# Asymmetric Synthesis of Isoquinoline Derivatives from Amino Acids

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*Dedicated to Prof. Dr. habil. Karl Gewald*

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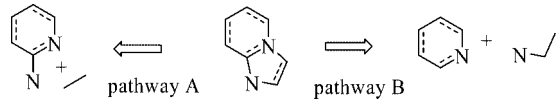
Reaction of isoquinolines **1** with *N*-arylsulfonylamino acid fluorides **2** provides a highly stereoselective access to new dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5** via intermediate *N*-acylisoquinolinium salts **3**. Addition reactions to the enamine double bond, such as hydrogenation or epoxidation with dimethyldioxirane, leads to tetrahydroimidazo[2,1-*a*]isoquinoline-3-ones **6**, **7** and oxiranes **8**, respectively. Opening of the oxirane ring of the **8** with nucleophiles allows the synthesis of hydroxytetrahydroimidazo[2,1-*a*]isoquinolin-3-ones **10** or **12** or of the polycyclic 1,4-dioxane **13** in high stereoselectivity. The regioselectivity of the oxiran ring opening depends on the kind of nucleophile and the conditions. Reaction of dihydroisoquinoline with *O*-TBDMS-mandelic acid chloride **15** leads to a tetrahydrooxazolo[2,3-*a*]isoquinoline **17** with opposite facial selectivity as compared with dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5**.


## Introduction

Recently, we investigated the stereoselective reaction of isoquinolines with α-aminoacyl fluorides[1,2] in the presence of $AlCl_3$ and trimethylsilyl chloride or trimethylsilyl cyanide affording either Reissert compounds (2-acyl-1-cyano-1,2-dihydroisoquinolines)[3] or novel dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5** [4] via intermediate *N*-acyliminium salts. Remarkably the outcome of the reaction with trimethylsilyl cyanide depended on the type of protective group attached to the amino acid fluoride. While Z- and FMOC-protected amino acid fluorides gave Reissert compounds similar to **4**, the NH-acidic α-sulfonylamino acid fluorides **2** undergo cyclisation reaction to the dihydroimidazo[2,1-*a*]isoquinolines **5** by attack of the sulfonamido group at the position 1 of the intermediate *N*-α-tosylaminoacyl isoquinolium salts **3**. This synthesis of imidazo[2,1-*a*]isoquinolines **5** corresponds to a novel retrosynthetic pattern where the imidazo[2,1-*a*]pyridine core is established from a condensed pyridine as a C-N building block and an amino acid as a N-C-C building block (Scheme 1, pathway B). So far imidazo[2,1-*a*]pyridine systems are only known in the fully aromatic series,[5–7] as compounds with saturated imidazole and pyridine ring[8,9] as systems with a C–C double bond in the imidazole ring,[10] or with a fully aromatic pyridinium ring.[11] Such known compounds were synthesized from 2-aminopyridines as N–C–N building block and a suitable C–C bielectrophile (Scheme 1). It has to be mentioned that a higher homologue of condensed dihydroimidazo[2,1-*a*]pyridines is found in the naturally occurring Evodiamine.[12]




Scheme 1

Here, we report the scope and limitation of this synthesis of dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5**, the stereoselective transformation of the **5** into new tetrahydroimidazo[2,1-*a*]isoquinoline-3-ones and full experimental detail of all reactions.

## Results and Discussion

In order to optimize the yields of the synthesis of dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5** reaction conditions were systematically varied for the alanine-derived product **5a**. Reversion of the sequence of the addition of reactants from adding the amino acid fluoride **2** to a solution of isoquinoline and 0.2 equivalents of $AlCl_3$ in dry solvent at –10 °C followed by the addition of one equivalent of trimethylsilyl cyanide or trimethylsilyl chloride at –78 °C toward the addition of isoquinoline to a solution of **2** and $AlCl_3$ followed by the addition of the TMS reagent resulted in a considerable drop in yield from 45 % to 20 % (Scheme 2). Lowering the ratio of TMS chloride or TMS cyanide or omitting these reagents, again lowered the yield

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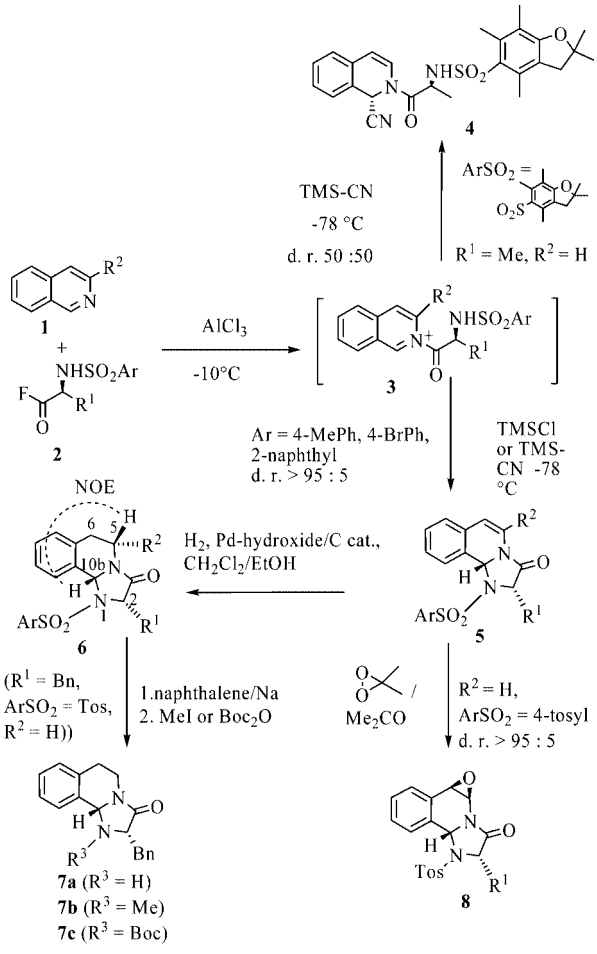
of product **5a.** On the other hand, increasing the quantity of TMS chloride or TMS cyanide did not increase the yield. Working under higher dilution, in order to prevent eventual formation of oligomeric or polymeric products, such as peptides, did not show a positive effect on the yield either. Changing the ratio of reactants **1** and **2** had no impact on the yield, if the yield is calculated according to the minor component. Variation of the type and quantity of Lewis acid revealed that other Lewis acids than $AlCl_3$ were less effective and that application of a Lewis acid is indispensable (Table 1, Entry 1). Equimolar quantities of $AlCl_3$ prevent formation of the product **5a** (Table 1, Entry 4). Variation of the temperature during the addition of the amino acid fluoride **2** from –10 °C to –78 °C and –100 °C showed an optimal yield and stereoselectivity at –78 °C.




Scheme 2

This variation of reaction conditions resulted in an optimal procedure using reactants **1** and **2** and TMS-Cl in equimolar quantities and 0.2 equivalents of $AlCl_3$ at –78 °C in dichloromethane. Applying this procedure afforded a number of dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5** (see Table 2). The diastereomeric ratio was higher than 95:5 in all cases. Application of (D)-*N*-tosylalanyl fluoride thus led to the formation of the antipode **ent-5a**. The benzothiazol-2-sulfonyl-substituted dihydroimidazo[2,1-*a*]isoquinolin-3-one **5d** was obtained using the corresponding alanyl chloride instead of the fluoride **2.** Substituents in position 3 and in particular in position 1 of the isoquinoline **1** – the latter would have led to the formation of a quaternary asymmetric carbon atom – hamper the formation of dihydroimidazoisoquinolines **5** due to steric hindrance. Thus 3-methylisoquinoline afforded the corresponding product **5i** in lower yield (12 %) while 1-methylisoquinoline and 6,7-dimethoxy-1-methylisoquinoline were recovered unchanged under the standard conditions. Interestingly, the reaction of isoquinoline with the pentamethylbenzofurylsulfonyl-protected alanyl fluoride **2** and trimethylsilyl cyanide did not result in the formation of imidazoisoquinolines **5** but lead to the Reissert compound **4** as a 1:1 mixtures of epimers. Obviously, the steric hindrance by the methyl groups at the benzofurylsulfonyl group of **2** hampered the cyclization and thus the smaller cyanide group attacks position 1 of the corresponding intermediate *N*-acyliminium salt **3.** In general, yields of imidazoisoquinolines **5** were below 50 % because of the formation of considerable quantities of polar by-products, which, however, could not be separated from the reaction mixture and analyzed. We suppose that competing formation of polyamides occurs as was reported for other amino acid halides.[13]

Table 1. Variation of type and quantities of Lewis acids in the reaction of (*S*)-*N*-tosylalanine **2a** with isoquinoline and TMS-Cl to imidazo[2,1-*a*]isoquinolin-3-one **5a**

| Entry | Lewis acid | Equiv. of Lewis acid[a] | Yield of **5a** |
|---|---|---|---|
| 1 | – | – | 0 |
| 2 | $AlCl_3$ | 0.1 | 41 |
| 3 | $AlCl_3$ | 0.2 | 45 |
| 4 | $AlCl_3$ | 1.0. | 0 |
| 5 | $ZnCl_2$ | 0.2 | 39 |
| 6 | $ZnF_2$ | 0.2 | 19 |
| 7 | $Et_2AlCl$ | 0.2 | 0 |

[a] According to the quantity of isoquinoline.

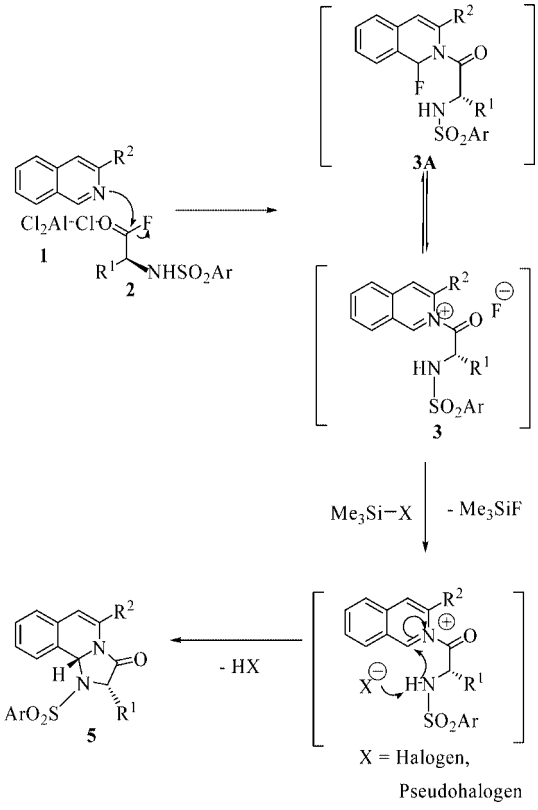
Table 2. Dihydroimidazo[2,1-*a*]isoquinolin-3-ones **5**, tetrahydrohydroimidazo[2,1-*a*]isoquinolin-3-ones **6** and **7**, and oxiranes **8**

| $R^1$ | $R^2$ | Ar or $R^3$ | **5** % yield[a] | **6** % yield[a] | **7** % yield[a] | **8** % yield[a] |
|---|---|---|---|---|---|---|
| Me | H | 4-tolyl | **5a**/47 | **6a**/88 | | **8a**/98 |
| Me | H | 2-naphthyl | **5b**/46 | | | |
| Me | H | 4-Br-phenyl | **5c**/46 | | | |
| Me | H | benzthiazol-2-yl | **5d**/24[b] | | | |
| Bn | H | 4-tolyl | **5e**/45 | **6b**/99 | | **8b**/98 |
| Bn | H | H | | | **7a**/30 | |
| | | Me | | | **7b**/60 | |
| | | boc | | | **7c**//89 | |
| *i*Pr | H | 4-tolyl | **5f**/44 | | | |
| *i*Pr | H | 2-naphthyl | **5** /46 | | | |
| *i*Bu | H | 4-tolyl | **5h**/46 | | | |
| Bn | Me | 4-tolyl | **5i**/12 | **6c**/99[c] | | |

[a] *dr* > 95:5. [b] *N*-(Benzothiazol-2-yl)alanyl chloride was used. [c] *dr* = 82:12.

The aforementioned results are in agreement with the mechanism shown in Scheme 3. The complex of amino acid fluoride **2** and $AlCl_3$ attacks the isoquinoline **1** at the nitrogen atom in position 2. The resulting *N*-acyliminium salts **3** could be in an equilibrium with the corresponding less reactive 1,2 adduct **3A**, but the silyl reagent traps the fluoride ion transforming all fluoroisoquinoline **3A** in the highly reactive *N*-acyliminium salt **3**. The latter can loose a proton and by attack of the resulting sulfonamide anion at position 1 of the *N*-acyliminium ion the final product **5** is formed. A similar equilibrium as between **3** and **3A** was proposed in the addition of α-phthalimido acid chlorides to (benzylidene)aniline.[14]




Scheme 3

Structure elucidation of the products **5** is based on a X-ray crystal analysis of products **5a** [4] and **5c** (see Figure 1) and consistent spectroscopic data, and is in agreement with the chemical behavior.

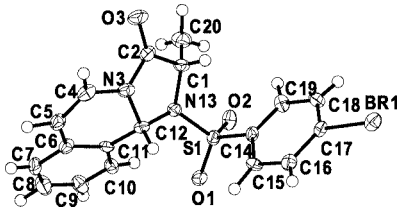


Figure 1. X-ray crystal analysis of the tetrahydroimidazo[2,1-*a*]isoquinoline **5c**

Addition reactions to the enamine double bond of the dihydroimidazo[2,1-*a*]isoquinolines **5** can be expected to occur from the convex side of the bowl-shaped structure (see Figure 2). In practice only products of *exo*-attack to the enamine double bond were observed.

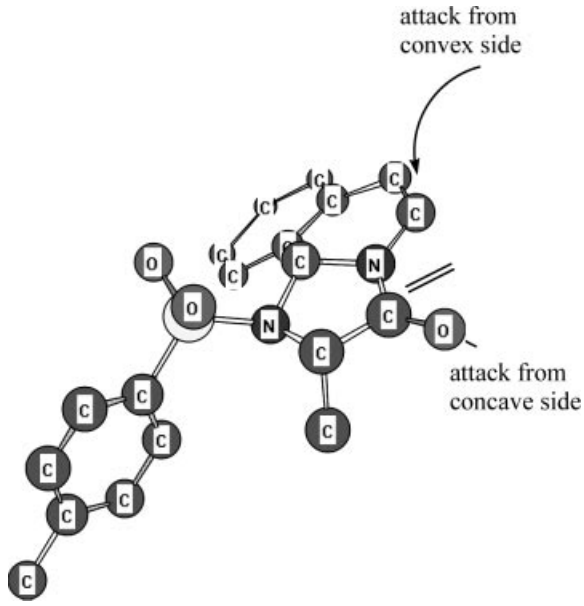



Figure 2. Stereochemical modes of attack at the enamine C–C double bond of dihydroimidazo[2,1-*a*]isoquinolines **5**

In analogy to other known *N*-acylenamines[15] compounds **5** could be hydrogenated at atmospheric pressure in the presence of Pd-hydroxide/C yielding the corresponding tetrahydroimidazo[2,1-*a*]isoquinolines **6** (see Scheme 2). The configuration of the new stereogenic center in position 5 of **6c** could be proved by the NOE effect between the hydrogen atoms connected to position 5 and 10b, thus revealing the attack of the hydrogen from the ß-phase, i. e. from the convex side of **5** (see Figure 2). As could be shown with the tosyl-substituted tetrahydroisoquinoline **5e** deprotection is possible by reaction with Na-naphthalide.[16] Since the resulting *N*-unsubstituted product **7a** readily decomposed during the aqueous work-up in the presence of $NH_4Cl$, it was preferably *N*-methylated or *N*-boc-protected to **7b** and **7c**, respectively (see Scheme 2). The structure of the tetrahydroimidazol[2.1-*a*]isoquinoline **7c** was proved by X-ray crystal analysis (see Figure 3).

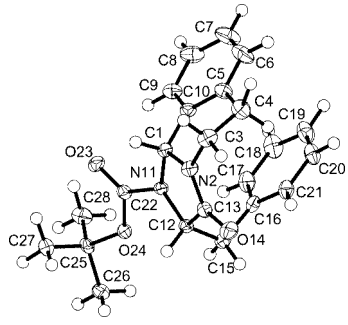
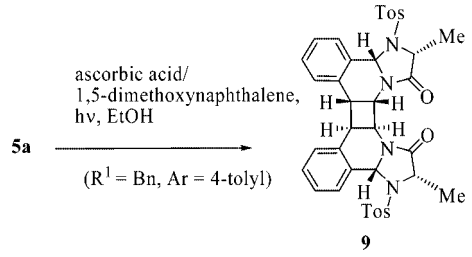


Figure 3. X-ray Crystal Analysis of compound **7c**

Attempts to remove the tosyl protective group from the 2-benzyldihydroimidazo[2,1-*a*]isoquinoline **5e** by photore-

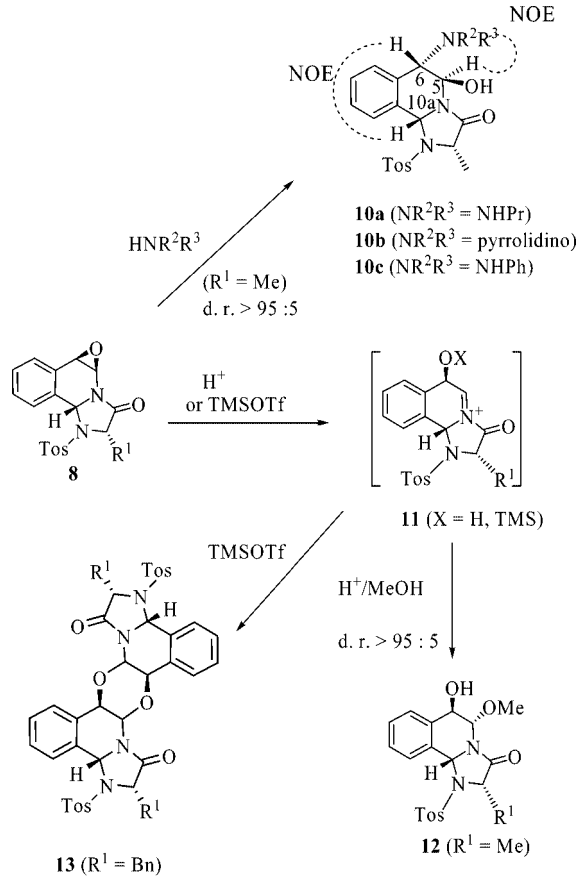
duction[17,18] with ascorbic acid in the presence of 1,8-dimethoxynaphthalene resulted in the formation of a polycyclic [2+2] cycloadduct **9**, while the tosyl group was not affected (Scheme 4). The configuration of **9** was tentatively assigned on the basis of the NMR data, where the total number of resonance signals is half the number of H-atoms or C-atoms, respectively, and doublets are seen in the $^1$H NMR spectra for the cyclobutane H-atoms.




Scheme 4

Dimethyldioxirane[19,20] has become a reliable reagent in epoxidation of *N*-acylenamine moieties.[21–24] Its reaction with dihydroimidazo[2,1-*a*]isoquinolines **5** was highly stereoselective (*dr* > 95:5) affording excellent yields of the oxiranes **8a**,**b** (see Scheme 2). MCPBA was successfully applied in the epoxidation of an anthraquinone-derived acylenamine.[25] This was less favorable for **5** because the stereoselectivity was lower (*dr* about 80:20) and it was not possible to separate the epoxidation product from resulting *m*-chlorobenzoic acid. As in the hydrogenation (vide supra) the preferred attack of the epoxidizing reagent to the enamine double bond of the dihydroimidazo[2,1-*a*]isoquinolines **5** occurred from the convex side (see Figure 2). However, the configuration of the dioxirane ring could not be proved directly but after ring opening with amines to 6-amino-5-hydroxyimidazo[2,1-*a*]isoquinolines **10** (*dr* > 95:5, Scheme 5).

NOE analysis showed proximity of the H-atoms at positions 6 and 10a of **10** on the one hand, and at position 5 and the aminoalkyl substituent on the other hand. As expected, the attack of the amine at the oxirane ring of **8** occurred by inversion of configuration. Remarkably, the regioselectvity of the cleavage of the oxirane ring of **8** was inverted when methanol was used as nucleophile. Acidic conditions had to be applied in order to implement the reaction, which led to the formation of 6-hydroxy-5-(methoxy)tetrahydroimidazo[2,1-*a*]isoquinolines **12** (Scheme 5). Presumably, protonation of the ring O-atom by the acid caused formation of intermediate *N*-acyliminium ions **11**, which react with the nucleophile at position 5 rather than 6. The *trans*-coupling constants of the H-atoms at positions 5 and 6 of the 6-hydroxy-5-(methoxy)tetrahydroimidazo[2,1-*a*]isoquinoline **12** is in agreement with the assigned configuration. The ring-opened products **12** were formed in high yield but repeated column chromatography led only to 34 % yield of analytically pure material. Attempts to open the oxirane ring in **8b** by allylation with allyltrimethylsilane in the presence of trimethylsilyl triflate as used by Burgess et al.[23] resulted in the formation of a dimer **13** without the

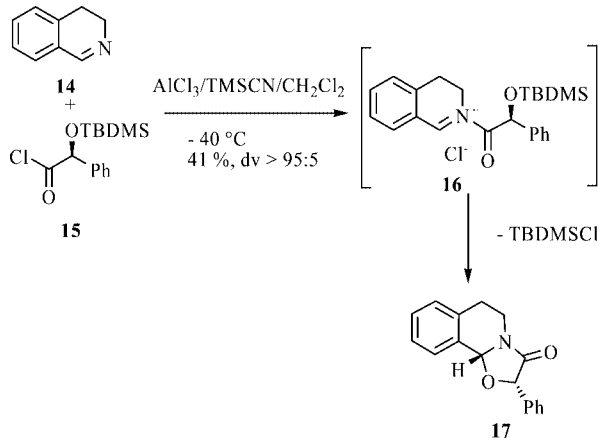



Scheme 5

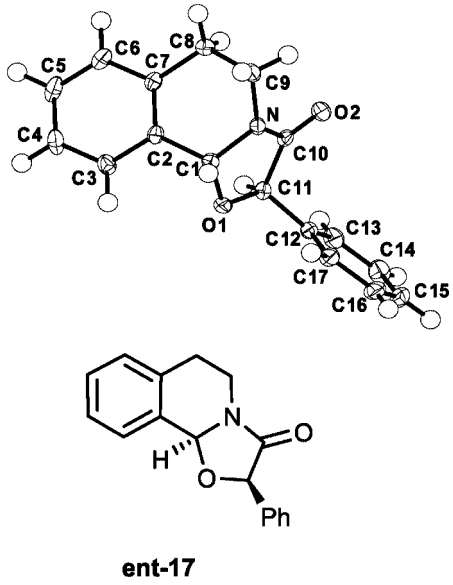
incorporation of the allyl substituent. Obviously, the trimethylsilyl triflate attacks the oxirane O-atom of **8** affording an intermediate *N*-acyliminium ion similar to structure **11**, which reacts with unchanged epoxide **8** under ring opening and subsequent formation of the six-membered dioxane ring. The heptacyclic dioxane system found in compound **13** has not been reported in the literature before.

In our research about scope and outcome of reactions of isoquinolines with chiral acyl halides and nucleophiles we also included reaction of 3,4-dihydroisoquinoline **14** with (*S*)-*O*-TBDMS mandelic acid chloride **15** and TMS cyanide (Scheme 6). As in the cases of sulfonylamino acid fluorides **2** the TMS-CN was not incorporated into the product, but cyclisation of the corresponding intermediate *N*-acylisoquinolinium salt **16** occurred. Obviously the TBDMS group was split off as TBDMS-Cl in the course of the intramolecular attack of the α-O-atom of the acyl substituent at position 1 of the isoquinolinium salt **16** leading to the oxazolo[2,3-*a*]isoquinoline **17**. Similar formation of oxazoline rings was observed before in reactions of dihydro-ß-carbolines with **15** [26] or α-hydroxylactones,[27] however in modest stereoselectivity. We also used (*R*)-*O*-TBDMS mandelic acid chloride **ent-15** in the reaction with TMSCN in the presence of $AlCl_3$ and obtained the other antipode **ent-17** from which a X-ray crystal analysis was obtained (Figure 4).




Scheme 6




**ent-17**

Figure 4. X-ray crystal analysis of **ent-17**

Remarkably, the stereochemical outcome in the formation **17** is opposite to the reaction of isoquinolines **1** with amino acid fluorides **2**. This phenomenon is probably caused by the different conformation of the six-membered N-containing ring in the *N*-acyliminium intermediates **3** as compared with **16**. We observed similar changes in stereoselectivity in intermolecular 1,2-additions to isoquinolines versus 3,4-dihydroisoquinolines. These results will be published in more detail in due course.

## Conclusions

Reaction of isoquinolines with *N*-arylsulfonylamino acid fluorides provides a straightforward and highly stereoselective access to dihydroimidazo[2,1-*a*]isoquinolines **5**. Addition reactions to the enamine moiety of these products **5** allow to synthesize a variety of new interesting tetrahydroisoquinoline derivatives, which all are formed in high regio- and stereoselectivity.

## Experimental Section

**General Remarks:** All reactions were carried out under argon in oven-dried glassware. Solvents were dried and deoxygenated by standard procedures. If not otherwise mentioned, starting materials were commercial. (Benzthiazolylsulfonyl)alanyl chloride was obtained from the known (benzthiazolylsulfonyl)alanine.[28]
TLC analysis was performed on Merck silica gel 60$F_{254}$ plates and visualized by exposure to UV light and charring with phosphomolybdic acid in EtOH (5 %, v/v) or 0.3 % ninhydrine in EtOH. Column chromatography was conducted with Merck silica gel 60 (400–639 mesh). $^1$H NMR and $^{13}$C NMR spectra were recorded at 300 and 75.5 MHz, respectively with a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. Mass spectra were measured at 70 eV. Optical rotations were determined with a Perkin–Elmer polarimeter 241 ($d$ = 2 mm). Enantiomeric purity was proved by analytical HPLC with a Chiracel-OD column (Daicel Chemical Industries LTD).

**2-{[(2,2,4,6,7-Pentamethyl-2,3-dihydro-5-benzofuryl)sulfonylamino]-1-ethylcarbonyl}-1,2-dihydroisoquinoline-1-carbonitrile (4):** A solution of isoquinoline (0.299 g, 232 mmol) in dry $CH_2Cl_2$ (50 mL) was added dropwise to a mixture of the racemic α-amino acid fluoride (0.885 g, 2.59 mmol), $CH_2Cl_2$ (20 mL) and anhydrous $AlCl_3$ at –40 °C over a period of 30 min. After stirring for 2 h the temperature was lowered from –40 °C to –78 °C and a solution of TMS-CN (0.206 g, 0.26 mL, 2.07 mmol) in dry $CH_2Cl_2$ (10 mL) was slowly added within 1 h. After stirring at –78 °C for 4 h the mixture was poured into ice/water (100 mL). It was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with satd. aq. $NH_4Cl$ and 5 % aq. $NaHCO_3$ and dried with $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography ($CH_2Cl_2$/$CH_3OH$, 100:1.5) affording 0.427 g (0.89 mmol, 43 %) of the product **4** as colorless oil. *dr* = 50:50. $R_f$ = 0.57 ($CH_2Cl_2$/$CH_3OH$, 100:2). $^1$H NMR ($CDCl_3$): $\delta$ = 1.32 (s, 6 H, 2 $CH_3$), 1.47 (d, $J$ = 6.2 Hz, 3 H, CH-C$H_3$), 2.19 (s, 3 H, $CH_3$), 2.52 (s, 3 H, $CH_3$), 2.55 (s, 3 H, $CH_3$), 2.97 (s, 2 H, $CH_2$), 3.38 (m, 1 H, C*H*-$CH_3$), 5.50 (1 H, NH), 6.15 (d, $J$ = 7.6 Hz, 1 H, C*H*CH-N), 6.75 (d, $J$ = 7.6 Hz, 1 H, C*H*CH-N), 6.87 (s, 1 H, CH-CN), 7.21–7.54 (m, 4 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 12.5 (CH-*C*$H_3$), 17.4 ($CH_3$), 19.3 ($CH_3$), 26.7 ($CH_3$), 28.4 ($CH_3$), 30.1 ($CH_3$), 43.1 ($CH_2$), 45.9 (*C*H-CN), 53.1 (*C*H-$CH_3$), 87.0 ($C_q$-O), 104.6 (*C*H-CH-N), 116.9 (CN), 118.2 ($C_{ar.}$), 120.9 ($C_{ar.}$), 121.6 ($CH_{ar.}$), 122.4 ($C_{ar.}$), 123.3 ($CH_{ar.}$), 123.7 ($CH_{ar.}$), 125.9 ($C_{ar.}$), 126.7 (CH-*C*H-N), 127.2 ($C_{ar.}$), 128.1 ($CH_{ar.}$) 134.3 ($C_{ar.}$), 139.7 ($C_{ar.}$), 163.1 ($C_{ar.}$-O), 169.9 (CO) ppm. HRMS (+EI): $C_{26}H_{29}N_3O_4S$: calcd. 479.1878; found 479.1878.

**General Procedure for the Synthesis of 1-Arylsulfonyl-Substituted (2*S*,10b*R*)-1,10b-Dihydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-ones 5:** Isoquinoline (1.76 mL, 2.000 g, 15.48 mmol) was added to a suspension of dry $AlCl_3$ (0.351 g, 2.60 mmol) in dry $CH_2Cl_2$ (60 mL) under argon in a Schlenk flask. After cooling to –78 °C, a solution of the amino acid fluoride **2** (13.00 mmol) in dry $CH_2Cl_2$ (5–10 mL) was added dropwise whilst stirring over a period of 45 min. The mixture was stirred at –78 °C for additional 45 min and at –10 °C for 2 h. After cooling to –78 °C TMS-Cl (1.64 mL, 1.410 g, 13.00 mmol) was added dropwise whilst stirring within a period of 1 h. The mixture was warmed up whilst stirring overnight. The mixture was quenched by pouring into ice water (230 mL). After extraction with $CH_2Cl_2$ (3 × 120 mL) the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography providing the pure product as colorless solid. NMR spectra of the crude products showed only one diastereomer, i.e. *dr* > 95:5.

**(2*S*,10b*R*)-2-Methyl-1-(*p*-tolylsulfonyl)-1,10b-dihydroimidazo[2,1-*a*]-isoquinolin-3(2*H*)-one (5a):** Yield: 47 %. M.p. 142–143 °C, $R_f$ (hexanes/AcOEt, 6:4) = 0.36. $[\alpha]_D^{20}$ = +159.5 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.40 (d, *J* = 7.2 Hz, 3 H, CH-C*H*$_3$), 2.39 (s, 3 H, $C_{ar.}$-C*H*$_3$), 4.09 (q, *J* = 7.0 Hz, 1 H, C*H*-CH$_3$), 5.91 [s, 1 H, N-C*H*-($C_{ar.}$)N], 6.19 (d, *J* = 7.5 Hz, 1 H, $C_{ar.}$-C*H*=CH), 6.60 (d, *J* = 7.3 Hz, 1 H, CH=C*H*-N), 7.09–7.79 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 20.5 (CH-*C*H$_3$), 21.7 ($C_{ar.}$-*C*H$_3$), 57.5 (*C*H-CH$_3$), 72.1 ($CH_{ar.}$), 116.5 (N-CH=*C*H), 120.9 (N-*C*H=CH), 124.8 ($CH_{ar.}$), 125.2($CH_{ar.}$), 128.1 (2 $CH_{ar.}$), 128.9 ($CH_{ar.}$), 129.0 ($CH_{ar.}$), 130.2 ($C_{ar.}$), 130.5 (2 $CH_{ar.}$), 130.9 ($C_{ar.}$), 132.3 ($C_{ar.}$), 145.3 ($C_{ar.}$), 168.8 (CO) ppm. $C_{19}H_{18}N_2O_3S$ (354.42): calcd. C 64.39, H 5.12, N 7.90, S 9.05; found C 64.44, H 5.01, N 7.88, S 9.02. The (2*R*,10b*S*)-enantiomer was obtained accordingly starting from (2*R*)-alanyl fluoride as colorless solid. M.p. 143–145 °C, $[\alpha]_D^{20}$ = –159.6 (*c* = 1; $CH_2Cl_2$).

**(2*S*,10b*R*)-2-Methyl-1-(2-naphthylsulfonyl)-1,10b-dihydroimidazo-[2,1-*a*]isoquinolin-3(2*H*)-one (5b):** Yield: 46 %. M.p. 101–103 °C, $R_f$ (hexane/ethyl acetate, 7:3) = 0.34. $[\alpha]_D^{20}$ = +134.9 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.47 (d, *J* = 7.0 Hz, 3 H, CH-C*H*$_3$), 4.21 (q, *J* = 7.0 Hz, 1 H, C*H*-CH$_3$), 6.02 [s, 1 H, N-C*H*-($C_{ar.}$)N], 6.17 (d, *J* = 7.4 Hz, 1 H, C*H*=CH-N), 6.55 (d, *J* = 7.4 Hz, 1 H, CH=C*H*-N), 7.07–7.96 (m, 10 H, $CH_{ar.}$), 8.39 (s, 1 H, $C_{ar.}$-C*H*=$C_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 20.6 (CH-*C*H$_3$), 57.6 (C*H*-CH$_3$), 72.1 [N-*C*H-($C_{ar.}$)N], 116.5 (CH=*C*H-N), 121.0 ($C_{ar.}$-*C*H=CH), 122.6 ($CH_{ar.}$), 124.8 ($CH_{ar.}$), 125.3 ($CH_{ar.}$), 127.9 ($CH_{ar.}$), 128.0 ($CH_{ar.}$), 128.9 ($CH_{ar.}$), 129.0 ($C_{ar.}$), 129.5 ($CH_{ar.}$), 129.6 ($CH_{ar.}$), 130.1 ($CH_{ar.}$), 130.2 ($CH_{ar.}$), 130.2 ($CH_{ar.}$), 130.8 ($C_{ar.}$), 132.2 (2 $C_{ar.}$), 135.4 ($C_{ar.}$), 168.6 (CO) ppm. $C_{22}H_{18}N_2O_3S$ (390.45): calcd. C 67.68, H 4.65, N 7.17, S 8.21; found C 66.90, H 4.67, N 7.00, S 8.28.

**(2*S*,10b*R*)-1-(4-Bromophenylsulfonyl)-2-methyl-1,10b-dihydroimidazo-[2,1-*a*]isoquinolin-3(2*H*)-one (5c):** Yield: 46 %. M.p. 144–146 °C, $R_f$ ($CH_2Cl_2$) = 0.42. $[\alpha]_D^{20}$ = +168.7 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.44 (d, *J* = 7.0 Hz, 3 H, CH-C*H*$_3$), 4.07 (q, *J* = 7.0 Hz, 1 H, C*H*-CH$_3$), 5.88 [s, 1 H, N-C*H*-($C_{ar.}$)N], 6.20 (d, *J* = 7.5 Hz, 1 H, $C_{ar.}$-C*H*=CH), 6.61 (d, *J* = 7.5 Hz, 1 H, CH=C*H*-N), 7.08–7.73 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 20.5 (CH-*C*H$_3$), 57.6 (*C*H-CH$_3$), 72.1 ($CH_{ar.}$), 116.6 (N-CH=*C*H), 120.9 (N-*C*H=CH), 124.6 ($CH_{ar.}$), 125.4 ($CH_{ar.}$), 129.0 (2 $CH_{ar.}$), 129.4 ($CH_{ar.}$), 129.6 ($CH_{ar.}$), 130.2 ($C_{ar.}$), 130.5 ($C_{ar.}$), 131.0 ($C_{ar.}$), 133.1 (2 $CH_{ar.}$), 134.3 ($C_{ar.}$), 168.4 (CO) ppm. $C_{18}H_{15}BrN_2O_3S$ (419.29): calcd. C 51.56, H 3.61, N 6.68, S 7.65, Br 19.06; found C 50.98, H 3.55, N 6.69, S 7.80, Br 19.90.

**X-ray Crystal Analysis of 5c:**[29] Empirical formula: $C_{18}H_{15}BrN_2O_3S$, formula mass: 419.29, temperature: 180(2) K, wavelength: 0.71073 Å, crystal system: orthorhombic, space group: *P* 21 21 21, unit cell dimensions: *a* = 10.0035(12), *b* = 13.167(2), *c* = 26.577(8) Å, Volume: 3500.6(13) Å$^3$, *Z* = 8, density (calcd.): 1.591 Mg/m$^3$, absorption coefficient: 2.488 mm$^{-1}$, $F_o$ = 1696, crystal size: 0.96 × 0.80 × 0.645 mm, Theta range for data collection: 1.53 to 25.25 °, limiting indices: $-12 \le h \le 12$, $-15 \le k \le 15$, $-0 \le l \le 31$; reflections collected/unique 8662/6254 [*R*(int) = 0.0598], completeness to theta = 25.25 (100 %), absorption correction: empirical ($\Psi$-scan), max. and min. transmission: 0.9960 and 0.9674, refinement method: Full-matrix least-squares on $F^2$, data/restraints/parameters: 6254/0/541, goodness-of-fit on $F^2$: 1.089, final $R_{int}$ [$I > 2\sigma(I)$]: *R*1 = 0.0488, *wR*2 = 0.1107, $R_{int}$ (all data): *R*1 = 0.0702, *wR*2 = 0.1278, absolute structure parameter: –0.007(11), largest diff. peak and hole: 0.545 and –0.475 e·Å$^3$

**(2*S*,10b*R*)-1-(1,3-Benzothiazol-2-ylsulfonyl)-2-methyl-1,10b-dihydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-one (5d):** Yield: 24 %. M.p. 157 °C, $R_f$ ($CH_2Cl_2$) = 0.46. $[\alpha]_D^{20}$ = + 73.6 (*c* = 1; $CH_2Cl_2$). *ee* ≥ 99 % (HPLC: Chiralcell ODH, hexane/isopropyl alcohol, 95:5, 0.5 mL/cm, $\lambda$ = 254 nm). $^1$H NMR ($CDCl_3$): $\delta$ = 1.52 (d, *J* = 7.0 Hz, 3 H, CH-C*H*$_3$), 4.65 (q, *J* = 7.0 Hz, 1 H, C*H*-CH$_3$), 6.22 (d, *J* = 7.4 Hz, 1 H $C_{ar.}$-C*H*=CH), 6.35 [s, 1 H, N-C*H*(-$C_{ar.}$)N], 6.71 (d, *J* = 7.4 Hz, 1 H, CH=C*H*-N), 7.09–8.13 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 20.5 (CH-*C*H$_3$), 58.3 (*C*H-CH$_3$), 72.6 (N-*C*H(-$C_{ar.}$)N), 116.4 (CH=*C*H-N), 121.0 ($C_{ar.}$-*C*H=CH), 122.1 ($CH_{ar.}$), 124.4 ($CH_{ar.}$), 15.4 ($CH_{ar.}$), 125.6 ($CH_{ar.}$), 127.9 ($CH_{ar.}$), 128.2 ($CH_{ar.}$), 129.0 (2 $CH_{ar.}$), 130.2 ($C_{ar.}$), 130.3 ($C_{ar.}$), 136.2 ($C_{ar.}$), 152.4 ($C_{ar.}$), 162.1 ($C_{ar.}$), 168.2 (C=O) ppm. $C_{19}H_{15}N_3O_3S_2$ (397.47): calcd. C 57.42, H 3.80, N 10.57, S 16.13; found C 57.29, H 3.98, N 10.22, S 16.12. Racemic **5d** was analogously obtained starting from racemic alanine.

**(2*S*,10b*R*)-2-Benzyl-1(*p*-tolylsulfonyl)-1,10b-dihydroimidazo[2,1-*a*]-isoquinolin-3(2*H*)-one (5e):** Yield: 45 %. M.p. 187–189 °C, $R_f$ ($CH_2Cl_2$/$CH_3OH$, 100:1) = 0.38. $[\alpha]_D^{20}$ = +224.7 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 2.38 (s, 3 H, $C_{ar.}$-C*H*$_3$), 3.08–3.23 (m, 2 H, CH-C*H*$_2$-Ph), 4.34 (m, 1 H, C*H*-CH$_2$), 5.81 [s, 1 H, N-C*H*(-$C_{ar.}$)N], 5.99 (d, *J* = 7.4 Hz, 1 H, $C_{ar.}$-C*H*=CH), 6.53 (d, *J* = 7.4 Hz, 1 H, CH=C*H*-N), 6.71–7.69 (m, 13 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 21.7 ($C_{ar.}$-*C*H$_3$), 38.7 (CH-*C*H$_2$-Ph), 62.8(*C*H-CH$_2$-Ph), 72.4 [N-*C*H(-$C_{ar.}$)N], 116.2 (CH=*C*H-N), 120.2 ($C_{ar.}$-*C*H=CH), 124.7 ($CH_{ar.}$), 125.3 ($CH_{ar.}$), 126.8 ($CH_{ar.}$), 128.0 (2 CH), 128.2 (2 CH), 128.3 ($CH_{ar.}$), 128.4 ($CH_{ar.}$), 129.4 ($C_{ar.}$), 129.8 ($C_{ar.}$), 129.9 (2 CH), 130.5 (2 CH), 132.1 ($C_{ar.}$), 134.4 ($C_{ar.}$), 145.3 ($C_{ar.}$), 167.4 (CO) ppm. $C_{25}H_{22}N_2O_3S$ (430.52): calcd. C 69.75, H 5.15, N 6.51, S 7.45; found C 69.82, H 5.18, N 6.47, S 7.58.

**(2*S*,10b*R*)-2-Isopropyl-1-(*p*-tolylsulfonyl)-1,10b-dihydroimidazo[2,1-*a*]-isoquinolin-3(2*H*)-one (5f):** Yield: 44 %. M.p. 147 °C, $R_f$ (hexane/ethyl acetate, 7:3) = 0.28. $[\alpha]_D^{20}$ = +164.1 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 0.82–0.87 [m, 6 H, CH(C*H*$_3$)$_2$], 2.11–2.17 [m, 1 H, CH-C*H*(CH$_3$)$_2$], 2.38 (s, 1 H, $C_{ar.}$-C*H*$_3$), 3.98 [d, *J* = 4.0 Hz, 1 H, C*H*-CH(CH$_3$)$_2$], 5.94 [s, 1 H, N-C*H*(-$C_{ar.}$)N], 6.11 (d, *J* = 7.4 Hz, 1 H, $C_{ar.}$C*H*=CH), 6.60 (d, *J* = 7.4 Hz, 1 H, CH=C*H*-N), 7.05–7.78 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 18.0, 18.3 [CH(*C*H$_3$)$_2$], 21.7 ($C_{ar.}$-*C*H$_3$), 32.8 [CH-C*H*(CH$_3$)$_2$], 66.7 [C*H*-CH(CH$_3$)$_2$], 72.6 [N-*C*H(-$C_{ar.}$)N], 115.7 ($C_{ar.}$*C*H=CH), 120.7 (CH=*C*H-N), 124.9 ($CH_{ar.}$), 125.4 ($CH_{ar.}$), 128.2 (2 $CH_{ar.}$), 128.7 ($CH_{ar.}$), 128.8 ($CH_{ar.}$), 130.2 ($C_{ar.}$), 130.4 (2 $CH_{ar.}$), 130.5 ($C_{ar.}$), 132.2 ($C_{ar.}$), 145.3 ($C_{ar.}$), 167.4 (CO) ppm. $C_{21}H_{22}N_2O_3S$ (382.48): calcd. C 65.95, H 5.80, N 7.32, S 8.38; found C 65.99, H 5.71, N 7.25, S 8.60.

**(2*S*,10b*R*)-2-Isopropyl-1-(2-naphthylsulfonyl)-1,10b-dihydroimidazo-[2,1-*a*]isoquinolin-3(2*H*)-one (5g):** Yield: 46 %. M.p. 82 °C, $R_f$ ($CH_2Cl_2$/$CH_3OH$, 100:1) = 0.41. $[\alpha]_D^{20}$ = +141.2 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 0.86 [d, *J* = 7.0 Hz, 3 H , CH-(C*H*$_3$)$_2$], 0.90 [d, *J* = 7.0 Hz, 3 H, CH-(C*H*$_3$)$_2$], 2.16–2.22 [m, 1 H, CH-C*H*(CH$_3$)$_2$], 4.13 [d, *J* = 4.1 Hz, 1 H, C*H*-CH(CH$_3$)$_2$], 6.06 [s, 1 H, N-C*H*-(-$C_{ar.}$)N], 6.10 [d, *J* = 7.4 Hz, 1 H, $C_{ar.}$-C*H*=CH], 6.55 (d, *J* = 7.4 Hz, 1 H, CH=C*H*-N), 7.06–7.97 (m, 10 H, $CH_{ar.}$), 8.38 (s, 1 H, $C_{ar.}$ = C*H*-$C_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 18.0 [CH-(*C*H$_3$)$_2$], 18.4 [CH-(*C*H$_3$)$_2$], 32.9 [CH-*C*H-(CH$_3$)$_2$], 66.7 [*C*H-CH-(CH$_3$)$_2$], 72.7 [N-*C*H(-$C_{ar.}$)N], 115.6 (CH=*C*H-N), 120.8 ($C_{ar.}$-C*H*=CH), 122.6 ($CH_{ar.}$), 125.0 ($CH_{ar.}$), 125.5 ($CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.9 ($CH_{ar.}$), 129.5 ($CH_{ar.}$), 129.6 ($CH_{ar.}$), 130.2 ($C_{ar.}$), 130.2 ($CH_{ar.}$), 130.3 ($CH_{ar.}$), 130.5 ($C_{ar.}$), 132.2 (2 $C_{ar.}$), 135.4 ($C_{ar.}$), 167.3 (CO) ppm. $C_{24}H_{22}N_2O_3S$ (418.51) calcd. C 68.88, H 5.30, N 6.69, S 7.66; found C 68.51, H 5.35, N 6.57, S 7.68.

**(2*S*,10b*R*)-2-Isobutyl-1-(*p*-tolylsulfonylamino)-1,10b-dihydroimidazo-[2,1-*a*]isoquinolin-3(2*H*)-one (5h):** Yield: 40 %. M.p. 152 °C, $R_f$ ($CH_2Cl_2$/$CH_3OH$, 100:1) = 0.38. $[\alpha]_D^{20}$ = +203.5 (*c* = 1, $CH_2Cl_2$),

$^1$H NMR ($CDCl_3$): $\delta$ = 0.74 [d, $J$ = 6.6 Hz, 3 H, CH($CH_3$)$_2$], 0.89 [d, $J$ = 6.6 Hz, 3 H, CH($CH_3$)$_2$], 1.42–1.65 [m, 2 H, CH-C$H_2$-CH($CH_3$)$_2$], 1.98–2.05 [m, 1 H, $CH_2$-C$H$($CH_3$)$_2$], 2.38 (s, 3 H, $C_{ar.}$-$CH_3$), 4.09 (t, $J$ = 6.2 Hz, 1 H, C$H$-$CH_2$), 5.95 [s, 1 H, N-C$H$(-$C_{ar.}$)N], 6.14 (d, $J$ = 7.4 Hz, 1 H, $C_{ar.}$-C$H$=CH), 6.57 (d, $J$ = 7.4 Hz, 1 H, CH=C$H$-N), 7.06–7.73 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 21.7 ($C_{ar.}$-$CH_3$), 22.4 [2 $CH_3$, CH($CH_3$)$_2$], 23.9 [CH-$CH_2$-$CH$($CH_3$)$_2$], 43.4 [CH-$CH_2$-CH($CH_3$)$_2$], 60.1 [$CH$-$CH_2$-CH($CH_3$)$_2$], 72.4 [N-$CH$(-$C_{ar.}$)N], 116.1 (CH=$CH$-N), 121.2 ($C_{ar.}$-$CH$=CH), 124.0 ($CH_{ar.}$), 125.4 ($CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.8 ($CH_{ar.}$), 128.9 ($CH_{ar.}$), 130.2 ($C_{ar.}$), 130.5 (2 $CH_{ar.}$), 130.7 ($C_{ar.}$), 132.5 ($C_{ar.}$), 145.2 ($C_{ar.}$), 169.1 (CO) ppm. HRMS (+EI): $C_{22}H_{24}N_2O_3S$: calcd. 396.1508; found 396.1494.

**(2*S*,10b*R*)-2-Benzyl-5-methyl-1-(*p*-tolylsulfonyl)-1,10b-dihydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-one (5i):** Yield: 12 %. M.p. 194 °C, $R_f$ ($CH_2Cl_2$) = 0.40. $[\alpha]_D^{20}$ = +263.1 ($c$ = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 2.15 [s, 3 H, CH=C(-N)C$H_3$], 2.39 (s, 3 H, $C_{ar.}$-C$H_3$), 3.07–3.11 (m, 2 H, CH-C$H_2$-Ph), 4.29–4.35 (m, 1 H, C$H$-$CH_2$-Ph), 5.84 [s, 1 H, $C_{ar.}$-C$H$=C(-N)$CH_3$], 5.85 [s, 1 H, N-CH(-$C_{ar.}$)N], 6.79–7.67 (m, 13 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 18.6 [CH=C(-N)$CH_3$], 21.7 ($C_{ar.}$-$CH_3$), 38.6 (CH-$CH_2$-Ph), 62.9 ($CH$-$CH_2$-Ph), 73.5 [N-$CH$(-$C_{ar.}$)N], 115.3 [$CH$=C(-N)$CH_3$], 123.9 ($CH_{ar.}$), 124.5 ($CH_{ar.}$), 126.9 ($CH_{ar.}$), 127.7 ($CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.1 (2 $CH_{ar.}$), 129.9 (2 $CH_{ar.}$), 130.3 ($CH_{ar.}$), 130.4 (2 $CH_{ar.}$), 130.4 ($C_{ar.}$), 132.6 ($C_{ar.}$), 133.5 ($C_{ar.}$), 135.1 ($C_{ar.}$), 145.1 ($C_{ar.}$), 168.7 (CO) ppm. $C_{26}H_{24}N_2O_3S$ (444.55): calcd. C 70.25, H 5.44, N 6.30, S 7.21; found C 70.11, H 5.95, N 6.05, S 6.90.

**1,5,6,10b-Tetrahydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-ones 6. General Procedure:** 10 % Pd-hydroxide/C (50 mg) were added to a solution of dihydroimidazo[2,1-*a*]isoquinolin-3-one **5**. The mixture was hydrogenated under atmospheric pressure whilst stirring for 3 h. The resulting mixture was filtered through Celite and the filtrate was evaporated under vacuum.

**(2*S*,10b*R*)-2-Methyl-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydroimidazo-[2,1-*a*]isoquinolin-3(2*H*)-one (6a):** Yield: 88 %. M.p. 171 °C, $R_f$ (hexane/EtOAc, 1:1) = 0.16. $[\alpha]_D^{20}$ = +25.9 ($c$ = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.19 (d, $J$ = 7.1 Hz, 3 H, CH-C$H_3$), 2.38 (s, 3 H, $C_{ar.}$-C$H_3$), 2.67–2.72 (m, 1 H, $C_{ar.}$-C$H_2$-$CH_2$), 2.90–2.96 (m, 1 H, $C_{ar.}$-C$H_2$-$CH_2$, $CH_2$-C$H_2$-N), 3.12–3.21 (m, 1 H, $CH_2$-C$H_2$-N), 3.80–3.86 (m, 1 H, $CH_2$-C$H_2$-N), 4.05 (q, $J$ = 7.0 Hz, 1 H, C$H$-$CH_3$), 5.93 [s, 1 H, N-C$H$-($C_{ar.}$)N], 7.03–7.86 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 19.6 (CH-$CH_3$), 21.6 ($C_{ar.}$-$CH_3$), 26.6 ($C_{ar.}$-$CH_2$-$CH_2$), 38.5 ($CH_2$-$CH_2$-N), 57.5 ($CH$-$CH_3$), 71.5 [N-$CH$(-$C_{ar.}$)N], 126.2 ($CH_{ar.}$), 127.2 ($CH_{ar.}$), 127.7 (2 $CH_{ar.}$), 128.3 ($CH_{ar.}$), 128.6 ($CH_{ar.}$), 130.3 (2 $CH_{ar.}$), 133.4 ($C_{ar.}$), 133.5 ($C_{ar.}$), 135.7 ($C_{ar.}$), 144.9 ($C_{ar.}$), 171.3 (CO) ppm. HRMS (+EI): $C_{19}H_{20}N_2O_3S$: calcd. 356.1195; found 356.1184.

**(2*S*,10b*R*)-2-Benzyl-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydroimidazo-[2,1-*a*]isoquinolin-3(2*H*)-one (6b):** Yield: 99 % M.p. 206–207 °C, $R_f$ ($CH_2Cl_2$/$CH_3OH$, 100:1) = 0.40. $[\alpha]_D^{20}$ = +13.4 ($c$ = 1, $CH_2Cl_2$). *ee* ≥ 99 %, HPLC: Chiralcell OD, hexane/isopropyl alcohol, 95:5, 0.5 mL/min, $\lambda$ = 254 nm). $^1$H NMR ($CDCl_3$): $\delta$ = 2.28–2.30 (m, 2 H, $C_{ar.}$-C$H_2$-$CH_2$-N), 2.39 (s, 3 H, $C_{ar.}$-C$H_3$), 2.84–3.07 (m, 3 H, $C_{ar.}$-C$H_2$-$CH_2$-N, CH-C$H_2$-Ph), 3.88–3.94 (m, 1 H, $C_{ar.}$-$CH_2$-C$H_2$-N), 4.30 (t, $J$ = 4.1 Hz, 1 H, C$H$-$CH_2$-Ph), 5.86 [s, 1 H, N-C$H$(-$C_{ar.}$)N], 6.65–7.72 (m, 13 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 21.6 ($C_{ar.}$-$CH_3$), 27.1 ($C_{ar.}$-$CH_2$-$CH_2$-N), 38.0 (CH-$CH_2$-Ph), 38.5 ($C_{ar.}$-$CH_2$-$CH_2$-N), 63.5 ($CH$-$CH_2$-Ph), 72.1 [N-$CH$(-$C_{ar.}$)N], 126.6 ($CH_{ar.}$), 126.8 ($CH_{ar.}$), 127.3 ($CH_{ar.}$), 127.4 (2 $CH_{ar.}$), 127.8 ($CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.6 ($CH_{ar.}$), 130.3 (4 $CH_{ar.}$), 132.8 ($C_{ar.}$), 133.2 ($C_{ar.}$), 134.1 ($C_{ar.}$), 134.2 ($C_{ar.}$), 145.1 ($C_{ar.}$), 168.8 (CO) ppm. HRMS (EI): $C_{25}H_{24}N_2O_3S$: calcd. 432.1508; found 432.1502.

**(2*S*,5*S*,10b*R*)-2-Benzyl-5-methyl-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-one (6c):** Yield: 99 %. M.p. 133 °C, $R_f$ = 0.42 ($CH_2Cl_2$). **Major Isomer:** $^1$H NMR ($CDCl_3$): $\delta$ = 0.95 (d, $J$ = 6.5 Hz, 3 H, CH-C$H_3$), 2.40 (s, 3 H, $C_{ar.}$-C$H_3$), 2.41–2.48 [dd, $^1J$ = 4.7, $^2J$ = 15.4 Hz, 1 H, *trans*-C$H$(H)-CH(-$CH_3$)N], 2.66–2.71 [dd, = 5.0, $^2J$ = 15.2 Hz, 1 H, *cis*-C$H$(H)-CH(-$CH_3$)N], 3.11 (d, $J$ = 4.2 Hz, 2 H, CH-C$H_2$-Ph), 3.71–3.77 [m, 1 H, $CH_2$-C$H$(-$CH_3$)N], 4.21 (t, $J$ = 4.2 Hz, 1 H, C$H$-$CH_2$-Ph), 5.61 [s, 1 H, N-C$H$(-$C_{ar.}$)N], 6.73–7.71 (m, 13 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 17.4 (CH-$CH_3$), 21.6 ($C_{ar.}$-$CH_3$), 35.2 [$C_{ar.}$-$CH_2$-CH(-$CH_3$)N], 37.9 (CH-$CH_2$-Ph), 48.3 [$C_{ar.}$-$CH_2$-$CH$(-$CH_3$)N], 63.6 (NH-C$H$-$CH_2$-Ph), 72.3 [N-$CH$(-$C_{ar.}$)N], 125.4 ($CH_{ar.}$), 126.6 (2 $CH_{ar.}$), 127.5 (2 $CH_{ar.}$), 127.7 ($CH_{ar.}$), 127.8 ($CH_{ar.}$), 128.3 (2 $CH_{ar.}$), 130.3 (2 $CH_{ar.}$), 130.7 (2 $CH_{ar.}$), 132.2 ($C_{ar.}$), 133.3 ($C_{ar.}$), 134.7 ($C_{ar.}$), 135.0 ($C_{ar.}$), 145.1 ($C_{ar.}$), 167.8 (CO) ppm. NOE: Irradiation at 3.71–3.77 [m, 1 H, $CH_2$-C$H$(-$CH_3$)N] resulted in a NOE-signal at 0.95 [d, 3 H, $CH_2$-C$H$(-$CH_3$)N], 2.66–2.71 [dd, $^1J$ = 5.0, $^2J$ = 15.2 Hz, 1 H, $C_{ar.}$-C$H$(H)-CH(-$CH_3$)N], 5.61 [s, 1 H, N-C$H$(-$C_{ar.}$)N], irradiation at 5.61 [s, 1 H, N-C$H$(-$C_{ar.}$)N] gave a NOE signal at 2.66–2.71 [dd, $^1J$ = 5.0, $^2J$ = 15.2 Hz, 1 H, *cis*-C$H$(H)-CH(-$CH_3$)N], 3.71–3.77 [m, 1 H, $CH_2$-C$H$(-$CH_3$)N], 7.38–7.71 (m, 3 H, $CH_{ar.}$) ppm. **Minor Isomer (2*S*,5*R*,10b*R*-Epimer):** $^1$H NMR ($CDCl_3$): $\delta$ = 0.96 [d, $J$ = 6.5 Hz, 3 H, CH-C$H_3$], 2.11–2.18 [dd, $^1J$ = 4.7, $^2J$ = 15.4 Hz, 1 H, *trans*-C$H$(H)-CH(-$CH_3$)N], 2.39 (s, 3 H, $C_{ar.}$-C$H_3$), 2.47–2.53 [dd, $^1J$ = 5.0, $^2J$ = 15.2 Hz, 1 H, *cis*-C$H$(H)-CH(-$CH_3$)N], 2.96 (d, $J$ = 4.2 Hz, 2 H, CH-C$H_2$-Ph), 4.02–4.07 [m, 1 H, $CH_2$-C$H$(-$CH_3$)N], 4.28 (t, $J$ = 4.2 Hz, 1 H, C$H$-$CH_2$-Ph), 5.79 [s, 1 H, N-C$H$(-$C_{ar.}$)N], 6.73–7.71 (m, 13 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 17.5 (CH-$CH_3$), 21.6 ($C_{ar.}$-$CH_3$), 33.4 [$C_{ar.}$-$CH_2$-CH(-$CH_3$)N], 38.1 (CH-$CH_2$-Ph), 44.3 [$C_{ar.}$-$CH_2$-$CH$(-$CH_3$)N], 63.9 (NH-$CH$-$CH_2$-Ph), 69.7 [N-$CH$(-$C_{ar.}$)N], 125.4 ($CH_{ar.}$), 126.7 (2 $CH_{ar.}$), 127.7 ($CH_{ar.}$), 127.8 ($CH_{ar.}$), 127.9 (2 $CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 130.2 (2 $CH_{ar.}$), 130.7 (2 $CH_{ar.}$), 132.1 ($C_{ar.}$), 133.5 ($C_{ar.}$), 135.1 ($C_{ar.}$), 135.6 ($C_{ar.}$), 145.1 ($C_{ar.}$), 168.7 (CO) ppm. $C_{26}H_{26}N_3O_2S$ (446.56): calcd. C 69.93, H 5.87, N 6.27, S 7.18; found C 69.90, H 5.91, N 6.08, S 6.86.

**(2*S*,10b*S*)-2-Benzyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]-isoquinolin-3(2*H*)-one (7a):** In a Schlenk flask a solution of Na-naphthalide (10.00 mmol) was prepared by addition of sublimed naphthalene (1.280 g, 10.00 mmol) to a mixture of Na (0.230 g, 10.00 mmol) in dry THF (25 mL). The mixture was kept in an ultrasound bath for 2 min and was then stirred for 2–3 h resulting in a homogeneous dark green solution of Na-naphthalide. This can be used as a stock solution in several reduction experiments but it must be used within 1 day. Portions of the stock solutions were added dropwise to a solution of the *N*-tosylated precursor **6b** (0.105 g, 0.24 mmol) in dry THF (20 mL) until decolorization ceased. After stirring at –100 °C for 30 min. satd. aq. $NH_4Cl$ (20 mL) was added in portions at –100 °C. The mixture was warmed to room temp. and was extracted with AcOEt (5 × 15 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. **7a** (0.020 g, 30 %) was obtained as colorless oil after column chromatography with AcOEt. $R_f$ (EtOAc) = 0.31. $[\alpha]_D^{20}$ = +4.2 ($c$ = 1, $CH_2Cl_2$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 28.3 ($C_{ar.}$-$CH_2$-$CH_2$-N), 37.0 (CH-$CH_2$-Ph), 37.2 ($C_{ar.}$-$CH_2$-$CH_2$-N), 61.9 ($CH$-$CH_2$-Ph), 70.0 [NH-$CH$(-$C_{ar.}$)N], 125.1 ($CH_{ar.}$), 126.7 ($CH_{ar.}$), 127.0 ($CH_{ar.}$), 128.0 ($CH_{ar.}$), 128.5 (2 $CH_{ar.}$), 129.0 ($CH_{ar.}$), 129.3 (2 $CH_{ar.}$), 133.7 ($C_{ar.}$), 135.3 ($C_{ar.}$), 137.4 ($C_{ar.}$), 172.9 (CO) ppm. HRMS (+EI): $C_{18}H_{18}N_2O$: calcd. 278.1419; found 278.1412.

**(2*S*,10b*S*)-2-Benzyl-1-methyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]-isoquinolin-3(2*H*)-one (7b):** According to the procedure used for the

synthesis of **7a** (vide supra) **6b** (0.240 g, 0.56 mmol) was detosylated. Before quenching the mixture with satd. aq. $NH_4Cl$, methyl iodide (0.08 mL, 0.018 g, 123 mmol) was added and stirring at –100 °C was continued for another 30 min. After extraction the combined organic layers were washed with aq. 2 M $NaS_2O_3$ solution (50 mL) and dried with $MgSO_4$. Yield: 0.104 g (60 %) of light yellow oil after column chromatography ($CH_2Cl_2$/MeOH, 100:1). $R_f$ ($CH_2Cl_2$/$CH_3OH$, 100:1) = 0.27. $[\alpha]_D^{20}$ = +16.2 (*c* = 1, $CH_2Cl_2$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 28.0 ($C_{ar.}$-*C*$H_2$-$CH_2$-N), 38.1 (CH-*C*$H_2$-Ph), 38.6 ($C_{ar.}$-$CH_2$-*C*$H_2$-N), 42.9 (N-*C*$H_3$), 69.9 (*C*H-$CH_2$-Ph), 77.2 [N-*C*H(-$C_{ar.}$)N], 124.6 ($CH_{ar.}$), 126.1 ($CH_{ar.}$), 126.7 ($CH_{ar.}$), 127.6 ($CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.3 ($CH_{ar.}$), 129.8 (2 $CH_{ar.}$), 134.5 ($C_{ar.}$), 137.3 ($C_{ar.}$), 138.3 ($C_{ar.}$), 171.4 (CO) ppm. HRMS (EI): $C_{19}H_{20}N_2O$: calcd. 292.1576; found 292.1546.

***tert*-Butyl (2*S*,10b*R*)-2-Benzyl-3-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-carboxylate (7c):** According to the procedure used for the synthesis of **7a** (vide supra) **6b** (0.400 g, 0.92 mmol) was detosylated. After the addition of Na-naphthalide was completed and the resulting solution was stirred at –100 °C for 1 h, di-*tert*-butyl dicarbonate (0.59 mL, 0.605 g, 2.77 mmol) was added. The mixture was slowly warmed to room temperature. Aq. satd. $NH_4Cl$ solution (50 mL) was added and the mixture was extracted with AcOEt (4 × 20 mL). After drying of the combined organic layers with $MgSO_4$, evaporation of solvent and column chromatography (hexane/AcOEt, 7:3 → AcOEt) 0.288 g (83 %) of the product **7c** was obtained as colorless solidifying oil, which could be recrystallized from EtOH. M.p. 215 °C, $R_f$ (hexane/EtOAc, 7:3) = 0.45. $[\alpha]_D^{20}$ = +6.7 (*c* = 1, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$): $\delta$ = 1.42 [s, 9 H, C(C$H_3$)$_3$], 2.39–2.51 (m, 2 H, $C_{ar.}$-C$H_2$-$CH_2$-N), 2.83 [br. m, 1 H, $C_{ar.}$-C*H*(H)-$CH_2$-N], 2.96–3.12 (m, 2 H, CH-C*H* $_2$-Ph), 4.08 [br. m, 1 H, $C_{ar.}$-CH(*H*)-$CH_2$-N], 4.51 (br. m, C*H*-$CH_2$-Ph), 6.12 [br. s, 1 H, N-CH(-$C_{ar.}$)N], 6.75–7.38 (m, 9 H, $CH_{ar.}$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 27.4 ($C_{ar.}$-*C*$H_2$-$CH_2$-N), 28.3 [C(*C*$H_3$)$_3$], 37.5 (CH-*C*$H_2$-Ph), 37.8 ($C_{ar.}CH_2$-$CH_2$-N), 62.2 (*C*H-$CH_2$-Ph), 70.2 [N-*C*H(-$C_{ar.}$)N], 81.5 [O-*C*(C$H_3$)$_3$], 126.4 ($CH_{ar.}$), 126.6 ($CH_{ar.}$), 127.5 ($CH_{ar.}$), 128.5 ($CH_{ar.}$), 130.0 (4 $CH_{ar.}$), 133.2 ($C_{ar.}$), 135.4 ($C_{ar.}$), 136.0 ($C_{ar.}$), 155.6 (N-*C*O*O*t*Bu*), 169.6 (CO) ppm. $C_{23}H_{26}N_2O_3$ (378.46): calcd. C 72.99, H 6.92, N 7.40; found C 72.51, H 6.89, N 7.24.

**X-ray Crystal Analysis of 7c:** [29] Empirical formula: $C_{23}H_{26}N_2O_3$, formula mass: 378.46, temperature: 180(2) K, wavelength: 0.71073 Å, crystal system: orthorhombic, space group: *Pbca*, unit cell dimensions: *a* = 11.971(2), *b* = 10.3825(14), *c* = 32.237(5) Å, volume 4006.9(12) Å$^3$, *Z* = 8, density (calcd.): 1.255 Mg/m$^3$, absorption coefficient: 0.083 mm$^{-1}$, $F_o$ = 1616, crystal size: 0.40 × 0.24 × 0.05 mm, Theta range for data collection: 2.67 to 25.25 °, limiting indices: $-14 \le h \le 14$, $-11 \le k \le 11$, $-38 \le l \le 38$; reflections collected/unique 23584/3531 [*R*(int) = 0.0573], completeness to theta = 25.25 (97.2 %), absorption correction: empirical ($\Psi$-scan), max. and min. transmission: 0.9960 and 0.9674, refinement method: full-matrix least-squares on $F^2$, data/restraints/parameters: 3531/0/332, goodness-of-fit on $F^2$: 0.975, final $R_{int}$ [$I > 2\sigma(I)$]: *R*1 = 0.0388, *wR*2 = 0.0885, $R_{int}$ (all data): *R*1 = 0.0526, *wR*2 = 0.0945, extinction coefficient: 0.0063(9), largest diff. peak and hole: 0.300 and –0.223 e·Å$^3$.

**Tetrahydroimidazo[2,1-*a*]oxirano[2,3-*c*]isoquinolin-3(1a*H*)-ones 8:** A freshly prepared 0.1 M solution of dimethyldioxirane in acetone (125 mL) was added to a solution of the dihydroimidazo[2,1-*a*]isoquinoline **5** (0.28 mmol) in acetone (30 mL) at 0 °C whilst stirring. The solution was allowed to warm up to r. t. slowly and was stirred overnight. The solution was dried with $MgSO_4$ and the solvent was distilled off. No sign of formation of diastereomers was observed in the NMR spectra of the crude products.

**(4*S*,5a*R*)-4-Methyl-5-(*p*-tolylsulfonyl)-4,5,5a,9b-tetrahydroimidazo-[2,1-*a*]oxirano[2,3-*c*]isoquinolin-3(1a*H*)-one (8a):** Yield: 99 %. Colorless solid. M.p. 140–143 °C, $R_f$ (hexane/EtOAc, 6:4) = 0.64. $[\alpha]_D^{20}$ = +72.4 (*c* = 1, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$): $\delta$ = 1.33 (d, *J* = 7.2 Hz, 3 H, CH-C$H_3$), 2.48 (s, 3 H, $C_{ar.}$-$CH_3$), 4.01 [d, *J* = 2.3 Hz, 1 H, $C_{ar.}$-C*H*(O)CH-N], 4.21 (q, *J* = 7.2 Hz, 1 H, C*H*-$CH_3$), 5.39 [d, *J* = 2.3 Hz, 1 H, $C_{ar.}$-CH(O)C*H*-N], 6.05 [s, 1 H, N-CH(-$C_{ar.}$)N], 7.26–7.91 (m, 8 H, $CH_{ar.}$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 20.0 (CH-*C*$H_3$), 21.7 ($C_{ar.}$-*C*$H_3$), 52.4 [*C*H(O)CH-N], 58.9 (*C*H-$CH_3$), 60.4 [CH(O)*C*H-N], 69.8 [N-*C*H(-$C_{ar.}$)N], 125.8 ($CH_{ar.}$), 127.8 ($CH_{ar.}$), 128.9 (2 $CH_{ar.}$), 129.3 ($CH_{ar.}$), 129.8 ($CH_{ar.}$), 130.4 ($C_{ar.}$), 130.5 (2 $C_{ar.}$), 132.7 ($C_{ar.}$), 133.4 ($C_{ar.}$), 145.3 ($C_{ar.}$),171.6 (CO) ppm. $C_{19}H_{18}N_2O_4S$ (370.42): calcd. C 61.61, H 4.90, N 7.56, S 8.65; found C 60.04, H 5.21, N 7.24, S 8.15.

**(4*S*,5a*R*)-4-Benzyl-5-(*p*-tolylsulfonyl)-4,5,5a,9b-tetrahydroimidazo-[2,1-*a*]oxirano[2,3-*c*]isoquinolin-3(1a*H*)-one (8b):** Yield: 98 %. Colorless solid. M.p. 149–151 °C, $R_f$ (hexane/EtOAc, 6:4) = 0.60. $[\alpha]_D^{20}$ = +88.1 (*c* = 1, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$): $\delta$ = 2.39 (s, 3 H, $C_{ar.}$-C$H_3$), 3.03–3.11 (m, 2 H, CH-$CH_2$-Ph), 3.78 [d, *J* = 3.0 Hz, 1 H, $C_{ar.}$-C*H*(O)CH-N], 4.36–4.39 (m, 1 H, C*H*-$CH_2$-Ph), 5.30 [d, *J* = 3.0 Hz, 1 H, CH(O)C*H*-N], 5.83 [s, 1 H, N-C*H*(-$C_{ar.}$)N], 6.73–7.71 (m, 13 H, $CH_{ar.}$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.7 ($C_{ar.}$-*C*$H_3$), 38.4 (CH-*C*$H_2$-Ph), 52.1 (*C*H(O)CH-N), 60.1 (*C*H-$CH_2$-Ph), 64.6 (CH(O)*C*H-N), 69.9 [N-*C*H(-$C_{ar.}$)N], 126.4 ($CH_{ar.}$), 126.9 ($CH_{ar.}$), 127.7 ($CH_{ar.}$), 127.8 (2 $CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.1 ($CH_{ar.}$), 128.9 ($C_{ar.}$), 129.3 ($CH_{ar.}$), 130.0 (2 $CH_{ar.}$), 130.5 (2 $CH_{ar.}$), 132.2 ($C_{ar.}$), 132.4 ($C_{ar.}$), 134.6 ($C_{ar.}$), 145.4 ($C_{ar.}$), 169.6 (CO) ppm. HRMS (EI): $C_{25}H_{22}N_2O_4S$: calcd. 446.1300; found 446.1297.

**[2+2] Cycloadduct 9 of Dihydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-one 5e:** A solution of the dihydroimidazoisoquinolinone **5e** (0.092 g, 0.25 mmol), 1,5-dimethoxynaphthalene (0.024 g, 0.13 mmol), and ascorbic acid (0.229 mg, 1.30 mmol) in 96 % EtOH (120 mL) was irradiated by a 150-W Hg lamp at room temp for 4 h. The resulting solution was concentrated under vacuum and the residue was dissolved in $CH_2Cl_2$ (20 mL). The solution was washed with water, dried with $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography (hexane/EtOAc, 7:3) affording 0.061 g (66 %) of unreacted starting material and 0.027 g (29 %) of the product **9** as colorless solid. M.p. > 240 °C under decomposition. $R_f$ = 0.18. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.18 (d, *J* = 7 Hz, 6 H, 1 Hz, 2 CH-C$H_3$), 2.33 (s, 6 H, 2 $C_{ar.}$-C$H_3$), 3.52 (d, *J* = 8.1 Hz, 2 H, 2 C*H* [cyclobutane]), 4.04–4.11 (m, 2 H, 2 C*H*-$CH_3$), 4.48 (d, *J* = 8.1 Hz, 2 H, 2 C*H* [cyclobutane]), 6.93 [s, 2 H, 2 N-C*H*(-$C_{ar.}$)N], 7.19–7.87 (m, 16 H, $CH_{ar.}$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 19.4 (2 CH-*C*$H_3$), 21.6 (2 $C_{ar.}$-*C*$H_3$), 44.0 (2 *C*H[cyclobutane]), 49.3 (2 *C*H[cyclobutane]), 57.4 (2 C*H*-$CH_3$), 69.6 [2 N-*C*H(-$C_{ar.}$)N], 126.7 (2 $CH_{ar.}$), 127.3 (4 $CH_{ar.}$), 128.1 (4 $CH_{ar.}$), 129.6 (2 $CH_{ar.}$), 130.6 (4 $CH_{ar.}$), 132.9 (2 $C_{ar.}$), 134.3 (2 $C_{ar.}$), 134.6 (2 $C_{ar.}$), 145.4 (2 $C_{ar.}$), 169.7 (2 C=O) ppm. HRMS (+EI): $C_{38}H_{36}N_4O_6S_2$: calcd. 708.2076; found 708.2081.

**(1*R*,2*S*,5*R*,6*S*)-5-Hydroxy-2-methyl-6-propylamino-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydro-2*H*-imidazo[2,1-*a*]isoquinolin-3-one (10a):** A solution of the oxirane **8a** 0.300 g (0.80 mmol) and the corresponding amine (0.80 mmol) in $CH_2Cl_2$ (20 mL) was refluxed for 10 h (TLC). The solution was evaporated and the residue was recrystallized from hexane/AcOEt affording 0.305 g (88 %) of the light-yellow product. M.p. 127–130 °C, $R_f$ (hexane/EtOAc, 6:4) = 0.42. $[\alpha]_D^{20}$ = –26.4 (*c* = 1, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$): $\delta$ = 0.92–0.96 (m, 3 H, $CH_2$-C$H_3$), 1.33 (d, *J* = 7.1 Hz, 3 H, CH-C$H_3$), 1.52–1.58 (m, 2 H, C*H* $_2$-$CH_3$), 2.21 (br., OH), 2.44 (s, 3 H, $C_{ar.}$-C$H_3$), 2.70–2.74 (m, 2 H, NH-C*H* $_2$-$CH_2$), 3.74 [d, *J* = 6.4 Hz, 1 H, $C_{ar.}$-C*H*(NH)CH-N], 4.09–4.13 (m, 1 H, C*H*-$CH_3$), 5.13 [d, *J* = 6.4 Hz,

1 H, $C_{ar.}$-CH-C*H* -(OH)-N], 6.10 [s, 1 H, N-C*H*-($C_{ar.}$)N], 7.38–7.81 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 11.7 ($CH_2$-*C*$H_3$), 19.6 (CH-*C*$H_3$), 21.6 ($C_{ar.}$-*C*$H_3$), 23.5 (NH-$CH_2$-*C*$H_2$), 42.7 (NH-*C*$H_2$-$CH_2$), 50.0 [$C_{ar.}$-*C*H(NH)CH-N], 57.6 (*C*H-$CH_3$), 60.3 [$C_{ar.}$-CH-*C*H-(OH)-N], 69.5 [N-*C*H-($C_{ar.}$)N], 124.5 ($CH_{ar.}$), 126.1 ($CH_{ar.}$), 127.2 ($CH_{ar.}$), 127.8 ($CH_{ar.}$), 128.8 ($CH_{ar.}$), 130.4 ($C_{ar.}$), 133.2 ($C_{ar.}$), 134.7 ($C_{ar.}$), 136.1 ($C_{ar.}$), 145.0 ($C_{ar.}$), 171.5 (CO) ppm. HRMS (EI): $C_{22}H_{27}N_3O_4S$: calcd. 429.1722; found 429.1729.

**(1*R*,2*S*,5*R*,6*S*)-5-Hydroxy-2-methyl-6-pyrrolidinyl-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydro-2*H*-imidazo[2,1-*a*]isoquinolin-3-one (10b):** In analogy to **10a**, pyrrolidine (0.60 mL, 0.050 g, 0.67 mmol) was reacted with the epoxide **8a** (0.250 g, 0.67 mmol) in $CH_2Cl_2$ (20 mL) for 3 h. **10b** was obtained as a yellow solid product (0.272 g, 91 %) after recrystallisation from hexane/EtOAc. M.p. 137–139 °C, $R_f$ (EtOAc) = 0.64. $[\alpha]_D^{20}$ = –19.1 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.27 (d, *J* = 6.8 Hz, 3 H, CH-C*H*$_3$), 1.82–1.88 (m, 4 H, N-$CH_2$-C*H* $_2$), 2.14 (br., OH), 2.43 (s, 3 H, $C_{ar.}$-C*H*$_3$), 3.03–3.07 (m, 4 H, NH-C*H* $_2$-$CH_2$), 3.75 [d, *J* = 2.6 Hz, 1 H, $C_{ar.}$-C*H*(NH)CH-(OH)], 4.09–4.13 (m, 1 H, C*H*-$CH_3$), 5.65 [d, *J* = 3.0 Hz, 1 H, $C_{ar.}$-CH-C*H*-(OH)-N], 6.15 [s, 1 H, N-C*H*-($C_{ar.}$)N], 6.52 (s, 1 H, O*H*), 7.34–7.93 (m, 8 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 19.9 (CH-*C*$H_3$), 21.6 ($C_{ar.}$-*C*$H_3$), 23.6 und 24.7 (NH-$CH_2$-*C*$H_2$), 45.5 und 50.1 (NH-*C*$H_2$-$CH_2$), 58.3 [N-*C*H-($C_{ar.}$)N], 63.6 (*C*H-$CH_3$), 69.2 [$C_{ar.}$-*C*H(N)CH-N], 74.4 [$C_{ar.}$-CH-*C*H(OH)-N], 125.8 ($CH_{ar.}$), 127.9 ($CH_{ar.}$), 128.0 (2 $CH_{ar.}$), 128.2 ($CH_{ar.}$), 129.5 ($CH_{ar.}$), 130.3 ($C_{ar.}$), 133.5 (2 $C_{ar.}$), 134.7 ($C_{ar.}$), 144.8 ($C_{ar.}$), 170.3 (CO) ppm. HRMS (EI): $C_{23}H_{27}N_3O_4S$: calcd. 441.1722; found 441.1726.

**(1*R*,2*S*,5*R*,6*S*)-5-Hydroxy-2-methyl-6-phenylamino-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydro-2*H*-imidazo[2,1-*a*]isoquinolin-3-one (10c):** In analogy to **10a**, aniline (0.050 g, 0.54 mmol) was reacted with **8a** (0.200 g, (0.54 mmol) in $CH_2Cl_2$ (20 mL). After 8 h reflux and evaporation of the solvent 0.211 g (80 %) of the product were obtained as yellow oil. $R_f$ (EtOAc) = 0.38. $[\alpha]_D^{20}$ = –39.8 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.35 (d, *J* = 6.8 Hz, 3 H, CH-C*H*$_3$), 2.37 (s, 3 H, $C_{ar.}$-C*H*$_3$), 3.69 (br., 2 H, NH, OH), 4.15 (q, *J* = 6.8 Hz, 1 H, C*H*-$CH_3$), 4.41 [d, *J* = 6.4 Hz, 1 H, $C_{ar.}$-C*H*(N)CH(OH)], 5.17 [d, *J* = 6.8 Hz, 1 H, $C_{ar.}$-CH-C*H*-(OH)-N], 6.19 [s, 1 H, N-C*H*-($C_{ar.}$)N], 6.62–7.83 (m, 13 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 19.6 (CH-*C*$H_3$), 21.6 ($C_{ar.}$-*C*$H_3$), 56.7 [N-*C*H-($C_{ar.}$)N], 57.4 (*C*H-$CH_3$), 69.3 [$C_{ar.}$-*C*H(N)CH-N], 76.1 [$C_{ar.}$-CH-*C*H(OH)-N], 113.5 ($CH_{ar.}$), 115.2 ($CH_{ar.}$), 118.6 ($CH_{ar.}$), 124.2 ($CH_{ar.}$), 126.8 ($CH_{ar.}$), 127.8 ($CH_{ar.}$), 129.2 (2 $CH_{ar.}$), 129.3 ($CH_{ar.}$), 130.4 ($CH_{ar.}$), 133.0 ($C_{ar.}$), 133.6 (2 $C_{ar.}$), 136.2 ($C_{ar.}$), 145.1 ($C_{ar.}$), 146.3 ($CH_{ar.}$), 147.0 ($CH_{ar.}$), 171.4 (CO) ppm. HRMS (EI): $C_{25}H_{25}N_3O_4S$: calcd. 463.1565; found 463.1570.

**(1*R*,2*S*,5*S*,6*R*)-6-Hydroxy-5-methoxy-2-methyl-1-(*p*-tolylsulfonyl)-1,5,6,10b-tetrahydro-2*H*-imidazo-[2,1-*a*]isoquinolin-3-one (12):** Concentrated sulfuric acid (3 drops) was added to a solution of the epoxide **8a** (0.200 g, 0.51 mmol) in MeOH (15 mL). After 5 h (TLC) the solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ (about 20 mL). The solution was washed with water and dried with $MgSO_4$. The product (0.072 g, 34 %) was isolated as colorless oil by evaporation first with a rotary evaporator followed by high-vacuum conditions. $R_f$ = 0.60 (hexane/EtOAc, 6:4) = 0.60. $[\alpha]_D^{20}$ = –23.3 (*c* = 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ = 1.29 (d, *J* = 6.8 Hz, CH-C*H*$_3$), 2.44 (s, 3 H, $C_{ar.}$-C*H*$_3$), 3.36 (s, 3 H, $OCH_3$), 4.01–4.07 (m, 1 H, C*H*-$CH_3$), 4.68 [d, 1 H, *J* , 3 H= 5.3 Hz, $C_{ar.}$-CH-C*H*($OCH_3$)-N], 4.73 [d, *J* = 5.3 Hz, 1 H, $C_{ar.}$-C*H*-(OH)CH-N], 6.17 [s, 1 H, N-C*H*-($C_{ar.}$)N], 7.35–7.83 (m, 8 H, C*H* $_{ar.}$), 7.89 (br., OH) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.2 (CH-*C*$H_3$), 21.6 ($C_{ar.}$-*C*$H_3$), 58.1 (O*C*$H_3$), 58.5 (*C*H-$CH_3$), 69.6 [$C_{ar.}$-*C*H(OH)CH-N], 71.5 [N-*C*H-($C_{ar.}$)N], 88.0 [$C_{ar.}$-CH-*C*H($OCH_3$)-N], 125.3 ($CH_{ar.}$), 127.8 ($CH_{ar.}$), 128.0 ($CH_{ar.}$), 129.0 ($CH_{ar.}$), 129.1 ($CH_{ar.}$), 130.3 ($C_{ar.}$), 132.8 (2 $C_{ar.}$), 134.2 ($C_{ar.}$), 136.1 ($C_{ar.}$), 145.1 ($C_{ar.}$), 171.7 (CO) ppm. HRMS (EI): $C_{20}H_{22}N_2O_5S$: calcd. 402.1249; found 402.1247.

**1,4-Dioxane 13:** TMS-OTf (44 µL, 0.24 mmol) was added to a solution of the oxirane **8b** in dry $CH_2Cl_2$ (25 mL). After 30 min stirring allyl-TMS (28 mg, 0.24 mmol) was added at –78 °C. Stirring was continued for 1 h. The mixture was warmed to room temp. and was washed with satd. aq. $Na_2CO_3$. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was distilled off under vacuum. After column chromatography with hexane/EtOAc (6:4) the product was obtained as colorless solid (0.068 g, 58 %). M.p. 95–96 °C, $R_f$ (hexane/EtOAc, 6:4) = 0.72. HRMS (FAB): $C_{50}H_{44}N_4O_8S_2$: calcd. 915.2497 [M + $Na^+$]; found 915.2492.

**(2*S*,10b*R*)-2-Phenyl-6,10b-dihydro-5*H*-[1,3]oxazolo[2,3-*a*]-isoquinolin-3(2*H*)-one (17):** In analogy to the synthesis of the Reissert product **4** (*S*)-*O*-TBDMS mandelic acid chloride **15 (**0.346 g, 1.21 mmol) was reacted with $AlCl_3$ (0.032 g, 0.24 mmol), 3,4-dihydroisoquinoline (0.159 g, 1.21 mmol) and TMS-CN (0.18 mL, 0.144 g, 1.21 mmol) affording 0.132g (41 %) of the product **17** as colorless crystals. M.p. 124–126 °C, $[\alpha]_D^{20}$ = –23.4 (*c* = 0.5, $CH_2Cl_2$), $R_f$ (hexane/EtOAc, 6:4) = 0.42. $^1$H NMR ($CDCl_3$): $\delta$ = 2.73 (m, 1 H, $CH_2$), 3.03 (m, 1 H, $CH_2$), 3.26 (m, 1 H, $CH_2$), 4.16 (m, 1 H, $CH_2$), 5.23 (s, 1 H, CH), 6.30 (s, 1 H, CH), 7.12–7.46 (m, 9 H, $CH_{ar.}$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 27.6 ($CH_2$), 37.4 ($CH_2$), 79.9 (CH), 86.1 (CH), 125.6 ($CH_{ar.}$), 126.2 (2 $CH_{ar.}$), 127.1 ($CH_{ar.}$), 128.6 ($CH_{ar.}$), 128.7 (2 $CH_{ar.}$), 128.8 ($CH_{ar.}$), 128.9 ($CH_{ar.}$), 133.8 ($C_{ar.}$), 134.5 ($C_{ar.}$), 136.3 ($C_{ar.}$), 169.5 (CO) ppm. $C_{17}H_{15}NO_2$ (265.31): calcd. C 76.96, H 5.70, N 5.28; found C 76.05, H 5.99, N 5.31. The (2*R*,10b*S*)-enantiomer **ent-17** was obtained accordingly from (*R*)-O-TBDMS mandelic acid chloride.

**X-ray Crystal Analysis of *ent*-17:** [29] Empirical formula: $C_{17}H_{15}NO_2$, formula mass: 265.30, temperature: 180(2) K, wavelength: 0.71073 Å, crystal system: monoclinic, space group: *P*21, unit cell dimensions: *a* = 9.724(2), *α* = 90 °, *b* = 6.4224(12), *β* = 93.75(4) °, *c* = 10.883(4), *γ* = 90 °. volume: 678.2(3) Å$^3$, *Z* = 2. density (calcd.): 1.299 Mg/m$^3$, absorption coefficient: 0.085 mm$^{-1}$, *F*(000) = 280, crystal size: 0.80 × 0.69 × 0.16 mm, Theta range for data collection: 2.72 to 25.83 °, limiting indices:–11 ≤ *h* ≤ 11, –7 ≤ *k* ≤ 7, –13 ≤ *l* ≤ 13; reflections collected/unique 4673/2542 [*R*(int) = 0.0202], completeness to theta = 25.83 (97.8 %), absorption correction: empirical (*Ψ*-scan), max. and min. transmission: 0.9865 and 0.9348, refinement method: full-matrix least-squares on $F^2$, data/restraints/parameters: 2542/1/241, goodness-of-fit on $F^2$: 1.049, final $R_{inr}$ [$I > 2\sigma(I)$]: *R*1 = 0.0250, *wR*2 = 0.0631, $R_{int}$ (all data): *R*1 = 0.0276 *wR*2 = 0.0643, absolute structure parameter: 0.2(8), largest diff. peak and hole: 0.125 and –0.125 e·Å$^3$.

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[29] CCDC-250562, -250563 and -250564 contain the supplementary crystallographic data for for **5c**, **ent-17**, and **7c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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