ring opening of epoxides derived from 5-aminocyclohept-1-enes (Scheme 1).[4] This reaction involves the desymmetrization of the starting material under catalyst control and provides a variety of 5-alkyl and 5-aryl substituted 8-azabicyclo[3.2.1]octan-2-ols in high yields and excellent stereocontrol. We have already demonstrated the performance of this methodology with the enantioselective total synthesis of (−)-α-tropanol and (+)-ferruginine.



Scheme 1. Enantioselective synthesis of tropanes through Brønsted acid-catalyzed desymmetrizative pseudotransannular epoxide ring-opening and its application to the total synthesis of (−)-α-tropanol and (+)-ferruginine.

[a] *Dr. S. Rodriguez, Dr. U. Uria, Dr. E. Reyes, Dr. L. Prieto, Dr. M. Rodríguez-Rodríguez, Prof. Dr. J. L. Vicario*
Department of Organic and Inorganic Chemistry,
University of the Basque Country (UPV/EHU)
P.O. Box 644, 48080 Bilbao, Spain
E-mail: uxue.uria@ehu.es
joseluis.vicario@ehu.es
[b] *Prof. Dr. T. Tejero*
Instituto de Síntesis Química y Catálisis Homogénea (ISQCH)
Universidad de Zaragoza, CSIC
50009 Zaragoza, Spain
[c] *Prof. Dr. P. Merino*
Instituto de Biocomputación y Física de Sistemas Complejos (BIFI)
Universidad de Zaragoza
50009 Zaragoza, Spain
E-mail: pmerino@unizar.es

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Following our aim to provide further evidence of the synthetic potential of this methodology as a general tool for the enantioselective synthesis of other members of the family of tropane alkaloids, we wish to present herein our attempts to apply this reaction to the total synthesis of ferrugine, an alkaloid isolated from the extracts of the species *Darlingia Ferruginea*.[5] It should also be pointed out that there are only a few literature examples regarding previous syntheses for ferrugine, either as enantiopure material[6] or in racemic form.[7]

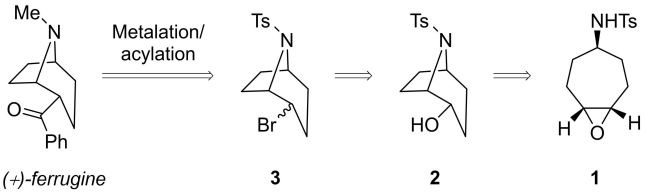
Results and Discussion

We initially envisaged a direct route to ferrugine from adduct **2**, which is the product obtained in the enantioselective desymmetrizative ring-opening reaction of aminoepoxide **1**. The synthetic approach would involve the formation of a 2-bromo-8-azabicyclo[3.2.1]octane **3** through nucleophilic substitution and the lateral benzoyl side chain was planned to be introduced through metalation followed by acylation. Final deprotection/methylation would lead to the target product (Scheme 2).

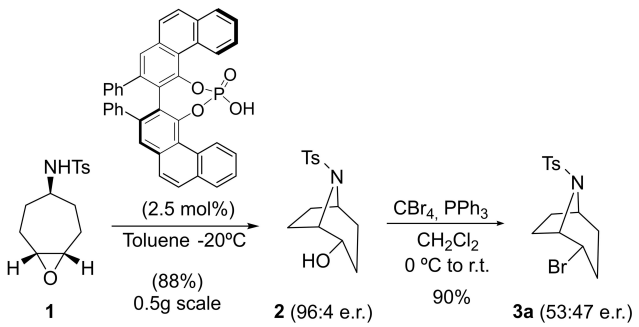
We started the synthesis by carrying out the enantioselective desymmetrization of the starting material (Scheme 3). This reaction was carried out on a 0.5 g scale, providing the desired 8-azabicyclo[3.2.1]octan-2-ol adduct **2** in high yield and an excellent enantiocontrol, demonstrating the excellent performance of our reported methodology also at a convenient scale for preparative purposes. The substitution of the alcohol by the bromide was carried out through standard Appel reaction obtaining the corresponding bromide **3a** in excellent yield. However, NMR analysis of this adduct showed that the stereochemistry at C2 was not consistent with the expected S_N2 process, which was confirmed by X-ray analysis of a crystalline sample of this compound.[8] We also evaluated the enantiomeric excess of compound **3a** observing that it had been obtained as an almost racemic material.

Several additional experiments were performed in order to carry out the projected nucleophilic substitution of the alcohol moiety (Table 1). The attempt to obtain the same bromide **3a** using PBr_3 as brominating agent provided the same result (entry 1) and focusing on obtaining the corresponding chloride **3b** using either the same Appel conditions as used in Scheme 3 (entry 2) or through reaction with $SOCl_2$ (entry 3) also led to the formation of almost racemic material. Substitution *via* the corresponding mesylate was also tested but this reaction also failed to retain the enantiopurity of the starting material (entry 4). We could verify that mesylation took place without any racemization when the mesylate intermediate was isolated (entry 5) and subsequently it was reacted with NaCN under standard conditions to favor the desired S_N2 process. However, this led once again to substitution product **3d** as a racemate (entry 6). Mitsunobu reaction from **2** was also unsuccessful (entry 7).

We also surveyed the performance of 5-methyl substituted derivative **4** in the nucleophilic substitution with halides (Scheme 4). Interestingly, both the chlorination and the bromination reactions took place with some degree of racemization, although to a much lesser extent to that observed with substrate **2**, especially in the case of the bromination reaction

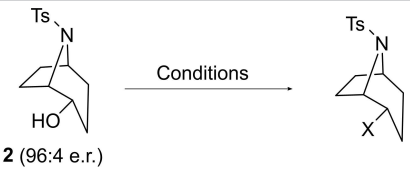


Scheme 2. Initial retrosynthetic analysis for the preparation of (+)-ferrugine from enantioenriched 8-azabicyclo[3.2.1]octan-2-ol **2**.



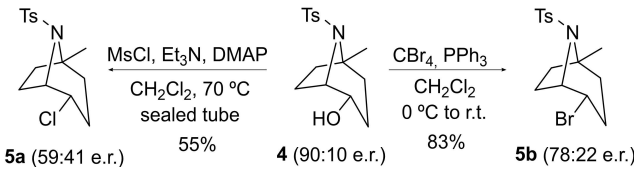
Scheme 3. Synthesis of compound **3a**.

Table 1. Attempts to carry out an S_N2 reaction on substrate **2**.



Entry	Conditions	X	Yield [%][a]	e.r.[b]
1	PBr_3, CH_2Cl_2, −78 °C to r.t.	Br (**3a**)	39	53:47
2	CCl_4, PPh_3, CH_2Cl_2, r.t. to reflux	Cl (**3b**)	82	52:48
3	$SOCl_2$, 1,4-dioxane, r.t.	Cl (**3b**)	73	53:47
4	MsCl, Et_3N, DMAP, CH_2Cl_2, 70 °C sealed tube	Cl (**3b**)	68	50:50
5	MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t.	OMs (**3c**)	99	96:4
6[c]	NaCN, DMSO, 50 °C	CN (**3d**)	24	50:50
7	NaCN, PPh_3, $EtO_2CN{=}NCO_2Et$, THF, r.t.	CN (**3d**)	<5	n.d.[d]

[a] Yield of pure isolated compound after flash column chromatography. [b] Calculated by HPLC on chiral stationary phase (See ESI for details). [c] Compound **3c** was used as starting material. [d] Not determined.



Scheme 4. Halogenation of alcohol **4**.

under standard Appel conditions, that provided adduct **5b** with a 78:22 e.r. starting from alcohol **4** that had a 90:10 e.r.

In order to gain a better understanding of this racemization process, a computational study (for details see ESI) was carried out for the reaction of alcohols **2** (R=H) and **4** (R=Me) with mesyl chloride to give adducts **3b** and **5a** respectively (Scheme 5). The reaction is expected to proceed, once the mesylated derivative **RG1** is formed, via a substitution by the chloride ion present in the medium. The reaction takes place with complete retention of configuration so, we focus our attention on the formation of an intermediate through the anchimeric assistance of the tosyl group, i.e. the oxathiazolium-1-oxide **IN1** (Scheme 5). The subsequent ring-opening of **IN1** by the chloride ion yields the product. The energy barrier for this reaction was found to be 37.7 and 31.4 kcal/mol for **TS1a** and **TS1b**, respectively. However, this approach although explains the retention of configuration does not explain the observed racemization. On the other hand, a similar system with a bridged nitrogen atom close to the carbocation has already been described previously,[9] proposing the formation of an aziridinium cation (through the anchimeric assistance of the nitrogen atom) as a more stable intermediate.

Compounds **RG1** can be easily converted into conformers **RG2** (via a pyramidal inversion and a rotation around the N–S bond) which have the nitrogen atom correctly oriented to assist expulsion of the mesyl group. The resulting aziridinium cation **IN2** is stable enough as a minimum (any attempt of locating the open carbocation failed, converging to either **IN1** or **IN2**, depending on the conformation of the tosyl group), and it is symmetric so, any chiral information has been lost. In fact, the two possible attacks of the chloride at positions 2a and 2b of **IN2** are equivalent leading to enantiomeric compounds (Scheme 5), thus explaining both the retention of configuration and the racemization observed experimentally. The corresponding barriers for this route are lower than for the formation of **IN1** (29.0 and 26.1 kcal/mol for **TS2a** and **TS2b**, respectively) and agree with the experimental conditions (70 °C, sealed tube). The compared energy profiles for both routes corresponding to the reaction of mesylates derived from **2** and **4** are illustrated in Figure 1.

Actually, the process is more complex than the mechanism represented in Scheme 5. Both the pyramidal inversion at the bridged nitrogen[10] and the rotation of the N–S bond[11] could require some energy that might be competitive with the energy barrier of the process, particularly the last one. All these possibilities have been calculated including the corresponding conformational transition structures and the complete analysis is given in ESI. More conformers, in addition to **RG1a,b** and **RG2a,b**, are possible. In all cases, the energy barriers between all the conformers are markedly lower than the energy barriers of the reaction giving rise to a typical Curtin-Hammett scenario.[12]

A similar situation accounts for the reactive intermediate **IN2** as illustrated for **IN2a** in Scheme 6. There are three possible

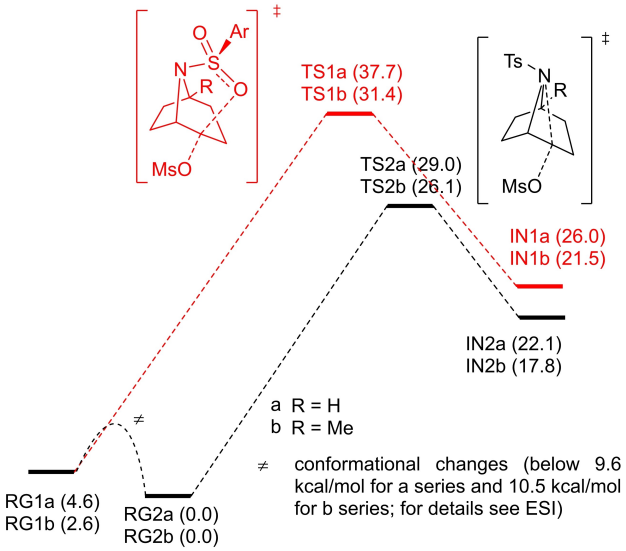
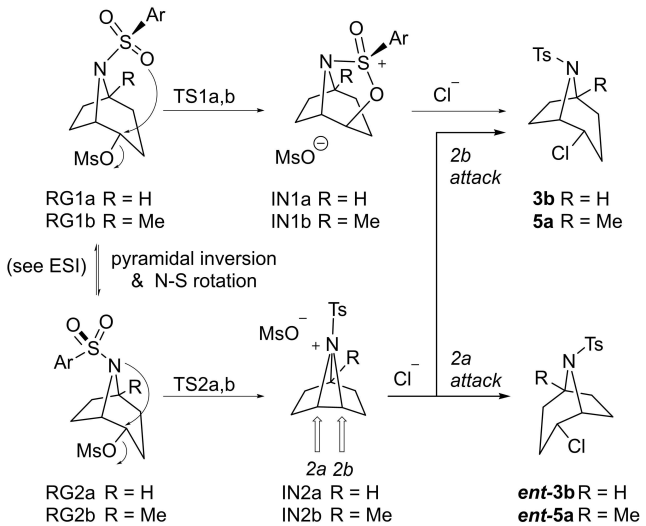
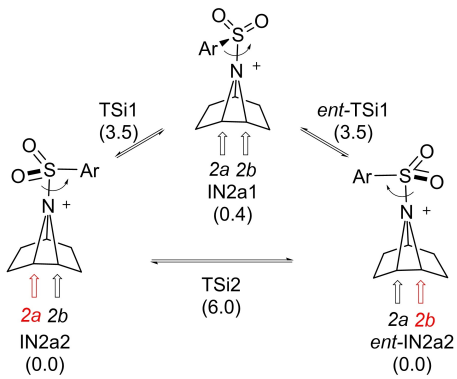


Figure 1. Energy profiles for the reaction of **RG1a** and **RG1b**. Black pathway corresponds to the favored formation of the symmetric aziridinium ion. Red pathway corresponds to the disfavored formation of **IN1**.



Scheme 5. Mechanistic pathways for the reaction of the mesylates derived from compounds **2** and **4**.



Scheme 6. Conformation of the reactive intermediate **IN2a**. A similar situation accounts for **IN2b** (see ESI).

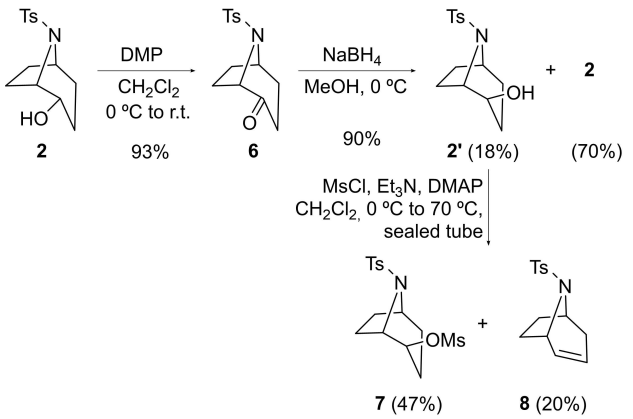
conformers, one symmetric (**IN2a1**) and the other two enantiomeric (**IN2a2**), which are the most stable by only 0.4 kcal/mol. The values of the corresponding barriers between the conformers make it possible to assume that they are in equilibrium. The attacks at positions 2a and 2b in **IN2a2** are not equivalent but the presence in equal amounts of both enantiomers also leads to racemic compounds. The observed slight deviations of complete racemization as in the case of compound **4** are compatible with the energy differences between the two transition structures **TS1** and **TS2** ($\Delta\Delta G = 8.7$ kcal/mol for **a** series and $\Delta\Delta G = 5.3$ kcal/mol for **b** series). The lower difference observed for the mesylate derived from **4** suggests that a minor part of the reaction might go through the oxathiazolium-1-oxide **IN1**.

Therefore, calculations correctly predict both the retention of configuration and the racemization also suggesting an explanation for the lower racemization when a methyl group is present in position 5. The neighboring group participation is crucial for the reaction and any attempt to change its stereochemical course should consider the nature of the nitrogen protecting group.

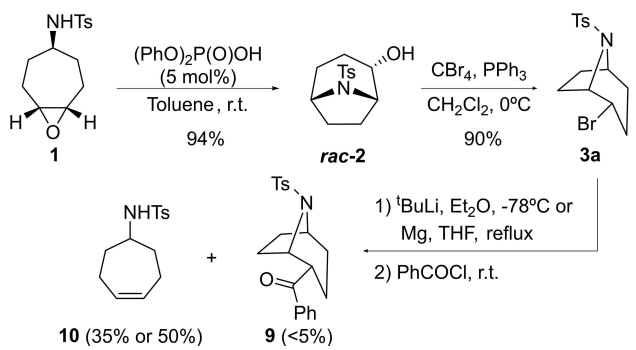
Next, and in order to avoid this competitive racemization pathway, we also prepared the C2-epimer of tropanol substrate **2** for which the formation of this intermediate aziridinium cation would not be operative. The synthesis of this derivative **2'** was achieved through oxidation of enantioenriched **2** to the corresponding ketone **6** followed by reduction (Scheme 7). This provided a mixture of epimers **2** and **2'**, being the latter the minor diastereoisomer formed. Attempted chlorination of **2'** through mesylation as performed in entry 4 of Table 1 did not lead to the formation of the desired chloride but delivered instead of the corresponding mesylate **7** as a single diastereoisomer and dehydration product **8**. Other conditions tested for the conversion of the alcohol **2'** into the corresponding bromide or chloride were unsuccessful, observing in all cases either unreacted starting material or extensive decomposition. We also subjected mesylate **7** to conditions for S_N2 reaction with NaCN but with the same unsuccessful results.

At this point, and in view of our failure in avoiding the racemization process during the manipulation of the alcohol moiety on substrate **2** we decided to carry on to accomplish the total synthesis of ferrugine in a non-enantioselective way. Therefore, we started by carrying out the pseudotransannular epoxide ring opening of compound **1** using diphenylphosphoric acid as an achiral catalyst to promote the transformation. This took place with the same high yield as previously shown in the enantioselective version depicted in Scheme 3 (see Scheme 8) and the obtained alcohol ***rac*-2** was subsequently converted into bromide **3a** in an excellent yield through standard Appel reaction. Next, and following our retrosynthetic design, we proceed to carry out the metalation/acylation sequence that would incorporate the required benzoyl substituent at the 2-position, starting from bromide **3a** (Scheme 8). Disappointingly, all our attempts to carry out a lithium/halogen exchange through metalation with ^{t}BuLi or trying to generate the corresponding Grignard reagent were also unsuccessful, observing in all cases the formation of significant amounts of 5-tosylaminocycloheptene **10**. This was interpreted in terms of poor stability of the generated α-aminoalkyllithium or magnesium organometallic reagent that showed a tendency to undergo elimination facilitated by the release of ring strain associated with the overall process.

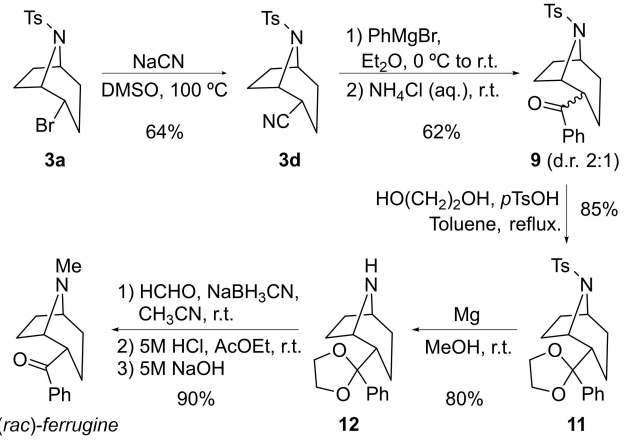
As an alternative, we decided to evaluate the use of nitrile **3d** as substrate capable to undergo 1,2-addition with phenylmagnesium bromide that would directly generate the required benzoyl substituent after hydrolytic work-up (Scheme 9). This compound **3d** was obtained from racemic **3a** through nucleophilic displacement with NaCN as shown in Table 1, only requiring to increase the temperature to 100 °C to increase the overall yield of the process (compare with entry 6). Next, a reaction with PhMgBr took place smoothly to form adduct **9** after quenching with aqueous ammonium chloride. Despite the fact that compound **9** was obtained as a 2:1 mixture of diastereoisomers we decided to carry on with the synthesis having in mind the lability of this stereocentre because of the acidity associated with the carbonyl α-hydrogen. Indeed, we next focused on the removal of the N-tosyl group that was required for the previous protection of the ketone moiety as the ethyleneglycol acetal. This was formed as a single diastereoisomer under standard conditions, obtaining acetal **11** in excellent yield. Next, detosylation was carried out through Mg-promoted reduction, obtaining secondary amine **12** in an



Scheme 7. Synthesis and reactivity of the 2-epimer of alcohol **2**.



Scheme 8. Attempts to carry out the metalation/acylation of **3a**.



Scheme 9. Synthesis of (rac)-ferrugine.

excellent 80% yield. Completion of the synthesis only required for a reductive amination protocol followed by a final hydrolytic cleavage of the acetal moiety that was carried out in a one-pot manner. The spectroscopic properties of the obtained sample of (±)-ferrugine matched perfectly with those reported in the literature.

Conclusion

We have demonstrated that 2-tropanol derivatives such as **2** show a pronounced tendency to undergo racemization when trying to manipulate the hydroxyl moiety through standard S_N2 reactions and this racemization is occurring through the formation of an achiral symmetric aziridinium intermediate. As a consequence, all our attempts to achieve the enantioselective total synthesis of enantiopure ferrugine have been unsuccessful. On the other hand, the complete synthesis of racemic (±)-ferrugine has been accomplished starting from 5-aminocyclohept-1-ene in an 8-step linear sequence that takes place with a good overall yield (21%).

Experimental Section

Analytical grade solvents and commercially available reagents were purchased from commercial sources and used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[13] For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 °C, and allowed to cool under a dehumidified atmosphere.[14] Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator. Reactions were monitored using analytical thin-layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kiesegel 60 F254). These were visualized by ultraviolet irradiation, *p*-anisaldehyde, phosphomolybdic acid or potassium permanganate dips.[15] For flash chromatography Silicycle 40–63, 230–400 mesh silica gel was used.[16] Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25 °C on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) at the indicated temperature. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.16 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; app, apparent; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broadband decoupled mode using DEPT experiments (Distorsionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Assignments were made based upon the IUPAC numbering system. Mass spectra (MS) were recorded on an Agilent 7890 A gas chromatograph coupled to an Agilent 5975 C quadrupole mass spectrometer under electronic impact ionization (EI) at 70 eV. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%). High-resolution mass spectra were recorded on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI^+).

(*rac*)-(1*R*,2*R*,5*S*)-8-Tosyl-8-azabicyclo[3.2.1]octan-2-ol (***rac*-2**). A reaction tube equipped with a magnetic stirring bar was charged with epoxide *trans*-**1** (495.8 mg, 1.76 mmol) and diphenylphosphoric acid (11.0 mg, 0.044 mmol). Toluene (1.76 mL, 1 M) was added to the mixture under argon atmosphere at r.t. After 48 h the reaction was judged complete (monitored by ^{1}H NMR analysis) and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography (petroleum ether/Et_2O, 3:7) to afford the corresponding 8-azabicyclo[3.2.1]octane (***rac*)-2** (466.1 mg, 1.66 mmol, 94%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H, C_{arom}–H), 7.27 (d, J = 8.0 Hz, 2H, C_{arom}–H), 4.20–4.12 (m, 1H, C_5–H), 4.12–4.04 (m, 1H, C_1–H), 4.02–3.86 (m, 1H, C_2–H), 2.42 (s, 3H, CH_3), 1.97–1.68 (m, 4H, C_3-**H$_a$**H$_b$, C_4-**H$_a$**H$_b$, C_7-**H$_a$**H$_b$, OH), 1.57–1.19 (m, 5H, C_3-H$_a$**H$_b$**, C_4-H$_a$**H$_b$**, C_7-H$_a$**H$_b$**, C_6–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 (**C$_{arom}$**–CH_3), 137.1 (C_{arom}–S), 129.8 (2× C_{arom}–H), 127.4 (2×C_{arom}–H), 69.9 (C_2), 61.4 (C_1), 56.4 (C_5), 31.3 (C_4), 27.8 (C_6), 25.9 (C_3), 22.9 (C_7), 21.6 (CH_3). IR (ATR): 3505 (O–H st), 1336 (SO_2 st as), 1156 (SO_2 st sim), 1096 (C–O st) cm^{-1}. MS (EI) m/z (%): 281 (M^+, 1), 127 (8), 126 ([M−Ts]$^+$, 100), 91 (4-Me$C_6H_4^+$, 26), 82 (9), 68 (8), 65 (9). HRMS (UPLC MS ESI^+): Calculated for $[C_{14}H_{20}NO_3S]^+$: 282.1164 ([M + H]$^+$); found: 282.1171. M.p. (petroleum ether/Et_2O): 140–144 °C.

(*rac*)-(1*R*,2*R*,5*S*)-2-Bromo-8-tosyl-8-azabicyclo[3.2.1]octane (*rac*-3 a): Tetrabromomethane (292.0 mg, 0.88 mmol) was added to a solution of alcohol **(*rac*)-2** (233.9 mg, 0.83 mmol) in dry CH_2Cl_2 (1.4 mL) under Ar atmosphere. After cooling to 0 °C, triphenylphosphine (263.9 mg, 1.00 mmol) was added portionwise, and the mixture stirred at 0 °C for 0.5 h. After stirring at room temperature overnight, more tetrabromomethane (292.0 mg, 0.88 mmol) and triphenylphosphine (263.9 mg, 1.00 mmol) were added in order to achieve complete conversion of the starting alcohol **(*rac*)-2**. After stirring at room temperature for another 24 h, the solvent was evaporated *in vacuo* and the residue purified by column chromatography on silica gel (petroleum ether/EtOAc, gradient from 9:1 to 6:4) to give the corresponding bromide **(*rac*)-3 a** (257.3 mg, 0.75 mmol, 90% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H, C_{arom}–H), 7.20 (d, J = 8.1 Hz, 2H, C_{arom}–H), 4.27–4.09 (m, 3H, C_1-H, C_2-H, C_5–H), 2.34 (s, 3H, CH_3), 2.11–2.00 (m, 1H, C_3–**H$_a$**H$_b$), 1.99–1.87 (m, 1H, C_4–**H$_a$**H$_b$), 1.86–1.74 (m, 2H, C_4–H$_a$**H$_b$**, C_7–**H$_a$**H$_b$), 1.56–1.31 (m, 4H, C_3–H$_a$**H$_b$**, C_6-H, C_7–H$_a$**H$_b$**). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9 (**C$_{arom}$**–CH_3), 136.9 (C_{arom}–S), 129.9 (2× C_{arom}–H), 127.3 (2×C_{arom}–H), 62.2 (C_1), 56.4 (C_5), 51.4 (C_2), 33.9 (C_4), 28.7 (C_6), 27.9 (C_3), 24.2 (C_7), 21.6 (CH_3). IR (ATR): 1338 (SO_2 st as), 1156 (SO_2 st sim), 1091, 665 (C–Br st) cm^{-1}. MS (EI) m/z (%): 264 ([M−Br]$^+$, 25), 222 (81), 155 (Ts^+, 43), 146 (38), 144 (100), 108 (19),

91 (4-$MeC_6H_4^+$, 85), 65 (29), 64 (23), 54 (16). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{19}BrNO_2S]^+$: 344.0320 ($[M+H]^+$); found: 344.0330. M.p. (petroleum ether/EtOAc): 13–137 °C.

(*rac*)-(1*R*,2*R*,5*R*)-8-Tosyl-8-azabicyclo[3.2.1]octane-2-carbonitrile ((*rac*)-3 d): An ordinary flask equipped with a magnetic stirring bar was charged, under inert atmosphere, with a solution of bromide **(*rac*)-3 a** (254.3 mg, 0.74 mmol) and sodium cyanide (54.3 mg, 1.11 mmol) in dry DMSO (1.5 mL). After stirring at 100 °C overnight, the reaction mixture was diluted with EtOAc (5 mL), washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, and the residue purified by column chromatography on silica gel (petroleum ether/EtOAc, gradient from 8:2 to 7:3) to give the corresponding carbonitrile **(*rac*)-3 d** (138.4 mg, 0.48 mmol, 64%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H, C_{arom}–H), 7.29 (d, J = 8.1 Hz, 2H, C_{arom}–H), 4.40–4.28 (m, 1H, C_1–H), 4.28–4.18 (m, 1H, C_5–H), 2.99 (ddd, J = 12.0, 5.1, 2.8 Hz, 1H, C_2–H), 2.43 (s, 3H, CH_3), 2.08–1.92 (m, 1H, C_3–$\mathbf{H_a}H_b$), 1.90–1.72 (m, 3H, C_3–$H_a\mathbf{H_b}$, C_4–$\mathbf{H_a}H_b$, C_6–$\mathbf{H_a}H_b$), 1.67–1.49 (m, 4H, C_4–$H_a\mathbf{H_b}$, C_6–$H_a\mathbf{H_b}$, C_7–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2 (**C_{arom}**–CH_3), 136.6 (C_{arom}–S), 130.0 (2× C_{arom}–H), 127.4 (2× C_{arom}–H), 120.0 (C≡N), 57.8 (C_1), 56.6 (C_5), 33.2 (C_2), 31.1 (C_6), 27.9 (C_7), 26.1 (C_4), 21.7 (CH_3), 21.4 (C_3). IR (ATR): 2241 (C≡N), 1339 (SO_2 st as), 1156 (SO_2 st sim) cm^{-1}. MS (EI) m/z (%): 290 (M^+, 40), 223 (17), 222 (92), 155 (Ts^+, 36), 135 ($[M-Ts]^+$, 71), 91 (4-$MeC_6H_4^+$, 100), 68 (19), 65 (31). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{19}N_2O_2S]^+$: 291.1167 ($[M+H]^+$); found: 291.1173. M.p. (petroleum ether/EtOAc): 123–126 °C

(*rac*)-Phenyl((1*R*,2*R*,5*R*)-8-tosyl-8-azabicyclo[3.2.1]octan-2-yl) methanone ((*rac*)-trans-9): Phenylmagnesium bromide (1.0 M in THF, 0.70 mL, 0.70 mmol) was added dropwise to a solution of carbonitrile **(*rac*)-3 d** (135.4 mg, 0.47 mmol) in dry Et_2O (1.86 mL) at 0 °C under Ar atmosphere. After stirring for 2 h at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3×10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel gave the corresponding ketones (±)-phenyl((1*R*,2*R*,5*R*)-8-tosyl-8-azabicyclo [3.2.1]octan-2-yl)methanone ((*rac*)-*trans*-**9**) (72.1 mg, 0.20 mmol, 42%) and (±)-phenyl((1*R*,2*S*,5*R*)-8-tosyl-8-azabicyclo[3.2.1]octan-2-yl)methanone ((*rac*)-*cis*-**9**) (34.4 mg, 0.09 mmol, 20%). Data for **(*rac*)-phenyl((1*R*,2*R*,5*R*)-8-tosyl-8-azabicyclo[3.2.1]octan-2-yl) methanone** ((*rac*)-*trans*-**9**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.3, 1.1 Hz, 2H, C_{arom}–H), 7.76 (d, J = 8.2 Hz, 2H, C_{arom}–H), 7.59 (tt, J = 7.0, 1.1 Hz, 1H, C_{arom}–H), 7.49 (app t, J = 7.7 Hz, 2H, C_{arom}–H), 7.28 (d, J = 8.2 Hz, 2H, C_{arom}–H), 4.45–4.39 (m, 1H, $C_{1'}$–H), 4.37–4.20 (m, 1H, $C_{5'}$–H), 3.87 (ddd, J = 11.8, 4.6, 2.3 Hz, 1H, $C_{2'}$–H), 2.43 (s, 3H, CH_3), 2.07–1.92 (m, 2H, $C_{3'}$–$\mathbf{H_a}H_b$, $C_{6'}$–$\mathbf{H_a}H_b$), 1.81–1.69 (m, 2H, $C_{3'}$–$H_a\mathbf{H_b}$, $C_{4'}$–$\mathbf{H_a}H_b$), 1.69–1.61 (m, 1H, $C_{4'}$–$H_a\mathbf{H_b}$), 1.56–1.46 (m, 2H, $C_{6'}$-$H_a\mathbf{H_b}$, $C_{7'}$–$\mathbf{H_a}H_b$), 1.44–1.32 (m, 1H, $C_{7'}$–$H_a\mathbf{H_b}$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1 (C=O), 143.7 (**C_{arom}**–CH_3), 137.4 (C_{arom}–S), 135.7 (**C_{arom}**–C=O), 133.5 (C_{arom}–H), 129.9 (2× C_{arom}–H), 129.0 (2× C_{arom}–H), 128.6 (2× C_{arom}–H), 127.5 (2× C_{arom}–H), 58.9 ($C_{1'}$), 57.2 ($C_{5'}$), 49.1 ($C_{2'}$), 31.8 ($C_{6'}$), 28.3 ($C_{7'}$), 25.2 ($C_{4'}$), 21.7 (CH_3), 19.4 (C_3). IR (ATR): 1717 (C=O st), 1333 (SO_2 st as), 1159 (SO_2 st sim) cm^{-1}. MS (EI) m/z (%): 369 (M^+, 2), 355 (15), 281 (27), 208 (26), 207 (100), 83 (17). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{21}H_{24}NO_3S]^+$: 370.1477 ($[M+H]^+$); found: 370.1486. M.p. (petroleum ether/EtOAc): 100–102 °C. Data for **(*rac*)-phenyl((1*R*,2*S*,5*R*)-8-tosyl-8-azabicyclo[3.2.1]octan-2-yl) methanone** ((*rac*)-*cis*-**9**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.65 (m, 2H, C_{arom}–H), 7.59–7.46 (m, 3H, C_{arom}–H), 7.39 (app t, J = 7.5 Hz, 2H, C_{arom}–H), 7.12 (d, J = 8.1 Hz, 2H, C_{arom}–H), 4.61–4.47 (m, 1H, $C_{1'}$–H), 4.40–4.23 (m, 1H, $C_{5'}$–H), 3.47–3.34 (m, 1H, $C_{2'}$–H), 2.37 (s, 3H, CH_3), 2.33–2.20 (m, 1H, $C_{3'}$–$\mathbf{H_a}H_b$), 2.13–1.98 (m, 2H, $C_{4'}$–$\mathbf{H_a}H_b$, $C_{6'}$–$\mathbf{H_a}H_b$), 1.98–1.80 (m, 2H, $C_{3'}$–$H_a\mathbf{H_b}$, $C_{4'}$–$H_a\mathbf{H_b}$), 1.80–1.62 (m, 2H, $C_{6'}$–$H_a\mathbf{H_b}$, $C_{7'}$–$\mathbf{H_a}H_b$), 1.57–1.44 (m, 1H, $C_{7'}$–$H_a\mathbf{H_b}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6 (C=O), 143.3 (**C_{arom}**–CH_3), 136.8 (C_{arom}–S), 136.0 (**C_{arom}**–C=O), 132.6 (C_{arom}–H), 129.4 (2× C_{arom}–H), 128.6 (2× C_{arom}–H), 128.2 (2× C_{arom}–H), 127.7 (2× C_{arom}–H), 58.9 ($C_{1'}$), 57.6 ($C_{5'}$), 48.2 ($C_{2'}$), 30.1 ($C_{6'}$), 29.7 ($C_{7'}$), 28.2 ($C_{4'}$), 21.6 (CH_3), 17.7 ($C_{3'}$). IR (ATR): 1683 (C=O st), 1340 (SO_2 st as), 1155 (SO_2 st sim) cm^{-1}. MS (EI) m/z (%): 215 (16), 214 ($[M-Ts]^+$, 100), 105 ($PhCO^+$, 30), 91 (4-$MeC_6H_4^+$, 21), 77 (Ph^+, 17). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{21}H_{24}NO_3S]^+$: 370.1477 ($[M+H]^+$); found: 370.1480. M.p. (petroleum ether/EtOAc): 166–169 °C.

(*rac*)-(1*R*,2*R*,5*R*)-2-(2-Phenyl-1,3-dioxolan-2-yl)-8-tosyl-8-azabicyclo[3.2.1]octane ((*rac*)-11): Ketones **(*rac*)-9** (103.5 mg, 0.28 mmol, *trans*:*cis* ratio 2.1:1), *p*-toluenesulfonic acid monohydrate (64.9 mg, 0.34 mmol), ethylene glycol (0.08 mL, 1.43 mmol) and toluene (22.7 mL) were mixed together in a round-bottom flask equipped with a Dean-Stark apparatus. The mixture was heated to reflux for 60 h, and then more ethylene glycol (0.08 mL, 1.43 mmol) and *p*-toluenesulfonic acid monohydrate (64.9 mg, 0.34 mmol) were added in order to achieve complete conversion of the starting ketones. After stirring at reflux for another 6 h, the mixture was allowed to warm to room temperature. The reaction was quenched with an aqueous solution of NH_3 (1% v/v, 12 mL), the organic layer separated, and the aqueous one extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (CH_2Cl_2/petroleum ether, gradient from 9:1 to CH_2Cl_2) gave the corresponding acetal **(*rac*)-11** (97.9 mg, 0.24 mmol, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H, C_{arom}–H), 7.35–7.27 (m, 5H, C_{arom}–H), 7.22 (d, J = 8.2 Hz, 2H, C_{arom}–H), 4.22–4.15 (m, 1H, C_5–H), 4.15–4.10 (m, 1H, C_1–H), 4.01–3.93 (m, 1H, O**$\mathbf{C}H_a$**$H_b$$CH_2$O), 3.90–3.82 (m, 1H, O$CH_a$**$\mathbf{C}H_b$**$CH_2$O), 3.74–3.62 (m, 2H, O$CH_2$**$\mathbf{C}H_2$**O), 2.41 (s, 3H, CH_3), 2.34–2.27 (m, 1H, C_2–H), 2.09 (ddd, J = 13.2, 9.2, 4.2 Hz, 1H, C_3–$\mathbf{H_a}H_b$), 1.73–1.50 (m, 3H, C_3–$H_a\mathbf{H_b}$, C_4–$\mathbf{H_a}H_b$, C_6-$\mathbf{H_a}H_b$), 1.50–1.32 (m, 4H, C_4–$H_a\mathbf{H_b}$, C_6–$H_a\mathbf{H_b}$, C_7–H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1 (**C_{arom}**-CH_3), 141.5 (**C_{arom}**-C–O), 137.9 (C_{arom}–S), 129.6 (2× C_{arom}–H), 128.2 (2× C_{arom}–H), 128.1 (C_{arom}–H), 127.4 (2× C_{arom}–H), 126.2 (2× C_{arom}–H), 110.5 (O–C-O), 64.8 (O**$\mathbf{C}H_2$**CH_2O), 63.9 (OCH_2**$\mathbf{C}H_2$**O), 57.8 (C_5), 57.2 (C_1), 49.3 (C_2), 31.9 (C_6), 28.5 (C_7), 25.4 (C_4), 21.7 (CH_3), 18.0 (C_3). IR (ATR): 1339 (SO_2 st as), 1154 (SO_2 st sim), 1092 (C–O–C st as), 1026 (C–O–C st sim) cm^{-1}. MS (EI) m/z (%): 150 (11), 149 ($C_9H_9O_2^+$, 100), 105 ($PhCO^+$, 26), 91 (4-$MeC_6H_4^+$, 20), 77 (Ph^+, 13). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{23}H_{28}NO_4S]^+$: 414.1739 ($[M+H]^+$); found: 414.1744. M.p. (CH_2Cl_2/petroleum ether): 145–148 °C.

(*rac*)-(1*R*,2*R*,5*R*)-2-(2-Phenyl-1,3-dioxolan-2-yl)-8-azabicyclo[3.2.1] octane ((*rac*)-12): A solution of sulfonamide **(*rac*)-11** (97.9 mg, 0.24 mmol) in dry MeOH (2.7 mL) was added to a suspension of Mg (59.8 mg, 2.46 mmol) in dry MeOH (2.7 mL), under Ar atmosphere. The resulting suspension was sonicated for 50 min, and then more Mg (59.8 mg, 2.46 mmol) was added in order to achieve full conversion. After sonicating for another 60 min, the mixture was diluted with brine (11 mL) and extracted several times with $CHCl_3$ (6×25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the corresponding free amine **(*rac*)-12** (49.3 mg, 0.19 mmol, 80%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.13 (m, 5H, C_{arom}–H), 3.98–3.77 (m, 2H, O**$\mathbf{C}H_2$**CH_2O), 3.74–3.52 (m, 2H, OCH_2**$\mathbf{C}H_2$**O), 3.44–3.33 (m, 1H, C_5–H), 3.33–3.23 (m, 1H, C_1–H), 2.67–2.41 (bs, 1H, NH), 2.22–2.02 (m, 2H, C_2-H, C_3–$\mathbf{H_a}H_b$), 1.80–1.63 (m, 1H, C_6–$\mathbf{H_a}H_b$), 1.63–1.35 (m, 6H, C_3–$H_a\mathbf{H_b}$, C_4-H, C_6–$H_a\mathbf{H_b}$, C_7–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (**C_{arom}**–C–O), 128.1 (2× C_{arom}–H), 127.9 (C_{arom}–H), 126.3 (2× C_{arom}–H), 111.0 (O–C–O), 64.9 (O**$\mathbf{C}H_2$**CH_2O), 63.9 (OCH_2**$\mathbf{C}H_2$**O), 55.4 (C_5), 54.8 (C_1), 50.1 (C_2), 32.2 (C_6), 29.2 (C_7), 25.8 (C_4), 18.2 (C_3). IR (ATR): 3329 (N–H st), 1260 (C–N st), 1053 (C–O–C st as), 1014 (C–O–C st sim) cm^{-1}. MS (EI) m/z (%): 259 (M^+, 1), 215 (26), 214 (100), 149 ($C_9H_9O_2^+$,

41), 105 ($PhCO^+$, 20), 77 (Ph^+, 10), 68 (13). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{22}NO_2]^+$: 260.1651 ($[M+H]^+$); found: 260.1649.

((*rac*)-(1*R*,2*R*,5*R*)-8-Methyl-8-azabicyclo[3.2.1]octan-2-yl)(phenyl) methanone (*(rac)-ferrugine*)[7] To a solution of amine **(*rac*)-12** (48.3 mg, 0.19 mmol) and 37% aqueous formaldehyde (73 μL, 0.99 mmol) in acetonitrile (0.6 mL), sodium cyanoborohydride (19.9 mg, 0.32 mmol) was added. After stirring the reaction mixture for 15 min, glacial acetic acid was added dropwise until the solution reached pH 7. Stirring was continued for further 45 min, glacial acetic acid being occasionally added in order to maintain the pH near neutrality. Then, the solvent was removed *in vacuo* and the residue was treated with KOH (2 M, 0.9 mL). The resulting mixture was extracted with Et_2O (3×6 mL), and the combined organic layers were subsequently washed with KOH (0.5 M, 4 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. EtOAc (0.64 mL) and HCl (5 M, 0.31 mL) were added to the crude and the biphasic mixture was stirred vigorously overnight. Then, the mixture was neutralized with an aqueous solution of NaOH (20% w/v) and extracted with Et_2O (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **(*rac*)-ferrugine** (38.4 mg, 0.17 mmol, 90%) as a yellowish oil. Spectroscopic data match those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.90 (m, 2H, C_{arom}–H), 7.60–7.40 (m, 3H, C_{arom}–H), 3.86–3.74 (m, 1H, $C_{2'}$–H), 3.40–3.31 (m, 1H, $C_{1'}$–H), 3.23–3.13 (m, 1H, $C_{5'}$–H), 2.36 (s, 3H, CH_3), 2.07–1.73 (m, 5H, $C_{3'}$-H, $C_{4'}$-H, $C_{6'}$–$\mathbf{H_a}H_b$), 1.64–1.43 (m, 3H, $C_{6'}$–$H_a\mathbf{H_b}$, $C_{7'}$–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8 (C=O), 136.6 ($\mathbf{C_{arom}}$-C=O), 133.0 (C_{arom}–H), 128.8 (2×C_{arom}–H), 128.4 (2×C_{arom}–H), 63.8 ($C_{1'}$), 61.3 ($C_{5'}$), 47.9 ($C_{2'}$), 40.5 (CH_3), 30.1 ($C_{6'}$), 26.2 ($C_{7'}$), 23.0 ($C_{4'}$), 18.7 ($C_{3'}$). IR (ATR): 1681 (C=O st), 1681 (C=C st), 1261 (C–N st) cm^{-1}. MS (EI) m/z (%): 229 (M^+, 38), 124 ($[M-PhCO]^+$, 25), 105 ($PhCO^+$, 25), 96 (64), 83 (46), 82 (100), 77 (Ph^+, 40). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{20}NO]^+$: 230.1545 ($[M+H]^+$); found: 230.1554.

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Conflict of Interest

The authors declare no conflict of interest.

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