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Transformation of (+)-thiomicamine into chiral non-racemic 3,4-dihydroisoquinolinium salts: application for catalytic asymmetric epoxidation of alkenes and oxidation of sulfides

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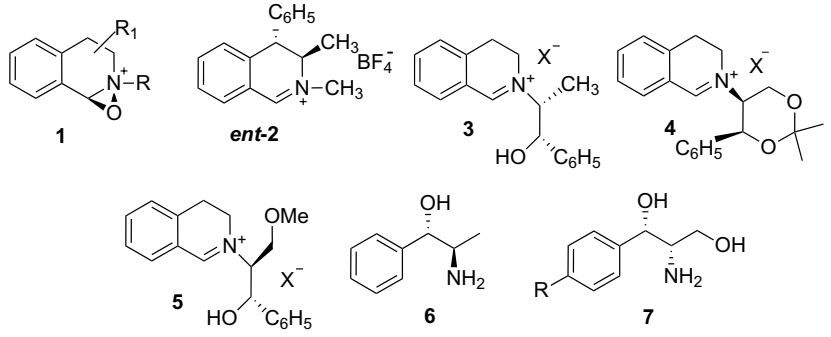
Abstract—(1*S*,2*S*)-(+)-Thiomicamine **7** (R = SCH_3) has been transformed into (3*S*,4*R*)-2,3-dimethyl-4-phenyl-3,4-dihydroisoquinolinium tetrafluoroborate **2** in a five-step reaction sequence involving (3*S*,4*R*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **14** as the key intermediate. Iminium salt **16** has been evaluated as a promoter of catalytic asymmetric epoxidation of *trans*-stilbene and oxidation of methyl-*p*-tolyl sulfide, affording products in satisfactory yield and with enantioselectivities up to 45% and 42% ee, respectively.

1. Introduction

Chiral oxaziridinium derivatives of type **1**, prepared from various dihydroisoquinolinium salts, for example, *ent*-**2**–**5**, by oxidation or generated in situ, have been used as oxygen transfer reagents for the asymmetric epoxidation of alkenes and oxidation of sulfides to sulfoxides, involving both stoichiometric and catalytic processes (Scheme 1).

In the synthesis of several dihydroisoquinolinium salts, some derivatives of (1*S*,2*R*)-norephedrine **6** and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol **7** (R = H) have been used to introduce chirality into the molecules (Scheme 1). In their pioneering work Bohé et al.[1,2] have prepared *ent*-**2** in four steps from norephedrine **6**, by *N*-benzylation and cyclization in acids to afford tetrahydroisoquinoline **8**; dehydrogenation with NaOCl to give dihydroisoquinoline **9** and finally *N*-methylation with $Me_3O^+BF_4^-$ (Scheme 2) to give the product. Oxaziridines **10** (R = -:, CH_3) have been prepared by *m*CPBA oxidation of imine **9** and iminium tetrafluoroborate *ent*-**2**, respectively, and were used as oxidants in the asymmetric epoxidation of unfunctionalized olefins and oxidation of sulfides to sulfoxides,[2,3] affording products with moderate enantioselectivities.



Scheme 1.

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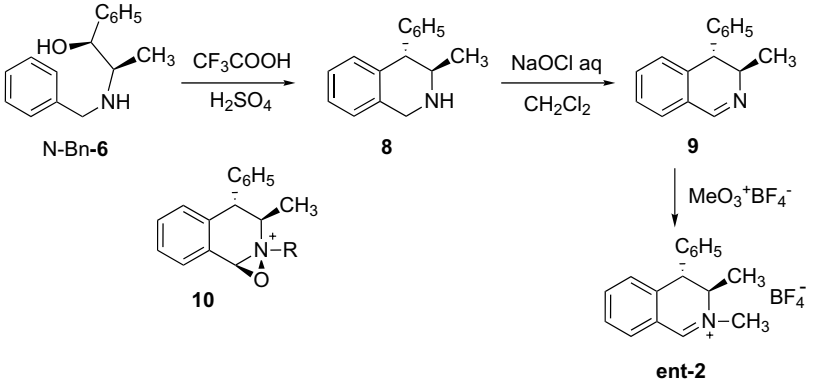


Scheme 2.

Page et al.[4–7] have synthesized a range of dihydroisoquinolinium tetraphenylborates (e.g., **3**–**5**) with chiral groups attached to the iminium nitrogen, simply by treating *o*-(2-bromoethyl)benzaldehyde with chiral amines,[4,5] including **6** and **7** (R = H), the latter as acetonide or *O*-methyl ether.[6] The effectiveness of **3**–**5** in catalytic epoxidation of alkenes with oxone has been evaluated giving selectivities of up to 73% ee.[4]

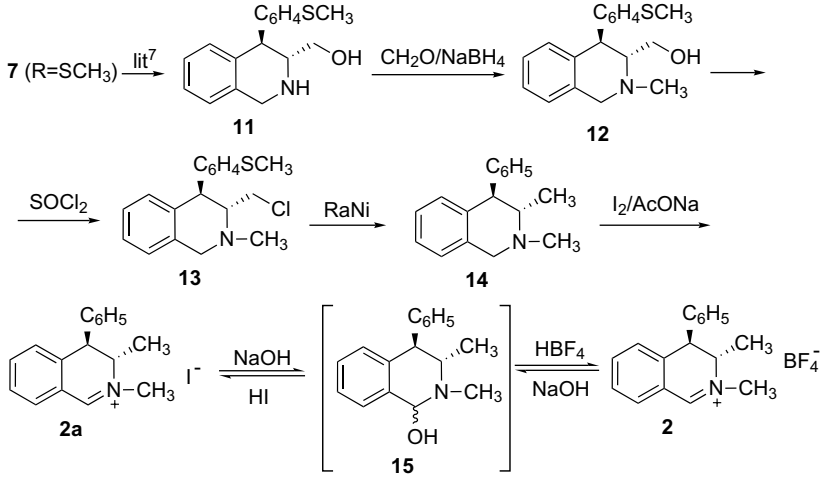
Herein, we report the results of our experiments with (+)-thiomicamine **7** (R = SCH_3), an analogue of **7** (R = H), an industrial waste product, which has been transformed into **2** which is the enantiomer of the Bohé dihydroisoquinolinium salt, *ent*-**2**. Over the course of this study, the ability of tetrafluoroborate **16** which is the hydroxymethyl analogue of **2**, to act as an oxygen transfer agent in catalytic, asymmetric oxidation of methyl-*p*-tolyl sulfide to the corresponding sulfoxide and epoxidation of *trans*-stilbene has been tested.

2. Results and discussion

In our earlier paper in this series[8] we have reported the synthesis of (3*R*,4*R*)-4-phenyl-Tic from (+)-thiomicamine **7** (R = SCH_3), in which tetrahydroisoquinoline **11** was one of the intermediates (Scheme 3). We envisaged that this type of compound could be a convenient starting material for the synthesis of iminium salts of type **2**, thus making use of (+)-thiomicamine **7** (R = SCH_3) and eventually its enantiomer, as alternatives to ephedrines, since both enantiomeric forms of the aminodiol are available.

The synthesis started with aminoalcohol **11**, which was *N*-methylated with $CH_2O/NaBH_4$ reagents system, to give tertiary amine **12**, which in turn was then treated with a large excess of $SOCl_2$ for 7 days at rt, or at reflux for 1 h, to give the unstable chloro-derivative **13**. Under the action of Raney nickel W-2 in THF, the methylthio- and chlorine substituents on **13** were reductively removed to yield tetrahydroisoquinoline **14** as an enantiomerically homogeneous (HPLC) compound in 55% yield from **11**.

Compound **14** was characterized by a molecular ion, $M^+ = 237$ *m*/*z*, present in the EI mass spectrum, and by NMR spectral data. In the ^1H NMR spectrum, the C–CH_3 group protons appeared at 1.07 δ as a doublet ($J = 6.3$ Hz) coupled with H-3 (2.71 δ). Absorption of the latter was found at 3.08 δ as qd-type splitting pattern ($J = 8.5$ Hz), due to the interaction with H-4. The ^{13}C



Scheme 3.

NMR spectrum confirmed the presence of two methyl and one methylene group carbon atoms as well as two aliphatic and nine aromatic methine along with three quaternary carbon atoms. The oily base **14** was additionally fully characterized as a stable and easy to handle, crystalline tetrafluoroborate salt, mp 175.5–179 °C, $[\alpha]_D = -47.2$ (*c* 1, methanol).

A *trans*-2,3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, which appeared to be enantiomeric to **14**, has once been mentioned in literature.[9] It was obtained as a result of LAH reduction of carbostiril formed in 18% yield as a minor product in the cyclization of (−)-*N*-benzoylephedrine in concentrated sulfuric acid. However, this compound has not been characterized, nor its absolute configuration established, except for the 3,4-*trans* arrangement of substituents, deduced from H-3/H-4 coupling constant, $J = 8.6$ Hz. 6,7-Dimethoxy analogues of **14** and *ent*-**14** have been prepared by cyclization of *N*-(3,4-dimethoxybenzyl) derivatives of (−)-*pseudo*-ephedrine and (−)-ephedrine, respectively.[10]

During our synthesis, the absolute (3*R*,4*R*) configuration of the starting tetrahydroisoquinoline **11** was preserved, as indicated by the (3*S*,4*R*)-stereochemistry of **14** and the target dihydroisoquinolinium salt **2** (change in priority of ligands at C-3 in the CIP convention). The *trans*-equatorial–*pseudo*-equatorial orientation of the C-3/C-4 substituents in **11** established by X-ray analysis[11] was also confirmed in solution by the magnitude of H-3/H-4 coupling constant, $J = 9.6$ Hz, characteristic of axial–*pseudo*-axial protons in cyclohexene derivatives[12] and other *trans*-3,4-disubstituted tetrahydroisoquinolines.[2,13] The values of H-3/H-4 coupling constants in the ^{1}H NMR spectra of the *N*-methylated tetrahydroisoquinolines **12**–**14**, ranging between 7.6 and 8.8 Hz, may indicate a compression of the H-3/H-4 dihedral angle due to steric interaction caused by the *N*-methyl substituent introduced.

Oxidation of **14** with iodine in the presence of sodium acetate afforded in quantitative yield the unstable iodide **2a**, which was directly transformed into the target tetrafluoroborate **2**, via the intermediate carbonylamine **15** (Scheme 3). The tetrafluoroborate salt **2**, which crystallized from 96% ethanol with one molecule of water of crystallization, showed mp 61.5–63.5 °C and $[\alpha]_D = -148.3$ (*c* 1, $CHCl_3$). These values corresponded to physical properties described by Bohé et al.[2] for the enantiomer, *ent*-**2**, mp 50–58 °C, $[\alpha]_D = +148.0$ (*c* 1.25, $CHCl_3$), which contained one quarter of the water molecule. The ^{1}H NMR spectra of both enantiomers were practically identical, while the ^{13}C NMR data differed in the aromatic region (apparently due to a technical error).

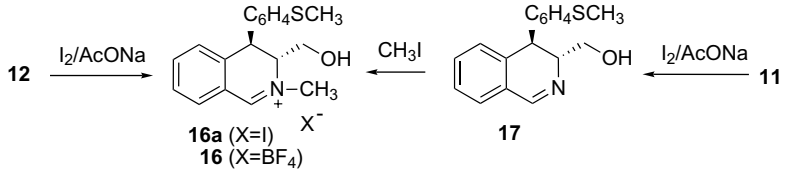
Next, we decided to synthesize iminium salt **16** with an exocyclic hydroxymethyl substituent, separated from the imine functionality, as in **3** and **5**, to test its ability and effectiveness to oxidize sulfides and alkenes. In the synthesis, both tetrahydroisoquinolines **11** and **12** were used as substrates and oxidized with iodine/ sodium acetate to the corresponding dihydro-derivatives (Scheme 4). Compound **12** afforded *N*-methyl iodide **16a**, in high yield, which was converted into tetrafluoroborate **16** via the corresponding carbinoloamine. Oxidation of tetrahydroisoquinoline **11** led to dihydro derivative **17** and this in turn was *N*-methylated with methyl iodide to give **16a**, which was transformed into **16**, as well.

An interesting ^{1}H NMR spectral feature of dihydroisoquinolinium salts synthesized was a small value of the H-3/H-4 coupling constant, $J = 2.4$ Hz, found in the spectra of **2** and **2a**, and the appearance of the H-4 proton as a singlet in the spectra of **16** and **16a**. This may suggest an inversion of conformation within this fragment of the molecule, placing the two bulky C-3 and C-4 substituents in perpendicular positions to the plane of the heterocyclic ring.

Having at hand the new, enantiomerically pure and easily accessible dihydroisoquinolinium tetrafluoroborate **16**, we were interested in testing its applicability as a promoter of organocatalyzed oxidations.[14] For this purpose, and for the sake of comparison, we undertook experiments of asymmetric epoxidation of *trans*-stilbene and oxidation of methyl-*p*-tolyl sulfide, obeying the reaction conditions developed by the Bohé et al.[2] and by Page et al.[6] catalyzed by *ent*-**2** and **3**. The results of the experiments performed are summarized in the Table 1.

As shown in Table 1, the best result (70% yield, 45% ee) in the epoxidation of *trans*-stilbene catalyzed by **16**, was achieved when *m*CPBA was used as an oxidant under the reaction conditions used by French researchers[15] (entry 3). Oxone turned out to be less effective (58% yield, 29% ee) in experiments carried out according to procedure A[2] (entry 1) and failed totally under B conditions[6] (entry 2), indicating the lack of catalytic activity of **16** in the latter case.

It is noteworthy that our experiments seem to support the suggestion made by Page et al.[6] explaining the very low selectivity observed in the asymmetric epoxidation of alkenes catalyzed by iminium salts containing an exo-



Scheme 4.

Table 1. Catalytic asymmetric oxidation of *trans*-stilbene and methyl-*p*-tolyl sulfide mediated by 10 mol% isoquinolinium salt **16**

Entry	Oxidant (equiv)	Temperature (°C)	Time (h)	Product		Reaction conditions[a]
				Yield (%)[b]	Ee (%)[c]	
			trans-stilbene → *(S,S)-(−)-trans*-stilbene oxide[d]			
1	Oxone (2)	RT	24	58	29	A
2	Oxone (2)	0 → RT	48	No reaction		B
3	*m*CPBA (1.3)	RT	1.5	70	45	C
			$CH_3C_6H_4{-}S{-}CH_3 \rightarrow (R)\text{-}(+)\text{-}CH_3C_6H_4{-}S(O){-}CH_3$[d]			
4	Oxone (1.3)	RT	4	84	14	D
5	Oxone (1.5)	0 → RT	26	73	40	B
6	Oxone (1.6)	0	24	65	42	B
7	Oxone (2)	0	24	50	42	B
8	*m*CPBA (1.2)	RT	1	88	0	C
9	*m*CPBA (1.2)	0	1.5	81	8	C

[a] Methods (conditions): (A) $NaHCO_3$ (4 equiv), CH_3CN/H_2O (30:1);[2] (B) Na_2CO_3 (4 equiv), CH_3CN/H_2O (1:1);[6] (C) $NaHCO_3$ (0.02 equiv), CH_2Cl_2;[15] (D) $NaHCO_3$ (8 equiv), CH_3CN/H_2O (15:2).[16]

[b] Reaction was carried until no more starting material was present; yields isolated after chromatographic separation.

[c] Established by HPLC using CHIRACEL OD-H column and/or by ^1H NMR spectroscopy using chiral shift reagents—$Eu(hfc)_5$ for epoxides and DNBA for sulfoxides.

[d] Absolute configuration was determined by comparison of the sign of the specific rotation, (*S,S*)-(−)-stilbene oxide[17] and (*R*)-(+)-methyl-*p*-tolyl sulfoxide (Aldrich).

cyclic primary hydroxyl group, as resulting from equilibrium with inactive oxazolidine. Using iminium salt **16**, which also contained an exocyclic primary hydroxyl group, and due to steric reasons, could not cyclize to oxazolidine, we were able to achieve enantioselectivities up to 45% ee, comparable to that obtained with iminium catalysts lacking this functionality.[2,6]

Epoxidation of stilbene according to the Bohé et al. procedure,[2] mediated by **2**, produced (*S,S*) epoxide, enantiomeric to the (*R,R*) formed in the reaction catalyzed by *ent*-**2**; moreover, with the same enantioselectivity 35% *ee*.

In oxidation of methyl-*p*-tolyl sulfide, oxone was found to be more effective then *m*CPBA, producing the sulfoxide with enantiomeric excess reaching 42% (entries 6 and 7).

It is interesting to note, that when increasing the amount of oxone used, the yield of sulfoxide decreased (overoxidation to sulfone), while the enantioselectivity increased (entries 4–7), indicating that the oxidation process appears to be a kinetic resolution.

3. Conclusion

Enantiomerically pure (3*S*,4*R*)-2,3-dimethyl-4-phenyl-2,3-dihydroisoquinolinium tetrafluoroborate **2**, enantiomeric to the *ent*-**2**, an oxygen transfer agent, has been synthesized from (+)-thiomicamine **7** (R = CH_3), an industrial waste product, in a reaction sequence involving five steps. The key intermediate in the synthesis, (3*S*,4*R*)-2,3-dimethyl-4-phenyl-tetrahydroisoquinoline **14**, has been fully characterized and obtained in the crystalline form as tetrafluoroborate. Iminium salt **16**, a hydroxymethyl analogue of **2**, has been prepared in a simple way and been proven to promote enantioselective oxidation of *trans*-stilbene and methyl-*p*-tolyl sulfide in yields and selectivities comparable to those reported by others,[2,3,6] thus making a contribution to the family of isoquinolinium salts applicable as organocatalysts[18] in enantioselective processes.

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are not corrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, with TMS as internal standard. Mass spectra (EI): Joel D-100, 75 eV, and FAB (*m*-nitrobenzylalcohol) as the matrix. Specific rotation: Perkin–Elmer polarimeter 243B at 20 °C. Analytical HPLC: Waters HPLC system with Mallinkrodt–Baker Chiracel OD-H column. Merck DC-Alufolien Kieselger 60_{254} were used for TLC.

4.2. Synthesis of (3*S*,4*R*)-2,3-Dimethyl-4-phenyl-3,4-dihydroisoquinolinium tetrafluoroborate 2

4.2.1. (3*R*,4*R*)-3-Hydroxymethyl-2-methyl-4-(4-methylthiophenyl)-1,2,3,4-tetrahydroisoquinoline 12. Tetrahydroisoquinoline hydrobromide **11**·HBr[8] was transformed into the free base **11** by treatment with 5% NaOH and extraction with methylene chloride (83.4%); mp 95–98.5 °C (by digestion of the crude product with hexane), $[\alpha]_D = -34.4$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 2.11 (br s, 2H, OH, NH), 2.48 (s, 3H, SCH_3), 3.08 (ddd, *J* = 3.6, 7.9, 9.6 Hz, 1H, H-3), 3.42 (dd, *J* = 7.9, 10.7 Hz, 1H, C*H*H), 3.61 (dd, *J* = 3.6, 10.7 Hz, 1H, CH*H*), 3.80 (d, *J* = 9.6 Hz, 1H, H-4), 4.17 (ABq, *J* = 16.3 Hz, 2H, CH_2N), 6.76 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.02–7.25 (m, 7H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 15.79 (SCH_3), 46.68 (CH), 47.87 (CH_2), 62.12 (CH),

63.28 (CH_2), 125.58 (CH), 125.97 (CH), 126.45 (CH), 126.70 (2CH), 129.77 (2CH), 130.06 (CH), 135.40 (C), 136.44 (C), 137.95 (C), 140.28 (C). EI MS *m/z* (%): 258 (M^+, 4), 255 (19), 254 (100), 179 (56), 178 (24). HRMS calcd for $C_{17}H_{19}NOS$ 285.11863. Found 285.11874.

A mixture composed of free base **11** (3.27 g, 11.5 mmol), glacial acetic acid (1.2 mL, 21 mmol) and aqueous formaldehyde (37%), (1.56 mL, 21 mmol) in 96% ethanol (54 mL) was stirred at rt for 45 min, then cooled in ice-bath after which sodium borohydride (3.3 g, 87 mmol) was added in portions over ca. 2 h. The mixture was stirred at rt for 18 h, then the solvent removed under reduced pressure, water was added and the mixture extracted with ethyl ether until the Dragendorff test was negative. The organic phase was dried and the solvent evaporated to afford crude amine **12** (95.5%). Crystallization from ethyl ether/hexane gave enantiomerically pure (HPLC) **12**, mp 68–72.5 °C, $[\alpha]_D = -118.5$ (*c* 0.98, methanol). ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H, SCH_3), 2.47 (s, 3H, NCH_3), 2.85 (ddd, *J* = 4.1, 6.3, 10.2 Hz, 1H, H-3), 3.47 (dd, *J* = 6.3, 11.3 Hz, 1H, C*H*H), 3.58 (dd, *J* = 4.1, 11.3 Hz, 1H, CH*H*), 3.96 (ABq, *J* = 15.7 Hz, 2H, CH_2N), 4.02 (d, *J* = 8.2 Hz, 1H, H-4), 6.75 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.03–7.21 (m, 8H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 15.81 (SCH_3), 38.46 (NCH_3), 43.43 (CH), 57.38 (CH_2), 59.71 (CH_2), 67.32 (CH), 126.10 (CH), 126.19 (CH), 126.57 (CH), 126.71 (2CH), 129.54 (CH), 129.87 (2CH), 133.72 (C), 136.41 (C), 137.50 (C), 140.54 (C). MS *m/z* (%): 229 (M^+, 0.5), 268 (10), 226 (8), 179 (100). Anal. Calcd for $C_{18}H_{21}NOS \cdot 1/2\ H_2O$: C, 70.10; H, 7.19; N, 4.54; S, 10.37. Found: C, 70.48; H, 7.20; N, 4.40; S, 10.28.

Compound **12**·HBr, mp 201–203.5 °C (from ethanol), $[\alpha]_D = -84.2$ (*c* 1.05, methanol).

4.2.2. (3*R*,4*R*)-3-Chloromethyl-2-methyl-4-(4-methylthiophenyl)-1,2,3,4-tetrahydroisoquinoline 13. To isoquinoline **12** (1.23 g, 4.1 mmol), thionyl chloride (8.2 mL) was introduced dropwise at an ice-bath temperature with stirring and the solution left for 5–7 days (TLC) at rt. The excess of the reagent was evaporated and the residue partitioned between 20% sodium hydroxide and methylene chloride. The organic phase was washed with water, dried and the solvent removed under reduced pressure to give the crude, unstable **13** in quantitative yield. It was characterized by ^{1}H NMR and MS spectra and used in the next step of the synthesis without purification. ^{1}H NMR ($CDCl_3$) δ: 2.47 (s, 3H, SCH_3), 2,54 (s, 3H, NCH_3), 2.87 (m, 1H, H-3), 3.54 (dd, *J* = 3.0, 11.8 Hz, 1H, C*H*H), 3.62 (dd, *J* = 4.9, 11.7 Hz, 1H, CH*H*), 3.89 (ABq, *J* = 15.3 Hz, 2H, CH_2N), 4.35 (d, *J* = 7.7 Hz, 1H, H-4), 6.81 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.04–7.21 (m, 7H, Ar-H). MS *m/z* (%): 317 (M^+, 3), 268 (100), 179 (60).

4.2.3. (3*S*,4*R*)-2,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 14. A solution of crude chloride **13** (1.35 g, 4.26 mmol) in tetrahydrofuran (68 mL) was treated with wet Raney nickel W-2 (ca. 2 mL) and heated at reflux for 6 h with vigorous stirring. After cooling to rt, another portion of Raney nickel (ca. 2 mL) was added and heating continued for another 6 h. The hot suspension was filtered through a pad of Celite, the organic residue washed with hot tetrahydrofuran, followed by hot ethanol, and the combined filtrates were evaporated under reduced pressure to give crude, oily isoquinoline **14** (82%). It was purified by Kugelrohr distillation at 100–110 °C/1 mmHg. $[\alpha]_D = -71.3$ (*c* 0.96, methanol). ^{1}H NMR ($CDCl_3$) δ: 1.07 (d, *J* = 6.3 Hz, 3H, CCH_3), 2.44 (s, 3H, NCH_3), 2.71 (qd, *J* = 6.3, 8.5 Hz, 1H, H-3), 3.80 (d, *J* = 8.5 Hz, 1H, H-4), 3.68 (s, 2H, CH_2N), 6.72 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.02–7.25 (m, 8H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 16.39 (CH_3), 40.83 (CH_3), 52.17 (CH), 57.63 (CH_2), 62.50 (CH), 125.67 (CH), 125.72 (CH), 126.23 (CH), 126.26 (CH), 128.13 (2CH), 129.44 (2CH), 129.67 (CH), 133.90 (C), 137.56 (C), 144.69 (C). MS *m/z* (%): 237 (M^+, 28), 222 (47), 180 (80), 179 (100), 165 (28).

4.2.3.1. Tetrafluoroborate salt, 14·BF_4. Mp 175.5–179 °C (from 96% ethanol), $[\alpha]_D = -47.2$ (*c* 1, methanol). ^{1}H NMR (DMSO-d_6/100 °C) δ: 1.25 (d, *J* = 6.3 Hz, 3H, CCH_3), 2.91 (s, 3H, N^+CH_3), 3.87 (dq, *J* = 6.3, 12.6 Hz, 1H, H-3), 4.20 (d, *J* = 10.7 Hz, 1H, H-4), 4.51 and 4.76 (2d, *J* = 15.7 Hz, 2H, CH_2N^+), 6.72 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.16 – 7.41 (m, 8H, Ar-H). ^{13}C NMR (DMSO-d_6/100 °C) δ: 14.46 (CH_3), 40.05 (CH), 48.11 (NCH_3), 54.57 (CH), 61.42 (CH_2), 125.90 (CH), 126.32 (CH), 126.82 (CH), 127.0 (C), 127.48 (CH), 128.16 (2CH), 128.35 (CH), 128.70 (2CH), 134.76 (C), 140.44 (C). MS *m/z* (%): 283 (M^+, 4), (M^+-1, 23), 222 (46), 180 (71), 179 (100), 165 (28). Anal. Calcd for $C_{17}H_{20}NBF_4$: C, 62.78; H, 6.20; N, 4.31. Found C, 62.63; H, 6.17; N, 4.30.

4.2.4. (3*S*,4*R*)-2,3-Dimethyl-4-phenyl-3,4-dihydroisoqinolinium tetrafluoroborate 2. A mixture of tetrahydroisoquinoline **14** (0.44 g, 1.87 mmol), iodine (1.68 g, 6.6 mmol) and sodium acetate (0.54 g, 6.6 mmol) in 96% ethanol (18 mL) was heated under reflux for 2 h. The solvent was removed and the residue dissolved in methylene chloride and washed with satd sodium thiosulfate and water. The organic phase was dried and the solvent evaporated to give unstable iodide, **2a**, 0.65 g (96%) as a yellow foam, which was transformed directly into tetrafluoroborate **2**. A sample was characterized: IR (KBr), ν (cm^{-1}): 3508 and 3295 (br), 1662 (C=N^+). ^{1}H NMR ($CDCl_3$) δ: 1.59 (d, *J* = 6.9 Hz, 3H, CCH_3), 3.85 (s, 3H, N^+CH_3), 4.27 (dq, *J* = 2.75, 6.9 Hz, 1H, H-3), 4.39 (d, *J* = 2.5 Hz, 1H, H-4), 6.95 (m, 1H, Ar-H), 7.33 (m, 4H, Ar-H), 7.61 (m, 1H, H-7), 7.79 (m, 1H, H-6), 8.39 (d, *J* = 7.44 Hz, 1H, H-8), 10.52 (s, 1H, CH=N^+). MS *m/z* (%): 237 (M^++1, 17), 236 (M^+, 14), 234 (12), 222 (32), 221 (41), 220 (36), 180 (52), 179 (100), 178 (87), 165 (28). HRMS of (M^+–I) calcd for $C_{17}H_{18}N$ 236.14383. Found 236.14392.

Iodide **2a** (0.297 g, 0.82 mmol) in 96% ethanol (5 mL) was treated with 5% sodium hydroxide. The alcohol was then evaporated under reduced pressure and the residue extracted with methylene chloride. The organic

phase was washed with water, dried and the solvent evaporated. The residue (92%) was dissolved in 96% ethanol and treated at ice-bath temperature with 4.8% tetrafluoroboric acid (from aqueous 48% HBF_4 and ethanol) to reach pH ca. 1. Fine crystals of tetrafluoroborate salt **2** were collected, mp 61.5–63.5 °C, $[\alpha]_D = -148.3$ (*c* 1, chloroform), lit.[2] mp 50–58 °C, $[\alpha]_D = +148.0$ (*c* 1.25, chloroform). IR (KBr), *v* (cm^{-1}): 3424 (br), 1663 ($C{=}N^+$). ^1H NMR ($CDCl_3$) δ: 1.54 (d, $J = 6.9$ Hz, 3H, CCH_3), 3.73 (d, $J = 0.8$ Hz, 3H, N^+CH_3), 4.29 (dq, $J = 2.9$, 6.9 Hz, 1H, H-3), 4.35 (d, $J = 2.9$ Hz, 1H, H-4), 6.91 (m, 2H, Ar-H), 7.24 (m, 4H, Ar-H), 7.57 (dt, $J = 1.2$, 7.7 Hz, 1H, H-7), 7.76 (dt, $J = 1.4$, 7.8 Hz, 1H, H-6), 8.09 (dd, $J = 1.4$, 7.7 Hz, 1H, H-8), 9.25 (s, 1H, H-1). ^{13}C NMR ($CDCl_3$) δ: 17.18 (CH_3), 46.67 (NCH_3), 47.89 (CH), 64.53 (CH), 124.04 (C), 127.28 (2CH), 128.32 (CH), 129.45 (CH), 129.50 (2CH), 129.88 (CH), 134.79 (CH), 136.38 (C), 138.76 (CH), 139.05 (C), 166.93 (CH). MS *m*/*z* (%): 237 ($M^+ + 1 - BF_4$, 18), 237 ($M^+ - BF_4$, 18), 180 (52), 179 (100), 178 (98), 165 (25), 142 (18), 115 (11). Anal. Calcd for $C_{17}H_{18}NBF_4 \cdot 1H_2O$: C, 59.85; H, 5.91; N, 4.11. Found: C, 59.74; H, 5.68; N, 4.28.

4.3. (3*R*,4*R*)-3-Hydroxymethyl-2-methyl-4-(4-methylthiophenyl)-3,4-dihydroisoquinolinium tetrafluoroborate 16

4.3.1. From *N*-methyltetrahydroisoquinoline 12. Tetrahydroisoquinoline **12** (0.15 g, 0.5 mmol), iodine (0.76 g, 3 mmol) and sodium acetate (0.26 g, 3.2 mmol) in 96% ethanol (5 mL) were heated at reflux until no more starting material was present (TLC). The solvent was evaporated and the residue dissolved in methylene chloride, washed with satd sodium thiosulfate and water. After the standard work-up unstable iodide, **16a**, was obtained as a yellow oil (0.16 g, 73%) and directly transformed into the tetrafluoroborate **16**. A sample of the iodide **16a** was characterized: IR (KBr), *v* (cm^{-1}): 3284, 1660. ^1H NMR ($CDCl_3$) δ: 2.43 (s, 3H, SCH_3), 3.83 (s, 3H, N^+CH_3), 3.98 (dd, $J = 4.74$, 12.4 Hz, 1H, CH*H*), 4.12 (dd, $J =$ ca. 7, 12.4 Hz, 1H, C*H*H), 4.25 (m, 2H, H-3, OH), 4.57 (s, 1H, H-4), 6.88 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.16 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.34 (d, $J = 7.7$ Hz, 1H, H-5), 7.54 (m, 1H, H-7), 7.74 (m, 1H, H-6), 8.17 (d, $J = 6.9$ Hz, 1H, H-8), 9.79 (s, 1H, H-1). MS *m*/*z* (%): 423 ($M^+ - 2$, 1), 298 ($M^+ - I$, 14), 297 ($M^+ - 1$, $-I$, 37), 283 (22), 281 (13), 280 (12), 268 (79), 267 (41), 266 (35), 224 (45), 194 (68), 193 (14), 179 (23), 178 (25), 174 (10), 173 (79), 165 (28), 144 (100), 142 (24), 137 (13). HRMS of ($M^+ - 2$) calcd for $C_{18}H_{18}NOSI$ 423.01528. Found 423.01538.

4.3.1.1. Tetrafluoroborate, 16. Iminium iodide **16a** (0.733 g, 1.72 mmol) in ethanol (10 mL) was treated with 5% sodium hydroxide. Then alcohol was evaporated under reduced pressure and the residue extracted with methylene chloride. The organic phase was washed with water and the solvent evaporated. The residue was dissolved in ethanol again and treated with 4.8% tetrafluoroboric acid to pH ca. 1, to deposit 0.508 g (76%) of crystalline **16**; mp 123–128 °C (from 96% ethanol/hexane), $[\alpha]_D = -285.2$ (*c* 0.5, methanol). IR (KBr), *v* (cm^{-1}): 3509, 3288, 1662. ^1H NMR ($CDCl_3/D_2O$) δ: 2.44 (s, 3H, SCH_3), 3.80 (s, 3H, N^+CH_3), 3.96 (2ABq, $J = 5.2$, 5.5, 12.1 Hz, 2H, CH_2O), 4.24 (t, $J =$ ca. 5 Hz, 1H, H-3), 4.48 (s, 1H, H-4), 6.81 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.16 (m, 2H, Ar-H), 7.31 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.57 (dq, $J = 1.1$, 7.4 Hz, 1H, H-7), 7.77 (dq, $J = 1.1$, 7.7 Hz, 1H, H-6), 8.00 (d, $J = 7.7$ Hz, 1H, H-8), 9.09 (s, 1H, H-1). ^{13}C NMR (DMSO-d_6) δ: 14.51 (SCH_3), 41.65 (CH), 47.47 (NCH_3), 60.89 (CH_2), 68.19 (CH), 123.66 (CH), 126.30 (2CH), 127.92 (2CH), 128.62 (CH), 129.49 (CH), 133.53 (CH), 137.46 (C), 137.60 (C), 137.79 (C), 138.20 (C), 167.48 (CH). EI MS *m*/*z* (%): 298 (M^+, 6), 297 ($M^+ - 1$, 26), 267 (30), 254 (12), 224 (33), 194 (65), 173 (59), 165 (32), 144 (100). Anal. Calcd for $C_{18}H_{20}BF_4NOS \cdot 1/4\ H_2O$ (389.43): C, 55.47; H, 5.31; N, 3.59; S, 8.21. Found: C, 55.79; H, 5.70; N, 3.44; S, 8.15.

4.3.2. From dihydroisoquinoline 11

4.3.2.1. (3*R*,4*R*)-3-Hydroxymethyl-4-(4-methylthiophenyl)-3,4-dihydroisoquinoline 17. Tetrahydroisoquinoline **11** (3.46 g, 12.1 mmol), iodine (10.9 g, 42.9 mmol) and sodium acetate (3.64 g, 44 mmol) in 96% ethanol (120 mL) were heated at reflux for 1 h. The solvent was then evaporated and the residue dissolved in methylene chloride and washed with satd sodium thiosulfate, 5% sodium hydroxide and water. After the standard work-up of the organic phase, the oily product, obtained in quantitative yield, was crystallized from 96% ethanol and then from acetone to give crystalline **17**, mp 127–130 °C, $[\alpha]_D = -100.4$ (*c* 0.56, methanol), $[\alpha]_D = +64.4$ (*c* 0.25, chloroform). IR (KBr), *v* (cm^{-1}): 3237, 1625. ^1H NMR ($CDCl_3$) δ: 2.51 (s, 3H, SCH_3), 3.30 (br s, disappeared on treatment with D_2O, OH), 3.48 (m, 1H, C*H*H), 3.84 (m, 2H, H-3, CH*H*), 4.02 (d, $J = 14.0$ Hz, 1H, H-4), 6.77 (m, 1H, Ar-H), 7.15–7.39 (m, 6H, Ar-H), 8.44 (d, $J = 2.5$ Hz, 1H, H-1). ^{13}C NMR ($CDCl_3$) δ: 15.79 (CH_3), 43.22 (CH_2), 64.19 (CH), 64.28 (CH), 127.02 (2CH), 127.28 (CH), 127.41 (CH), 127.45 (CH), 127.91 (CH), 129.83 (2CH), 131.80 (CH), 137.26 (2C), 137.35 (C), 139.45 (C), 160.63 (CH). EI MS *m*/*z* (%): 283 (M^+, 100), 266 (74), 252 (32), 224 (31), 204 (16), 179 (19), 178 (59), 165 (24), 130 (24). HRMS calcd for $C_{17}H_{17}NOS$ 283.10299. Found 283.10309.

4.3.2.2. (3*R*,4*R*)-3-Hydroxymethyl-2-methyl-4-(4-methylthiophenyl)-3,4-dihydroisoquinolinium tetrafluoroborate 16. Compound **17** (0.529 g, 1.87 mmol) was dissolved in methyl iodide (4 mL) and left at rt for 6 h. Then the excess of methyl iodide was removed, and the oily residue crystallized two times from 96% ethanol to give 0.55 g (69%) of iodide **16a**, identical to that prepared by the oxidation of *N*-methyltetrahydroisoquinoline **12**. It was then transformed into the tetrafluoroborate salt **16** following the above procedure (Section 4.3.1).

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