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PAPER

Enantioselective radical cyclisation reactions of 4-substituted quinolones mediated by a chiral template†

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Six 4-substituted quinolones **6–8**, which bear an ω-iodoalkyl chain, were prepared and subjected to reductive radical cyclisation conditions employing BEt_3/O_2 as the initiator and either Bu_3SnH or TMS_3SiH as hydride source. 4-(4-Iodobutyl)-quinolone (**6a**) and 4-(3-iodopropylthio)-quinolone (**8a**) gave the respective 6-*endo*-cyclisation products in good yields. 4-(3,3-Dimethyl-4-iodobutyl)-quinolone (**6b**) cyclised in a 5-*exo*-fashion, while the other substrates delivered only reduction products. The cyclisation reactions could be conducted in the presence of a chiral template (**1**) with high enantiomeric excess (94–99% *ee*). The association behaviour of substrate **6a** to **1** was studied by NMR titration experiments. In the enantioselective cyclisation of **6b** a significant nonlinearity was observed when comparing the product *ee* with the *ee* of the template.

Introduction

Addition reactions to the double bond of α,β-unsaturated carbonyl compounds have significantly influenced the development of modern radical chemistry. The fact that nucleophilic carbon radicals exhibit high regio- and chemoselectivity in this reaction attracted the attention of organic chemists and alerted the synthetic community to the advantages of radical reactions.[1,2] If the double bond, to which a radical addition occurs, bears two different β-substituents, a stereogenic centre is formed. In acrylic acid derivatives this process can be rendered diastereoselective if the acryloyl group is attached to a chiral auxiliary.[3] Frequently used auxiliaries include amines, amides or alcohols linked by a C–N or C–O bond. Seminal studies in the area of auxiliary-induced diastereoselective radical addition reactions were performed in the late 1980 s by the groups of Giese, Porter and Curran.[3,4] In recent years, the area of radical addition chemistry was dominated by the search for methods to achieve a direct enantioselective C–C bond formation using chiral templates or chiral catalysts.[5,6] Lewis acids have turned out to be particularly well suited for combining an efficient stereocontrol with – in some cases remarkable – rate enhancements enabling catalytic enantioselective radical reactions.[5,7] Other templates relating on different but Lewis acid/base interactions have received less attention.[8] In our group the use of hydrogen bonds to bind a potential radical reaction precursor in a chiral environment has been considered. In an U-shaped template, as depicted in Fig. 1, binding to a lactam by two hydrogen bonds could occur and simultaneously a bulky substituent (steric shield) would prevent an approach of a given reagent from the upper face. For a conjugate radical addition the corresponding alkyl radical would approach the double bond from the lower face.

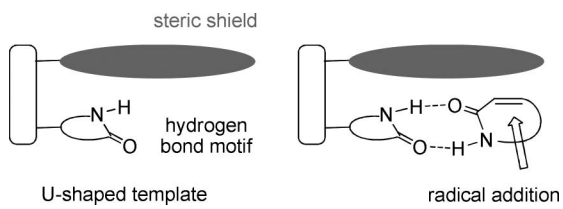

Fig. 1 Enantioselective addition to an α,β-unsaturated acrylic amide or lactam mediated by an U-shaped template.

In contrast to a covalent attachment, hydrogen bonding[9] offers only a relatively weak force, with which a substrate can be held in a chiral environment. This is the more true as the strength of two hydrogen bonds in a 1 : 1 template/substrate complex cannot be expected to be substantially different from a substrate dimer (*vide infra*). A possible chiral template for radical reactions evolved from our earlier work on photochemical reactions, in which the superior behaviour of the chiral templates **1** (Fig. 2) was shown.[10,11] They exhibit a lactam with a rigid 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton derived from Kemp's triacid.[12] A tetrahydronaphthalene serves as steric shield to prevent attack of a reagent from the upper face. Related 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones had been earlier used as chiral auxiliary[13] and in their oxidised imide form, *i.e.* as 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2,4-dione, for molecular recognition studies.[14] In our work, templates **1** were

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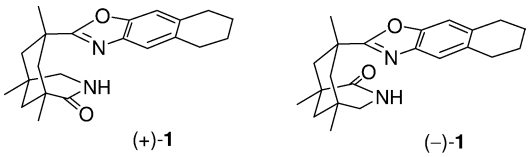
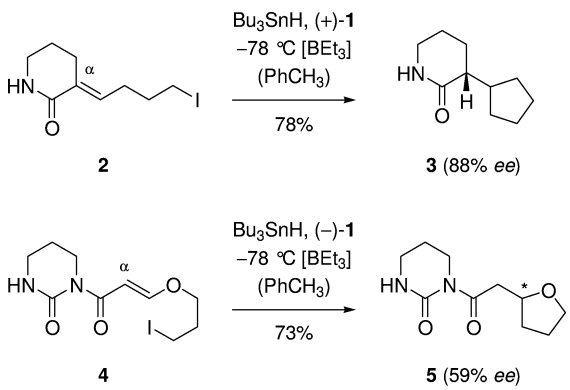


Fig. 2 Absolute configuration of the chiral templates (+)-**1** and (–)-**1**.

established as useful chiral complexing agents for applications in enantioselective photochemistry and found many applications, *e.g.* in [2+2]-photocycloadditions,[15] photoinduced Diels–Alder reactions,[16] [4+4]-photocycloadditions[17] and Norrish–Yang cyclisations.[18] More recently, it was shown that the tetrahydronaphthalene can be replaced by catalytically active sensitising substituents, enabling catalytic enantioselective photochemical reactions in solution.[19] Coordination of templates **1** to pyridones, quinolones and their hydrogenated derivatives has turned out to be particularly effective. Toluene and trifluorotoluene are preferred solvents.

Given the fact that many photochemical reactions proceed *via* radical intermediates it was evident that templates **1** could possibly be used in enantioselective radical reactions. Initial studies were concerned with hydrogen abstraction reactions by a prochiral radical.[20] To this end, 3-(ω-iodoalkylidene)-piperidin-2-ones were reductively cyclised to yield the corresponding products in high yields and with good enantioselectivities. As an example the reaction of substrate **2** is depicted in Scheme 1. Cyclopentane formation occurred upon generating the primary radical at the terminal alkyl carbon atom with concomitant formation of a prostereogenic radical centre in α-position to the carbonyl group. This radical was enantioselectively reduced by Bu_3SnH in the presence of template (+)-**1** delivering piperidone **3** in 88% *ee* if the reaction was run at a substrate concentration of 100 mM. Initial studies concerning an enantioselective addition to a double bond were conducted with derivatives of 3-(3-iodopropyloxy)propenoic acid.[21] In this case the C–C bond formation event is stereodetermining leading to a chiral 2-substituted tetrahydrofuran. The best acyl substituent for high selectivity was found to be a cyclic urea as shown for substrate **4**. Product formation proceeded in good yield but the enantioselectivity was 59% *ee* at best. The absolute configuration of the major enantiomer of product **5** was not determined.



Scheme 1 Examples of previously studied enantioselective radical reactions performed with substrates **2** and **4**.

While the latter result showed that enantioselective cyclisation reactions are feasible employing template **1** and while the enantioselectivity in this process was remarkable given the limited precedence for enantioselective radical cyclisations,[6] we sought to improve the selectivity in the radical addition by two modifications. Firstly, the α,β-unsaturated carboxylic acid derivative was to be embedded in a cyclic array to avoid any conformational freedom regarding a rotation around the CO–C_α bond. Secondly, a binding motif was to be used, which had turned out to be successful in previous experiments. These considerations led us to commence the study, which is described in detail in this account and which deals with the radical cyclisation of 4-substituted quinolones. Promising results were obtained with 4-(4-iodoalkyl)-quinolones,[22] which were to be extended to heteroatom (oxygen, sulphur) substituted quinolones. In addition, association constants were determined, which reveal a conclusive insight into the thermodynamics of complexation by template **1**, and it was shown that template **1** exhibits a nonlinear behaviour regarding the enantioselectivity of the cyclisation products to be achieved with enantiomerically enriched template (20–100% *ee*).

Preparation of starting materials

Quinolones **6–8** were selected as substrates for the present study (Fig. 3). They exhibit the well established quinolone binding motif and they carry an iodide substituent, the homolytic cleavage of which was expected to generate a radical suitable for intramolecular addition to the double bond at carbon atoms C3 or C4 of the quinolone.

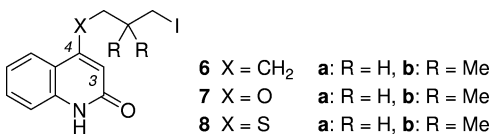
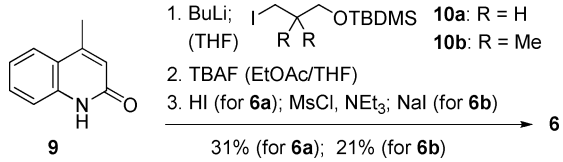


Fig. 3 Structures of the iodides **6–8**, which served as potential precursors for radical cyclisation reactions.

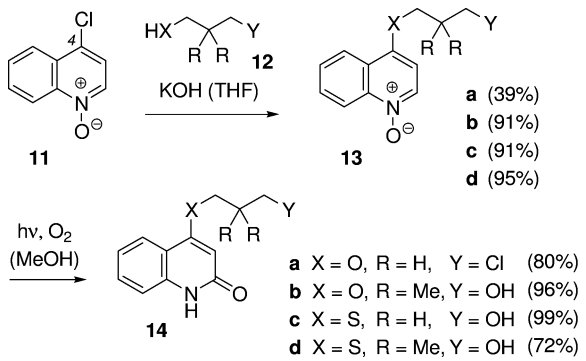
The preparation of the iodoalkyl-substituted quinolones (X = CH_2) commenced with readily available 4-methylquinolone (**9**),[23] which was deprotonated with butyl lithium and subsequently alkylated with iodides **10** (Scheme 2). Although yields in this step were relatively low (37–39%) the approach was favoured due to its brevity. Indeed, facile desilylation delivered almost quantitatively the primary alcohols, which were readily converted into the desired iodides **6**[22] either directly (for **6a**) or after mesylation in a Finkelstein reaction (for **6b**).[24]



Scheme 2 Preparation of the carbon-substituted quinolones **6** starting from 4-methylquinolone (**9**).

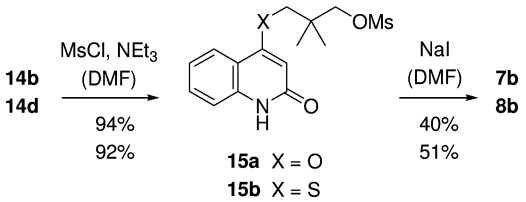
The oxygen- (X = O) and sulphur-substituted (X = S) quinolones were prepared from literature known[25] 4-chloroquinoline-*N*-oxide (**11**). Nucleophilic displacement of the chlorine substituent at

C4 was achieved by refluxing the corresponding alcohol or thiol **12** (1.2 equiv.) together with the *N*-oxide and KOH in THF. In most cases (**12b–d**) the diprotic alcohol (Y = OH) was employed. Only in one case, 3-chloropropanol (**12a**) was selected as the nucleophile. Subsequent rearrangement of *N*-oxides **13** to the corresponding quinolones **14** under standard conditions[26] (treatment with tosyl chloride followed by hydrolysis with aqueous sodium bicarbonate) resulted in decomposition of the respective *N*-oxides. Using a photochemical rearrangement,[26,27] the conversion of 3-chloropropoxy derivative **13a** could be conducted in a batch process employing a high-pressure mercury lamp (Original Hanau TQ 150). These conditions (deaerated methanol under argon, Duran filter), however, gave in the attempted rearrangement of substrates **13b–13d** very low yields, mostly due to the subsequent fast [2+2]-dimerisation of the intermediate quinolones **14b–14d**. During the optimisation of this reaction the concentrations were lowered from initially 30 mM to 6–7 mM and irradiation times were shortened to suppress the dimerisation. In the best case a selectivity of 88% was achieved (64% yield at 73% conversion) for quinolone **14c**. To further suppress the dimerisation the irradiation source and the addition of triplet quenchers were investigated. The *N*-oxide rearrangement proceeds exclusively *via* the lowest singlet state[28] whereas the photochemical dimerisation of 2-quinolone has been shown to originate from the reaction between a triplet excited and a ground state quinolone.[29] The effect of the addition of piperylene (1,3-pentadiene) or oxygen as triplet quencher was therefore tested in the reaction of substrate **13c** giving in both cases only traces of the dimerisation side product even at full conversion (Scheme 3). An oxidation of the thioether to the sulfoxide due to generated singlet oxygen was not observed.



Scheme 3 Preparation of the quinolones **14** from 4-chloroquinolone-*N*-oxide (**11**) by nucleophilic displacement and subsequent photochemical rearrangement.

The use of standard UV fluorescence lamps (419 nm, 366 nm) resulted in additional minor improvements. To further overcome the problems associated with the handling of rather large solvent volumes during the irradiation, a coiled tube flow reactor was used allowing for a very convenient conversion of *N*-oxides on gram scale. In order to convert the quinolones **14** into the desired substrates **7** and **8** for the radical cyclisation experiments the terminal functional group Y was modified (Scheme 4). For chloride **14a**, nucleophilic displacement by iodide could be achieved under Finkelstein conditions (NaI in acetone) delivering iodide **7a** in 78% yield. The alcohol **14c** was converted directly into iodide **8a** (61%) using a redox protocol[30] (PPh_3, I_2, imidazole in



Scheme 4 Preparation of the radical substrates **7b** and **8b** by nucleophilic displacement reactions of the corresponding mesylates **15**.

THF). The steric hindrance in substrates **14b** and **14d** precluded the use of a direct displacement of the hydroxy group in a similar fashion.

Instead, the alcohols were converted into the respective mesylates **15** (Ms = methanesulfonyl), which were subsequently transformed into the iodides **7b** and **8b** at elevated temperature (130 °C) in DMF as the solvent (Scheme 4).

Cyclisation experiments

Cyclisation of iodides **6–8** was attempted initially in the absence of template **1** in order to evaluate the principal possibility of such a reaction. To this end, reactions were performed in toluene as the solvent and with BEt_3/O_2 as the initiator at ambient temperature. The results of these experiments are listed in Table 1, while the products obtained in this study are depicted in Fig. 4.

The simple 4-iodobutyl-substituted quinolone **6a** gave exclusively the products **16a** of a 6-*endo*-cyclisation (entry 1). Both diastereoisomers (*trans*- and *cis*-**16a**) were formed in almost equal amounts (d.r. = 47/53). In contrast to this regioselective process, the cyclisation of the *gem*-dimethylsubstituted substrate **6b** resulted in a mixture of regioisomers. The 5-*exo*-product **17** prevailed but the 6-*endo*-products **16b** were also formed as a mixture of diastereoisomers (entry 2). As for **16a**, there was no significant preference for one diastereoisomer but the exact ratio could not be determined due to residual impurities. In contrast to their carbon analogues **6**, the oxygen-substituted quinolones **7a** and **7b** did not react to the desired radical cyclisation products. Instead, immediate reduction occurred to the deiodinated products **19a**[31] and **19b**. The hydro-de-iodination was high yielding with Bu_3SnH as the reducing agent (entries 3 and 4), irrespective of whether

Table 1 Attempted radical cyclisation reactions of substrates **6**, **7** and **8** in toluene as the solvent and with BEt_3/O_2 as the initiator (for products, see Fig. 4)

Entry	Substrate	Reducing agent	Product (yield)[a]	By-product (yield)[a]
1[b]	**6a**	Bu_3SnH	**16a** (88%)[c]	—
2[b]	**6b**	Bu_3SnH	**17** (49%)	**16b** (27%)[d]
3[b]	**7a**	Bu_3SnH	**19a** (quant.)	—
4[e]	**7b**	Bu_3SnH	**19b** (94%)	—
5[e]	**7b**	TMS_3SiH	**19b** (66%)	**21b** (17%)
6[e]	**8a**	Bu_3SnH	**20a** (57%)	**18** (28%)[f]
7[e]	**8a**	TMS_3SiH	**18** (42%)[g]	**20a** (21%)
8[e]	**8b**	Bu_3SnH	**22b** (45%)[h]	**20b** (29%)
9[e]	**8b**	TMS_3SiH	**22b** (36%)[h]	**20b** (14%)

[a] Yield of isolated products. [b] $c = 15$ mM. [c] d.r. = *trans*-**16a**/*cis*-**16a** = 47/53. [d] The diastereomeric ratio was not determined. [e] $c = 7.5$ mM. [f] d.r. = *trans*-**18**/*cis*-**18** = 90/10. [g] d.r. = *trans*-**18**/*cis*-**18** = 91/9. [h] Not isolated in pure form.

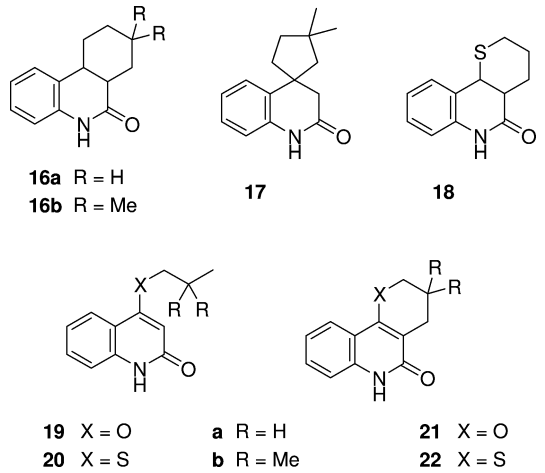


Fig. 4 Structure of the products **16–22** obtained from attempted radical cyclisation reactions of quinolones **6–8** (*cf.* Tables 1 and 2).

the reagent was added completely in the beginning of the reaction or generated *in situ* from Bu_3SnCl and $NaCNBH_3$. Even with TMS_3SiH (TMS = trimethylsilyl), which is known to react with a carbon-centred radical less rapidly,[32] there was no indication of a radical cyclisation. The by-product **21b** formed in this event (entry 5) could potentially be produced by a radical pathway. However, the fact, that by-product **21b** was also observed in the preparation of **7b** from mesylate **15a** and was even the exclusive product upon attempted conversion of alcohol **14b** to **7b** with HI, indicates that formation of this product can occur by an electrophilic aromatic substitution mechanism. Given that the electrophilic aromatic substitution provides **21b** directly whereas the radical cyclisation requires subsequent oxidation – which is not observed *e.g.* for products **16a** and **16b** – the formation of by-product **21b** from **7b** in the attempted radical cyclisation appears to be due to acidic impurities possibly produced from BEt_3.

The use of TMS_3SiH as reducing agent proved beneficial in the cyclisation of sulphur-substituted substrate **8a** (entries 6 and 7). While the reduction to hydro-de-iodinated product **20a** was predominant with Bu_3SnH, its formation was successfully suppressed with TMS_3SiH. In the latter case, the 6-*endo*-cyclisation products **18** were isolated as the major products (entry 7) with the *trans*-product *trans*-**18** being formed in excess (d.r. = 91/9). Surprisingly, quinolone **8b**, the *gem*-dimethylsubstituted analogue of **8a**, failed to produce any cyclisation products. The outcome of its reaction (entry 8) was similar to the outcome of the reaction with the related oxygen compound **7b**. Even with TMS_3SiH reduction product **20b** was formed (entry 9), which was isolated together with the aromatic quinolone **22b**. Unfortunately, product **22b** could not be obtained in pure form. As in the case of **21b**, the formation of the latter product can be accounted for either by an ionic cyclisation or by a radical cyclisation/oxidation sequence.

Radical cyclisation experiments in the presence of the chiral template were only performed with those substrates, that had provided in the previous set of experiments (Table 1) the desired cyclisation products. All experiments were conducted in the presence of the antipode (+)-**1** as chiral template and the results are listed in Table 2. The 6-*endo* cyclisation of substrate **6a** worked equally well as in the racemic series, *i.e.* in reactions run in the absence of a template as shown in Table 1. At 25 °C (entry 1) product **16a** was isolated in 84% yield and with an improved diastereomeric ratio *trans*-**16a**/*cis*-**16a** = 77/23. In the racemic series the ratio was 47/53. The major diastereoisomer *trans*-**16a** showed a significant enantiomeric excess (*ee*) of 96% and was dextrorotatory (*vide infra*). The diastereomeric ratio improved upon lowering the reaction temperature (0 °C, entry 2) to 88/12 and the enantioselectivity increased to 99% *ee* in favour of *trans*-**16a**.

For substrate **6b**, it was observed that the presence of template (+)-**1** improved the regioselectivity of the cyclisation. The 6-*endo* regioisomer **16b**, which was formed in the racemic series, could not be detected. Instead, the 5-*exo* regioisomer **17** was the only product, which was obtained in good yields. The enantioselectivity significantly increased when decreasing the reaction temperature (entries 3 and 4). Substrate **8a** showed similar behaviour as substrate **6a**. Exclusive cyclisation to the 6-*endo* product **18** was observed and there was essentially a single diastereoisomer *trans*-**18** being formed. However, reduction to compound **20a** occurred to a large extent (50%) if Bu_3SnH was employed as hydrogen atom donor (entries 5 and 6). As in the racemic series the use of TMS_3SiH led to a higher ratio of cyclisation products (entries 7 and 8). The best result was recorded at 0 °C (entry 8), providing product *trans*-**18** in 77% yield with perfect diastereo- (d.r. >99/1) and close to perfect enantioselectivity (96% *ee*).

The absolute configuration of the products was assigned based on the mechanistic model previously suggested for photochemical addition of olefins to the quinolone C3/C4 double bond.[15] Upon hydrogen binding to template (+)-**1** the given radical derived from **6a**, **6b** or **8a**, is forced to attack the double bond at

Table 2 Enantioselective radical cyclisation reactions of substrates **6a**, **6b** and **8a** in trifluorotoluene as the solvent and with BEt_3/O_2 as the initiator (for products, see Fig. 4)

Entry	Substrate	Hydride	T/°C	Product	Yield (%)[a]	*ee* (%)
1[b]	**6a**	Bu_3SnH	25	**16a**[c]	84	96[d]
2[b]	**6a**	Bu_3SnH	0	**16a**[e]	79	99[d]
3[b]	**6b**	Bu_3SnH	25	**17**	62	69
4[b]	**6b**	Bu_3SnH	0	**17**	66	94
5[f]	**8a**	Bu_3SnH	25	**18**[g]	42	91[d]
6[f]	**8a**	Bu_3SnH	0	**18**[h]	46	99
7[f]	**8a**	TMS_3SiH	25	**18**[h]	56	91
8[f]	**8a**	TMS_3SiH	0	**18**[h]	77	96

[a] Yield of isolated products. [b] c = 15 mM. [c] d.r. = *trans*-**16a**/*cis*-**16a** = 77/23. [d] The enantiomeric excess (*ee*) was determined for the major *trans*-diastereoisomer. [e] d.r. = *trans*-**16a**/*cis*-**16a** = 88/12. [f] c = 7.5 mM. [g] d.r. = *trans*-**18**/*cis*-**18** = 96/4. [h] d.r. = *trans*-**18**/*cis*-**18** = >99/1.

either carbon atom C3 or C4 from the bottom. The major enantiomers depicted in Fig. 5 should consequently be formed. Indeed, the absolute configuration of compound (*R*,*R*)-*trans*-**16a** was proven by comparison with known analytical data.[22,33] The assignments for (*S*)-**17** and (*S*,*R*)-*trans*-**18** are based on analogy. The regioselectivity of the attack at C3 (formation of 6-*endo*-product) *vs.* C4 (formation of 5-*exo*-product) has been discussed earlier.[22]

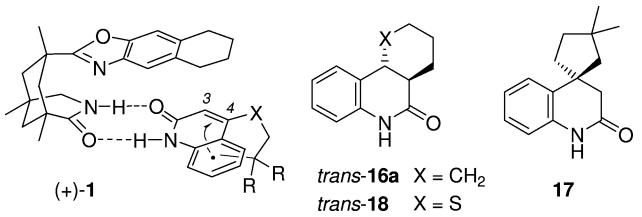


Fig. 5 Model for the enantioselective radical addition step at carbon atoms C3 (for products **16a** and **18**) or C4 (for product **17**).

The preference for a defined relative configuration is in the absence of the template (Table 1, entries 1, 6, 7) low for **16a** (*trans*/*cis* = 47/53) and already pronounced for **18** (*trans*/*cis* = 90/10). This result supports – in analogy to glycosyl radicals[1] – the stereoelectronic preference[34] for a conformation of a sulphur-substituted carbon radical **23**, in which the unpaired electron is placed in an axially positioned orbital (Fig. 6). Trapping of this radical by a hydrogen atom donor occurs with high facial selectivity. The carbon-substituted radical **24** does not show this conformational preference. The former effect (leading to *trans*-**16a**) is counterbalanced by the fact that the approach of a hydrogen donor in a *cis*-fashion is sterically more favourable.

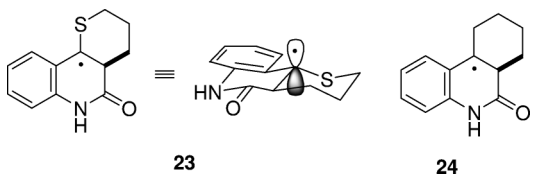


Fig. 6 Structure of the intermediate radicals **23** and **24** formed by 6-*endo* cyclisation.

In the presence of template (+)-**1**, also the hydrogen atom transfer is influenced by the chirality of the template. It was shown earlier that high enantioselectivities can be induced in this process.[20] If the cyclisation proceeds as shown in Fig. 5 at C3 leading to enantiomerically enriched radicals (*S*)-**23** and (*R*)-**24**, the hydrogen atom donor attacking with a *trans*-preference is in line with the chirality induced by the template. The already existing preference for the formation of *trans*-**18** is enforced (Table 2, entries 5–8) and in the case of *trans*-**16a**, the previously (in the racemic series) unselective hydrogen atom transfer becomes diastereoselective (Table 2, entries 1,2). The interplay of the two factors leads to the observed diastereo- and enantioselectivities. It also explains why the enantioselectivity for the *trans*-isomers **16a** and **18** is so high even at relatively high temperature (Table 2, entries 1, 5, 7). The formation of the enantiomer of the *trans*-isomer requires both the cyclisation and the hydrogen atom transfer to occur *against* the chirality preference exerted by the template. If either one of the processes delivers the opposite absolute configuration, the products are *cis*-isomers. Indeed, the *cis*-product *cis*-**16a** isolated from the reaction of substrate **6a** (Table 2, entry 2) showed only 16% *ee*.

Dimerisation and association constants

It was previously shown that the enantiomerically pure templates **1** do not form dimers in solution.[15c] The sterically demanding, tricyclic 1′-oxa-3′-azacyclopenta[*b*]naphthalene part of templates **1** would lead to a dramatic steric clash upon hydrogen bonding in the chair conformation of the 3-azabicyclo[3.3.1]nonan-2-one. A ring flip into the boat conformation of the 3-azabicyclo[3.3.1]nonan-2-one is energetically too costly. As a result the homochiral templates exist as monomeric structures in solution but are capable of binding to other amides or lactams. The formation of a 1 : 1 complex has been postulated and proven in previous studies.[15c,20b] However, we have not yet been able to generate reliable data for the association constant. A complication in measuring the association is the fact that the substrate can dimerise, which needs to be taken into account when calculating the association constant K_a. While available programs offer algorithms, which generate these data from measured NMR titration data, it must be ensured that the NMR titration has been conducted at reasonable concentration. In this respect the value for an association constant of a quinolone/template complex, which we determined earlier in toluene at 25 °C,[15c] appears from our present perspective incorrect because the dimerisation constant for the quinolone was assumed to be too low. Indeed, more recent titration experiments delivered dimerisation constants for quinolones, which were significantly higher.[35] In the light of these results, quinolone **6a** appeared to be a compound, the association behaviour of which was worth studying in order to obtain reliable data.

As apparent from Scheme 5 the global equilibrium is determined by the initial concentrations of the quinolone **6a** and the template (+)-**1** as well as by the respective equilibrium constants K_{dim} for the dimerisation of the substrate and K_a for the association. As shown earlier,[15c] higher stoichiometries are of no relevance (the 1 : 1 stoichiometry has been proven by Job plot experiments) and the dimerisation of the enantiopure templates is close to zero (*vide supra*).

$$K_{dim} = \frac{[(\mathbf{6a})_2]}{[\mathbf{6a}]^2} \quad (1)$$

$$K_a = \frac{[\mathbf{1}\cdot\mathbf{6a}]}{[\mathbf{1}]\cdot[\mathbf{6a}]} \quad (2)$$

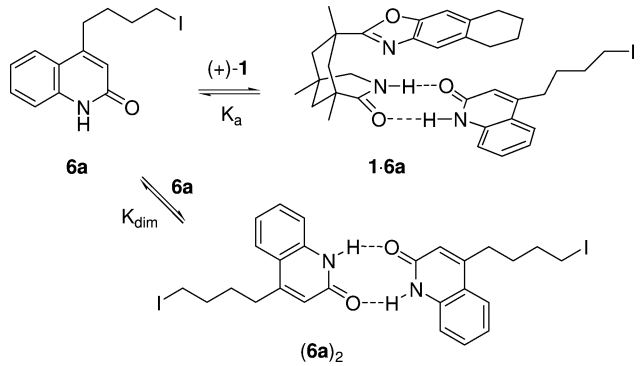
$$[\mathbf{6a}]_0 = [\mathbf{6a}] + 2\cdot[(\mathbf{6a})_2] + [\mathbf{1}\cdot\mathbf{6a}] \quad (3)$$

$$[\mathbf{1}]_0 = [\mathbf{1}] + [\mathbf{1}\cdot\mathbf{6a}]_0 \quad (4)$$

The definitions (1) and (2) for K_{dim} and K_a together with the initial concentrations ($[\mathbf{6a}]_0$ and $[\mathbf{1}]_0$) as boundary conditions ((3) and (4)) give an equation system with four variables and four equations. By adequate transformations the cubic eqn (5) results which can be solved analytically.

For a given set of K_{dim}, K_a, $[\mathbf{1}]_0$ and $[\mathbf{6a}]_0$ the concentration of **6a** is thus accessible and consequently the other equilibrium

$$2K_{dim}K_a[\mathbf{6a}]^3 + (2K_{dim} + K_a)[\mathbf{6a}]^2 + (K_a[\mathbf{1}]_0 - K_a[\mathbf{6a}]_0 + 1)[\mathbf{6a}] - [\mathbf{6a}]_0 = 0 \quad (5)$$



Scheme 5 Association of substrate **6a** to template **1** and its dimerisation.

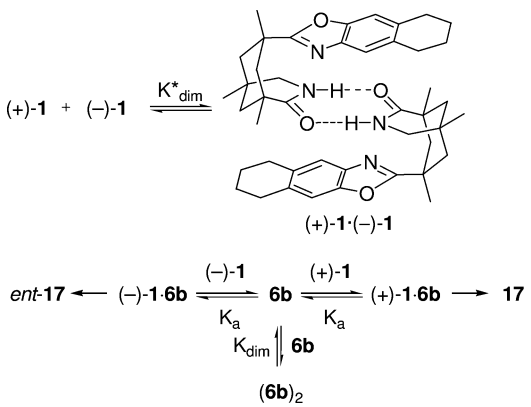
values ([**1**] and [**1**·**6a**]) as well as derived values like the expected enantiomeric excess of a reaction or the chemical shift in a NMR titration experiment can be calculated and *vice versa*. The latter is the prerequisite for the determination of the constants K_{dim} and K_a by means of NMR titration. The general assumption made in this kind of titrations[36] is that the equilibrium is established rapidly on the NMR timescale and therefore only the weighted average of the chemical shifts of the proton under investigation in its two possible environments is detectable. For the complex formation at least the shift of the unbound template (δ_1) is accessible ($[\mathbf{6a}]_0 = 0$) but the shift of the bound template ($\delta_{\mathbf{1}\cdot\mathbf{6a}}$) is usually only accessible as parameter in the nonlinear curve fitting process. As apparent from Table 3 (entries 1 and 4) the fitting of three parameters (K_a, K_{dim} and $\delta_{\mathbf{1}\cdot\mathbf{6a}}$) results in reliable results for the association constants (relative errors of about 6–7%). The results for the substrate dimerisation are in turn not satisfactory. However, reliable values for this parameter can easily be obtained by measuring the dimerisation constant K_{dim} of the substrate separately by means of a dilution experiment.[36a] This procedure has the advantage, that the value can then be used as a boundary in the nonlinear optimisation of the titration data to refine the association constant and it allows to reduce the number of parameters (K_a, $\delta_{\mathbf{1}\cdot\mathbf{6a}}$).

The errors given for the optimised parameters refer to a Monte–Carlo error analysis[39] using 1000 artificially scattered datasets (for details see the *ESI*) and refer to a confidence level of 95%. The dimerisation studies give significantly better results for K_{dim} as obtained in the titration studies, but still large errors (7% and 13% error for the 95% confidence level, entries 2 and 4) are observed (entries 3 and 6). This originates on one hand from the necessity to detect signals of very dilute samples (in the titration experiment the signal of the template is monitored, the concentration of which is kept constant). On the other hand, the nonlinear regression optimises in these cases still three parameters (K_{dim}, $\delta_{\mathbf{6a}}$ and $\delta_{(\mathbf{6a})_2}$) which is a second source of error. Nonetheless, the separately determined dimerisation constants can be used to avoid both issues in the association experiments which results in a refinement to smaller relative errors of about 5%. As already apparent from entries 1 and 4, the error propagation in the calculation of the association constant due to the uncertainty of the dimerisation constant must be very small and was determined for entries 3 and 6 to be significantly smaller (±9 L mol^{-1} for entry 3 and ±39 L mol^{-1} for entry 6) than the error due to the uncertainty of the measurement itself and was therefore neglected.

With these values at hand the question arises, why the observed high enantioselectivities are possible although the dimerisation constant K_{dim} exceeds the association constant K_a by a factor of about two. Using equations (1), (2) and (5) the expected enantiomeric excess in the beginning of the reaction can easily be calculated for the determined binding constants ($ee = [\mathbf{1}\cdot\mathbf{6a}]/[\mathbf{6a}]_0$) and compared with the results obtained in the cyclisation experiments. For reaction conditions similar to those applied in the titration (toluene as the solvent, 0 °C) an enantiomeric excess of 96% *ee* was found.[22] Using the obtained values for 0 °C (K_{dim} = 5770 L mol^{-1}, K_a = 2385 L mol^{-1}) an enantiomeric excess of 94% can be calculated which is in good agreement with the experimental value. Using arbitrary values of $[\mathbf{1}]_0$, $[\mathbf{6b}]_0$, K_a and K_{dim} it can moreover be shown, that the crucial factor for good substrate complexation and thus high enantiomeric excesses is the inability of the enantiopure template **1** to dimerise. This fact can be rationalised[35] by the notion, that upon association, one pair of hydrogen bonds is formed per substrate molecule whereas upon dimerisation a pair of hydrogen bonds is formed per *two* substrate molecules.

Nonlinear Behaviour

The fact, that 7-substituted 3-azabicyclo[3.1.1]nonan-2-ones show a strong heterochiral assocation[40] inspired us to investigate a potential nonlinear dependency[41] of the observed enantioselectivity in the cyclisation reaction upon varying the enantiomeric purity of the template **1**. As apparent from Scheme 6 a competitive heterochiral dimerisation of the template must be taken into account, which in turn should lead to an increase of the enantiomeric excess of the unbound template in solution and therefore to a possible increase of the observed optical purity of the product.



Scheme 6 Association of substrate **6b** to template **1** and its dimerisation.

This investigation was performed under optimised conditions (0 °C in $PhCF_3$ as the solvent) with substrate **6b**. In this reaction, only one product (**17**) was obtained in good yields. The formation

Table 3 NMR-titration to determine the binding constants K_{dim} and K_a for substrate **6a** and template **1**

Entry	T^a	Investigated equilibrium concentration (range)	a) Boundary conditions[b] b) Results[c]
1	25 °C	$(\mathbf{6a})_2 \overset{\mathbf{6a}}{\underset{K_{dim}}{\rightleftharpoons}} \mathbf{6a} \overset{\mathbf{1}}{\underset{K_a}{\rightleftharpoons}} \mathbf{1{\cdot}6a}$ $[\mathbf{6a}]_0$: 50 µmol L^{-1} – 2.5 mmol L^{-1} $[\mathbf{1}]_0$: 200 µmol L^{-1}	a) δ_1 (uncomplexed (+)-**1**) b) $K_a = 833 \pm 47$ L mol^{-1} $K_{dim} = 2030 \pm 385$ L mol^{-1}
2	25 °C	$2\,\mathbf{6a} \overset{}{\underset{K_{dim}}{\rightleftharpoons}} (\mathbf{6a})_2$ $[\mathbf{6a}]_0$: 75 µmol L^{-1} – 2.5 mmol L^{-1}	a) none b) $K_{dim} = 2001 \pm 133$ L mol^{-1} [d]
3	25 °C	$(\mathbf{6a})_2 \overset{\mathbf{6a}}{\underset{K_{dim}}{\rightleftharpoons}} \mathbf{6a} \overset{\mathbf{1}}{\underset{K_a}{\rightleftharpoons}} \mathbf{1{\cdot}6a}$ $[\mathbf{6a}]_0$: 50 µmol L^{-1} – 2.5 mmol L^{-1} $[\mathbf{1}]_0$: 200 µmol L^{-1}	a) $K_{dim} = 2000$ L mol^{-1}, δ_1 b) $K_a = 835 \pm 39$ L mol^{-1} [e]
4	0 °C	$(\mathbf{6a})_2 \overset{\mathbf{6a}}{\underset{K_{dim}}{\rightleftharpoons}} \mathbf{6a} \overset{\mathbf{1}}{\underset{K_a}{\rightleftharpoons}} \mathbf{1{\cdot}6a}$ $[\mathbf{6a}]_0$: 50 µmol L^{-1} – 2.5 mmol L^{-1} $[\mathbf{1}]_0$: 200 µmol L^{-1}	a) δ_1 (uncomplexed (+)-**1**) b) $K_a = 2394 \pm 162$ L mol^{-1} $K_{dim} = 5957 \pm 1931$ L mol^{-1}
5	0 °C	$2\,\mathbf{6a} \overset{}{\underset{K_{dim}}{\rightleftharpoons}} (\mathbf{6a})_2$ $[\mathbf{6a}]_0$: 75 µmol L^{-1} – 2.5 mmol L^{-1}	a) none b) $K_{dim} = 5769 \pm 743$ L mol^{-1} [d]
6	0 °C	$(\mathbf{6a})_2 \overset{\mathbf{6a}}{\underset{K_{dim}}{\rightleftharpoons}} \mathbf{6a} \overset{\mathbf{1}}{\underset{K_a}{\rightleftharpoons}} \mathbf{1{\cdot}6a}$ $[\mathbf{6a}]_0$: 50 µmol L^{-1} – 2.5 mmol L^{-1} $[\mathbf{1}]_0$: 200 µmol L^{-1}	a) $K_{dim} = 5770$ L mol^{-1}, δ_1 b) $K_a = 2385 \pm 125$ L mol^{-1} [e]

[a] The temperature was controlled using a B-VT-2000 control unit. [b] Fixed values, which have been determined in separate titration experiments or can be directly measured. [c] The given errors represent the 95% confidence interval resulting from Monte-Carlo error analysis. [d] Using HOSTEST[37] these results have been confirmed: $K_{dim,25} = 2001 \pm 160$ L mol^{-1}, $K_{dim,0} = 5614 \pm 706$ L mol^{-1} [e] Using a MS-Excel(tm) spreadsheet by J. M. Sanderson[38] these results have been confirmed (no confidence intervals available for single titration experiments): $K_{a,25} = 835$ L mol^{-1}, $K_{a,0} = 2385$ L/mol.

of diastereoisomers and regioisomers was not observed. Table 4 summarises the results, which were recorded upon using template (+)-**1** with varying optical purity (*ee* **1**). The effect on the nonlinearity is remarkable. Significantly higher enantioselectivities were found as compared to the values expected in a linear case. The most dramatic effects were recorded in the medium *ee* range (entries 3 and 4), where the measured *ee* for product **17** (*ee* **17** found) was 20% higher than the expected value (*ee* **17** expected).

When analysing the results of Table 3 based on equation (5), two borderline cases can be considered (Fig. 7). The first case is trivial, *i.e.* if a nonlinear effect is not observed ($K^*_{dim} = 0$ L mol^{-1}). The result would be simply a straight line (graph $\cdots$) connecting the point of origin with the maximum product *ee* (94%). The other extreme would be a perfect heterochiral dimerisation ($K^*_{dim} \rightarrow \infty$). This phenomenon can be analysed using a rough estimate for the association constant of **6b** in trifluorotoluene (a reasonable pair of binding constants would be $K_a \cong 3700$ L mol^{-1} and $K_{dim} \cong 5770$ L mol^{-1}). In equation (5) the concentration of **1** is simply reduced to the excess concentration of the major enantiomer of **1** as the minor enantiomer would be completely complexed by the major enantiomer. The values obtained for this borderline case are represented by the dashed line (graph -·-·-) in Fig. 7.

Table 4 Reaction of substrate **6b** in the presence template **1** with different optical purities

Entry[a]	*ee* **1** (%)[b]	*ee* **17** (%)[c] expected	*ee* **17** (%) found
1	100	94	94
2	80	75	80
3	60	56	73
4	40	38	62
5	20	19	29
6	0	0	0

[a] Substrate: **6b**, Bu_3SnH, Et_3B/O_2 ($PhCF_3$), c = 7.5 mmol L^{-1}, 0 °C. [b] Mixtures were generated by addition of the appropriate amounts of (–)-**1** to (+)-**1**. [c] Calculated from *ee* **1** · *ee* $\mathbf{17}_{max}$ – linear relationship.

The four state equilibrium shown in Scheme 6 can be treated in a similar way as presented for the association equilibrium in Scheme 5. Solving these equations leads to a more complex equation (for details see the *ESI*) which allows for a rough

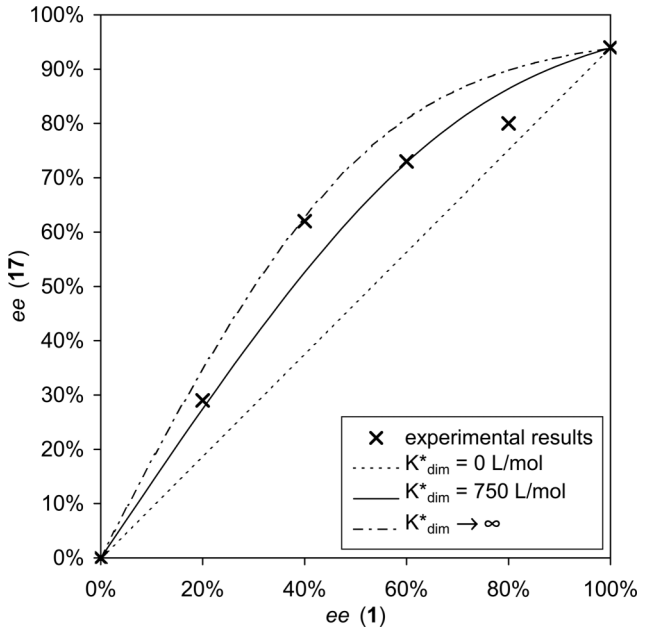


Fig. 7 Enantiomeric excess (*ee*) of the product **17** as a function of the template *ee* for different heterochiral dimerisation constants K^*_{dim}.

estimate of the heterochiral dimerisation constant K^*_{dim} to a value of about 750 L/mol. This value – being a result of a number of simplifications – is not to be taken as a quantitative measure for this binding constant but rather shows, that the heterochiral dimerisation of the template is as strong as expected from previous studies.[40] It gives raise to a noteworthy nonlinear dependence of the observed optical purity of the product from the optical purity of the template.

Conclusions

It was shown that radical cyclisation reactions of quinolones occur with high enantioselectivity (94–99% *ee*) in the presence of chiral template (+)-**1**. Unfortunately, not all substrates employed in this study underwent a cyclisation. Still, the results suggest that any radical addition at C3 or C4 of a given quinolone should lead to the respective product with high *ee*, if the reaction can be performed at 0 °C in trifluorotoluene. Association data obtained by NMR titration of compound **6a** in the presence of the chiral template confirm that the high enantioselectivities are in accord with the association behaviour of the individual compounds. At 25 °C, the dimerisation constant K_{dim} for **6a** was determined as 2000 (± 130) L mol^{-1} and the association constant K_a to **1** as 835 (±40) L mol^{-1}. At 0 °C, the respective values were K_{dim} = 5770 (±740) L mol^{-1} and K_a = 2385 (±125) L/mol. Complexation and decomplexation is rapid on the NMR time scale but further kinetic data for the association have not yet been obtained. The phenomenon, that the antipodes (+)-**1** and (–)-**1** undergo a heterochiral association while there is no homochiral complex formation, was confirmed by the nonlinear effect observed in the radical cyclisation **6b** → **17**. The observed enantioselectivities were significantly higher than the enantioselectivities to be expected from the *ee* of the template (+)-**1**.

Experimental

General methods

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Tetrahydrofuran (THF) was purified using a SPS-800 solvent purification system (M. Braun). Triethylamine was distilled over calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. TLC was performed on silica coated glass plates (silica gel 60 F_{254}) with detection by UV (254 nm) or $KMnO_4$ (0.5% in water) with subsequent heating. Flash column chromatography was performed on silica gel 60 (Merck, 230–400 mesh) with the indicated eluent. Common solvents for chromatography [pentane (P), ethyl acetate (EtOAc), diethyl ether (Et_2O), ethanol (EtOH), methanol (MeOH)] were distilled prior to use. HPLC analyses for the determination of the enantiomeric ratio of compound *trans*-**18** were performed on Chiralpak AS-H (Daicel, 250 × 4.6 mm, 5 μm) employing n-hexane/i-propanol as eluent and UV-detection at 20 °C. IR: JASCO IR-4100 (ATR) or Perkin-Elmer 1600 FT/IR. MS/HRMS: Finnigan MAT 8200 (EI)/Finnigan MAT 95S (HR-EI). ^{1}H and ^{13}C NMR: Bruker AV-250, Bruker AV-360, Bruker AV-500, recorded at 303 K. NMR-titrations where performed on a Bruker DMX-500 equipped with a B-VT-2000 temperature control unit. Chemical shifts are reported relative to tetramethylsilane. The multiplicities of the ^{13}C NMR signal were determined by DEPT experiments, assignments are based on COSY, HMBC and HMQC experiments. 4-Chloroquinoline-*N*-oxide (**11**) was synthesised in three steps starting from quinoline;[25] 2,2-dimethyl-3-mercaptopropionic acid was synthesised from 3-chloro-2,2-dimethylpropionic acid.[42]

Starting Materials

2,2-Dimethyl-3-hydroxypropanethiol (12d). 2,2-Dimethyl-3-mercaptopropionic acid (2.24 mmol, 300 g) dissolved in 8 mL anhydrous diethyl ether was added to 170 mg (4.47 mmol) lithiumaluminiumhydride in 12 mL anhydrous diethyl ether and the mixture was stirred at ambient temperature for 48 hours. A saturated aq. solution of NH_4Cl (15 mL) and 2 N aq. HCl (15 mL) were added successively. The aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* delivering compound **12d** as a colourless oil (255 mg, 2.12 mmol, 95%), which was of sufficient purity for further transformations. TLC: R_f = 0.13 (P/EtO_2 80/20) [$KMnO_4$]; ^{1}H-NMR (360 MHz, $CDCl_3$): δ (ppm) = 3.45 (s, 2H, H-3), 2.53 (d, ^3J = 8.7 Hz, 2H, H-2), 1.25 (t, ^3J = 8.7 Hz, 1H, SH), 0.95 (s, 6H, H-4); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 69.9 (t, C-3), 36.2 (s, C-2), 33.6 (t, C-1), 23.1 (q, C-4). The analytical data were in accord with literature values.[41]

General procedure I. Nucleophilic substitution at 4-chloroquinoline-*N*-oxide (**11**). 4-Chloroquinoline-*N*-oxide (**11**) (1 equiv.) was suspended in anhydrous THF. Powdered KOH was added to the stirred suspension followed by addition of the nucleophile. The mixture was heated under reflux for 12 hours. After cooling to room temperature the solvent was removed *in vacuo*

and the residue was purified by flash column chromatography on silica gel.

4-(3-Chloropropyloxy)-quinoline-*N*-oxide (13a). According to general procedure I, 1.08 g (6.01 mmol) of 4-chloroquinoline-*N*-oxide (**11**) were treated with 674 mg (12 mmol) KOH and 3.02 mL (36.1 mmol) 3-chloropropanol (**12a**) in 20 mL anhydrous THF. Purification by flash column chromatography (6 × 13 cm, EtOAc/EtOH 70/30 → 50/50) resulted in 555 mg (2.34 mmol, 39%) of compound **13a** as a colourless solid. mp: 71–73 °C; TLC: R_f = 0.29 (EtOAc/EtOH 75/25) [UV]; IR (KBr): $\tilde{\nu}$ = 3054 cm^{-1} (s, $C_{ar}H$), 1636 (w, C_{ar}), 1433 (m), 1388 (w), 1265 (vs, NO), 737 (s, C-Cl); ^{1}H-NMR (360 MHz, $CDCl_3$): δ (ppm) = 9.04 (d, ^3J = 7.1 Hz, 1H, H-2), 8.61 (d, ^3J = 8.7 Hz, 1H, H-8), 8.27 (dd, ^3J = 8.4 Hz, ^4J = 0.9 Hz, 1H, H-5), 7.98–7.94 (m, 1H, H-7), 7.77–7.71 (m, 1H, H-6), 7.08 (d, ^3J = 7.1 Hz, 1H, H-3), 4.54 (t, ^3J = 5.9 Hz, 1H, H-1′), 3.82 (t, ^3J = 6.2 Hz, 1H, H-3′), 2.45 (quint., ^3J = 6.1 Hz, ^3J = 5.8 Hz, 1H, H-2′); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 140.9 (s, C-4), 140.8 (d, C-2), 139.4 (s, C-8a), 133.4 (d, C-7), 128.9 (d, C-6), 122.8 (d, C-5), 122.1 (s, C-4a), 118.9 (d, C-8), 100.8 (d, C-3), 67.1 (t, C-1′), 40.7 (t, C-3′), 31.5 (t, C-2′); MS (EI, 70 eV): *m/z* (%) = 237 (2) [M^+], 221 (33) [M^+-O], 201 (5) [M^+-Cl], 186 (7), 173 (6), 160 (8) [M^+-C_3H_6Cl], 145 (100) [$C_9H_7NO^+$], 117 (18), 105 (8), 101 (8), 89 (13), 76 (14), 58 (76), 45 (47), 38 (12); HRMS (EI) ($C_{12}H_{12}NO_2Cl$): required: 237.05566, found: 237.05592.

4-(2,2-Dimethyl-3-hydroxypropyloxy)-quinoline-*N*-oxide (13b). According to general procedure I, 100 mg (556 µmol) of 4-chloroquinoline-*N*-oxide (**11**) were treated with 38.0 mg (668 µmol) KOH and 70.0 mg (668 µmol) 2,2-dimethylpropan-1,3-diol (**12b**) in 5 mL anhydrous THF. Purification by flash column chromatography (2 × 15 cm, EtOAc/MeOH 100/0 → 70/30) resulted in 105 mg (425 µmol, 76%) of compound **13b** as a colourless solid. TLC: R_f = 0.15 (EtOAc/MeOH 80/20) [UV]; IR (ATR): $\tilde{\nu}$ = 3229 cm^{-1} (w, OH), 2967 (w, CH), 2875 (w, CH), 1566 (m), 1465 (m), 1391 (m), 1281 (m), 1202 (w, NO), 1096 (m), 1052 (m), 965 (m), 829 (w), 757 (s, C_{ar}); ^{1}H-NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.57 (dd, ^3J = 8.7 Hz,^4J = 1.1 Hz, 1H, H-8), 8.22 (d, ^3J = 6.9 Hz, 1H, H-2), 8.04 (dd, ^3J = 8.3 Hz, ^4J = 1.0 Hz, 1H, H-5), 7.70 (ddd, ^3J = 8.7 Hz, ^3J = 7.0 Hz, ^4J = 1.0 Hz, 1H, H-7), 7.51 (ddd, ^3J = 8.3 Hz, ^3J = 7.0 Hz, ^4J = 1.1 Hz, 1H, H-6), 6.37 (d, ^3J = 6.9 Hz, 1H, H-3), 3.89 (s, 2H, H-1′), 3.62 (s, 2H, H-3′), 1.09 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 154.8 (s, C-4), 140.5 (s, C-8a), 136.4 (d, C-2), 131.1 (d, C-7), 127.9 (d, C-6), 122.4 (d, C-5), 122.4 (s, C-4a), 119.5 (d, C-8), 99.8 (d, C-3), 74.1 (t, C-1′), 67.8 (t, C-3′), 36.8 (s, C-2′), 21.7 (q, C-4′); MS (EI, 70 eV), *m/z* (%): 247 (2) [M^+], 231 (26) [M^+-O], 161 (9) [$C_9H_7NO_2^+$], 145 (100) [$C_9H_7NO^+$], 117 (9), 69 (8), 55 (8), 45 (8), 41 (13); HRMS (EI) ($C_{14}H_{17}NO_3$): required: 247.1209, found: 247.1207.

4-(3-Hydroxypropylthio)-quinoline-*N*-oxide (13c). According to general procedure I, 868 mg (4.83 mmol) of 4-chloroquinoline-*N*-oxide (**11**) were treated with 325 mg (5.79 mmol) KOH and 500 mL (534 mg, 5.79 mmol) 3-mercapto-1-propanol (**12b**) in 40 mL anhydrous THF. Purification by flash column chromatography (3 × 20 cm, EtOAc/MeOH 100/0 → 80/20) resulted in 1.05 g (4.25 mmol, 92%) of compound **13c** as a colourless solid. TLC: R_f = 0.11 (EtOAc/MeOH 80/20) [UV]; IR (ATR): $\tilde{\nu}$ = 3117 cm^{-1} (w, CH), 3060 (w, CH), 1372 (m), 1290 (m), 1202 (vs, NO), 1135 (m), 1042 (m), 858 (w), 767 (vs, C_{ar}); ^{1}H-NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.58 (dd, ^3J = 8.6 Hz, ^4J = 1.2 Hz, 1H, H-8), 8.50 (d,^3J = 6.6 Hz, 1H, H-2), 8.18 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1H, H-5), 7.87 (ddd, ^3J = 8.6 Hz, ^3J = 6.9 Hz, ^4J = 1.1 Hz, 1H, H-7), 7.78 (ddd, ^3J = 8.3 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, H-6), 7.39 (d, ^3J = 6.6 Hz, 1H, H-3), 4.64 (t, ^3J = 5.2 Hz, 1H, OH), 3.54 (*virt*. q, $^3J \approx$ 5.6 Hz, 2H, H-3′), 3.22 (t, ^3J = 7.3 Hz, 2H, H-1′), 1.86-1.79 (m, 2H, H-2′); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 140.0 (s, C-4), 134.4 (d, C-2), 133.4 (s, C-8a), 130.5 (d, C-7), 128.8 (d, C-6), 127.8 (s, C-4a), 124.4 (d, C-5), 119.7 (d, C-8), 118.2 (d, C-3), 59.0 (t, C-3′), 31.2 (t, C-1′), 27.9 (t, C-2′); MS (EI, 70 eV), *m/z* (%): 235 (100) [M^+], 219 (10) [M^+-O], 177 (83) [$C_9H_7NOS^+$], 161 (15) [$C_9H_7NS^+$], 145 (10) [$C_9H_7NO^+$], 129 (7) [$C_9H_7N^+$], 117 (10), 104 (6), 89 (9), 77 (9), 43 (12); HRMS (EI) ($C_{12}H_{13}NO_2S$): required: 235.0667, found: 235.0662.

4-(2,2-Dimethyl-3-hydroxypropylthio)-quinoline-*N*-oxide (13d). According to general procedure I, 100 mg (556 µmol) of 4-chloroquinoline-*N*-oxide (**11**) were treated with 38.0 mg (668 µmol) KOH and 80.0 mg (668 µmol) 2,2-dimethyl-3-hydroxypropanol (**12b**) in 5 mL anhydrous THF. Purification by flash column chromatography (2 × 15 cm, EtOAc/MeOH 100/0 → 70/30) resulted in 116 mg (440 µmol, 79%) of compound **13d** as a colourless solid. TLC: R_f = 0.36 (EtOAc/MeOH 80/20) [UV]; IR (ATR): $\tilde{\nu}$ = 2957 cm^{-1} (w, CH), 1494 (w), 1465 (w), 1421 (w), 1362 (m), 1266 (w), 1202 (w), 1047 (m), 849 (w), 728 (s, C_{ar}); ^{1}H-NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.58 (dd, ^3J = 8.6 Hz, ^4J = 1.2 Hz, 1H, H-8), 8.48 (d, ^3J = 6.6 Hz, 1H, H-2), 8.25 (dd, ^3J = 8.3 Hz, ^4J = 1.3 Hz, 1H, H-5), 7.87 (ddd, ^3J = 8.6 Hz, ^3J = 6.9 Hz, ^4J = 1.3 Hz, 1H, H-7), 7.79 (ddd, ^3J = 8.3 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, H-6), 7.43 (d, ^3J = 6.6 Hz, 1H, H-3), 4.79 (t, ^3J = 5.3 Hz, 1H, OH), 3.28 (d, ^3J = 5.3 Hz, 1H, H-3′), 3.13 (s, 2H, H-1′), 1.00 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 154.8 (s, C-4), 140.5 (s, C-8a), 136.4 (d, C-2), 131.1 (d, C-7), 127.9 (d, C-6), 122.4 (d, C-5), 122.4 (s, C-4a), 119.5 (d, C-8), 99.8 (d, C-3), 74.1 (t, C-1′), 67.8 (t, C-3′), 36.8 (s, C-2′), 21.7 (q, C-4′); MS (EI, 70 eV), *m/z* (%): 263 (23) [M^+], 247 (100) [M^+-O], 216 (16), 174 (59) [$C_{10}H_8NS^+$], 161 (91) [$C_9H_7NS^+$], 149 (26), 134 (16), 117 (20), 101 (15), 89 (17), 69 (23), 55 (31), 41 (26); HRMS (EI) ($C_{14}H_{17}NO_2S$): required: 263.0979, found: 263.0976.

4-(3-Chloropropyloxy)-2-quinolone (14a). 530 mg (2.23 mmol) of compound **13a** were dissolved in 80 mL anhydrous MeOH under argon. The solution was irradiated (Original Hanau TQ 150, Duran filter) in an immersion apparatus (UV-RS-1, UV-consulting Peschl, Mainz) until the conversion was complete (20 min). The solvent was removed and the product mixture was purified by flash column chromatography on silica gel (3 × 10 cm, EtOAc/MeOH 95/5). Compound **14a** was obtained as a colourless solid (424 mg, 1.78 mmol, 80%). mp: 163–165 °C; TLC: R_f = 0.30 (EtOAc) [UV]; IR (KBr): $\tilde{\nu}$ = 3428 cm^{-1} (br, NH), 2951 (s, $C_{ar}H$), 2830 (s, $C_{al}H$), 1647 (vs, C═O), 1220 (s), 754 (w); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.35 (s, 1H, NH), 7.82 (d, ^3J = 8.0 Hz, 1H, H-5), 7.52 (*virt*. t, $^3J \approx$ 7.0 Hz, 1H, H-7), 7.28 (d, ^3J = 8.2 Hz, 1H, H-8), 7.16 (*virt*. t, $^3J \approx$ 7.1 Hz, 1H, H-6), 5.90 (s, 1H, H-3), 4.24 (t, ^3J = 5.9 Hz, 2H, H-11), 3.87 (t, ^3J = 6.5 Hz, 2H, H-13), 2.28 (virt. quint., $^3J \approx$ 6.2 Hz, 2H, H-12); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ [ppm] = 163.1 (s, C-4), 162.0 (s, C-2), 138.5 (s, C-8a), 130.8 (d, C-7), 122.2 (d, C-5), 121.2 (d, C-6), 115.0 (s, C-4a), 114.4 (d, C-8), 97.0 (d, C-3), 65.1 (t, C-1′), 41.8 (1, C-3′), 31.1 (t, C-2′); MS (EI, 70 eV): *m/z* (%) = 221 (33) [M^+-O], 186 (2), 170 (1), 159 (6), 145

(100) [$C_9H_7NO^+$], 130 (1), 128 (6), 117 (23), 101 (7), 89 (11), 77 (10) [$C_6H_5^+$], 75 (10), 63 (5), 51 (5), 41 (18); HRMS (EI) ($C_{12}H_{12}ClNO$): required: 221.06075 [$M^{+\cdot}-O$], found: 221.06074.

General procedure II. Photochemical rearrangements of *N*-oxides in a continuous flow reactor. A double coiled tubular flow reactor (Duran tube 7 mm, coil outer diameter: 75 mm, height: 200 mm, internal volume: 150 mL) connected to a Heidolph 5001 peristaltic pump was pre-filled with distilled methanol and placed in the middle of Rayonet (RPR-100) photoreactor equipped with 16 lamps of the given wavelength. Reaction progress was monitored by UV-Vis spectroscopy passing the outlet stream of the flow reactor through a 1 mm flow cuvette and measuring the remaining absorbance of the *N*-oxide at a wavelength appropriate for the respective starting material. The quinoline-*N*-oxide was dissolved in distilled methanol ($c \approx 6$ mmol L^{-1}) in a septum stoppered flask and subsequently saturated with oxygen by bubbling a stream of oxygen into the solution for five minutes. The solution was pumped through the reactor with the given flow rate. The product solution was collected in a septum stoppered flask which was filled with inert gas and equipped with a balloon for pressure equalization. The reactor was flushed with distilled methanol until the detected absorbance was approximately zero. Before removing the collected solvents *in vacuo*, the product solution as well as the emptied flask of the starting material were purged with inert gas to remove the highly flammable oxygen/methanol vapour mixture. The crude product was purified by flash column chromatography on silica gel.

4-(2,2-Dimethylpropyloxy)-2-quinolone (14b). According to general procedure II, 1.20 g (4.85 mmol) of quinoline-*N*-oxide **13b** were dissolved in 800 mL MeOH and irradiated at a flow rate of 2.0 mL min^{-1} at λ = 366 nm. Purification by flash column chromatography (4 × 20 cm, EtOAc/MeOH 100/0 → 60/40) resulted in 1.16 g (4.69 mmol, 97%) of compound **14b** as a colourless solid. TLC: R_f = 0.43 (EtOAc/MeOH 80/20) [UV]; IR (ATR): $\tilde{\nu}$ = 3356 cm^{-1} (w, OH), 1631 (vs, C═O), 1602 (s, NH), 1415 (m), 1381 (s), 1251 (m), 1222 (s), 1159 (m), 1117 (m), 1059 (s), 1015 (m), 972 (m), 828 (m), 756 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.32 (s, 1H, NH), 7.80 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 1H, H-5), 7.50 (ddd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.3 Hz 1H, H-7), 7.27 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1H, H-8), 7.17 (ddd, ^3J = 8.2 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-6), 5.82 (s, 1H, H-3), 4.68 (t, ^3J = 5.4 Hz, 1H, OH), 3.83 (s, 2H, H-1′), 3.34 (d, ^3J = 5.4 Hz, 2H, H-3′), 0.99 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 163.2 (s, C-2), 162.5 (s, C-4), 138.5 (s, C-8a), 130.8 (d, C-7), 122.1 (d, C-5), 121.3 (d, C-6), 115.0 (s, C-4a), 114.7 (d, C-8), 96.7 (d, C-3), 73.3 (t, C-1′), 66.6 (t, C-3′), 36.3 (s, C-2′), 21.4 (q, C-4′); MS (EI, 70 eV), *m/z* (%): 247 (26) [M^+], 162 (100) 133 (10) [$C_8H_7NO^+$], 119 (14), [$C_7H_5NO^+$], 41 (7); HRMS (EI) ($C_{14}H_{17}NO_3$): required: 247.1209, found: 247.1205.

4-(3-Hydroxypropylthio)-2-quinolone (14c). According to general procedure II, 585 mg (2.49 mmol) of quinoline-*N*-oxide **13c** were dissolved in 800 mL MeOH and irradiated at a flow rate of 3.5 mL min^{-1} at λ = 366 nm. Purification by flash column chromatography (4 × 20 cm, EtOAc/MeOH 100/0 → 50/50) resulted in 581 mg (2.47 mmol, 99%) of compound **14c** as a colourless solid. TLC: R_f = 0.54 (EtOAc/MeOH 80/20) [UV]; IR (ATR): $\tilde{\nu}$ = 3327 cm^{-1} (w, OH), 2832 (w, CH), 1644 (vs, C═O), 1596 (s, NH), 1498 (m), 1421 (m), 1372 (m), 1261 (m), 1062 (m), 965 (m), 747 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.55 (s, 1H, NH), 7.73 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, H-5), 7.53 (ddd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, H-7), 7.31 (dd, ^3J = 8.3 Hz, ^4J = 1.0 Hz, 1H, H-8), 7.19 (ddd, ^3J = 8.2 Hz, ^3J = 7.2 Hz, ^4J = 1.0 Hz, 1H, H-6), 6.34 (s, 1H, H-3), 4.67 (s, 1H, OH), 3.55 (t, ^3J = 5.7 Hz, 2H, H-3′), 3.13 (t, ^3J = 7.3 Hz, 2H, H-1′), 1.84 (*virt.* quin., $^3J \approx$ 6.5 Hz, 2H, H-2′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.1 (s, C-2), 149.8 (s, C-4), 137.7 (s, C-8a), 130.7 (d, C-7), 123.3 (d, C-5), 121.6 (d, C-6), 117.5 (s, C-4a), 115.7 (d, C-8), 113.9 (d, C-3), 59.2 (t, C-3′), 30.8 (t, C-1′), 26.5 (t, C-2′); MS (EI, 70 eV), *m/z* (%): 235 (74) [M^+], 188 (20), 178 (100) [$C_9H_8NOS^+$], 160 (8) [$C_9H_6NS^+$], 149 (29), 134 (9), 121 (9), 117 (17), 105 (10), 89 (13), 77 (12), 71 (9), 57 (24), 44 (14), 41 (17); HRMS (EI) ($C_{12}H_{13}NO_2S$): required: 235.0667, found: 235.0664.

4-(2,2-Dimethyl-3-hydroxypropylthio)-2-quinolone (14d). According to general procedure II, 1.03 g (3.92 mol) of quinoline-*N*-oxide **13d** were dissolved in 650 mL MeOH and irradiated at a flow rate of 4.5 mL min^{-1} at λ = 419 nm. Purification by flash column chromatography (4 × 25 cm, EtOAc/MeOH 100/0 → 80/20) resulted in 62 mg (235 µmol, 6%) of compound **13d** (starting material) and 705 mg (2.67 mmol, 68%, 72% b.o.r.s.m.) of compound **14d** as a colourless solid. TLC: R_f = 0.75 (EtOAc/MeOH 80/20) [UV]; IR (ATR): $\tilde{\nu}$ = 3294 cm^{-1} (w, OH), 2948 (w, CH), 2871 (w, CH), 1640 (vs, C═O), 1592 (s, NH), 1505 (m), 1424 (m), 1371 (m), 1073 (m), 967 (m), 760 (m), 737 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.54 (s, 1H, NH), 7.79 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1H, H-5), 7.52 (ddd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-7), 7.31 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1H, H-8), 7.19 (ddd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-6), 6.36 (s, 1H, H-3), 4.82 (t, ^3J = 5.5 Hz, 1H, OH), 3.28 (d, ^3J = 5.5 Hz, 2H, H-3′), 3.02 (s, 2H, H-1′), 1.00 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.2 (s, C-2), 150.6 (s, C-4), 137.6 (s, C-8a), 130.7 (d, C-7), 123.4 (d, C-5), 121.6 (d, C-6), 117.6 (s, C-4a), 115.7 (d, C-8), 114.1 (d, C-3), 68.8 (t, C-3′), 39.4 (t, C-1′), 36.2 (s, C-2′), 23.7 (q, C-4′); MS (EI, 70 eV), *m/z* (%): 263 (46) [M^+], 216 (8), 190 (55) [$C_{10}H_8NOS^+$], 178 (100) [$C_9H_8NOS^+$], 159 (13), 146 (36), 121 (9), 116 (10), 89 (8), 77 (10), 55 (21), 44 (21); HRMS (EI) ($C_{14}H_{17}NO_2S$): required: 263.0980, found: 263.0979.

4-(3-Iodopropyloxy)-2-quinolone (7a). A solution of 302 mg (1.27 mmol) quinolone **14a** in 20 mL anhydrous acetone was treated with 571 mg (3.81 mmol) NaI. Subsequently, the mixture was heated under reflux for 36 hours. Upon cooling to room temperature, silica gel was added, the solvent removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (2 × 12 cm, P/EtOAc 20/80). Compound **7a** was obtained as a yellow solid: 324 mg (0.98 mmol, 78%). mp.: 204–206 °C; TLC $R_{f=}$ 0.33 (EtOAc) [UV]; IR (KBr): $\tilde{\nu}$ = 3345 cm^{-1} (br, NH), 2858 (s, $C_{ar}H$), 1628 (vs, C═O), 1366 (s), 901 (m), 824 (m), 754 (m); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.35 (s, 1H, NH), 7.82 (d, ^3J = 8.0 Hz, 1H, H-5), 7.52 (virt. t, $^3J \approx$ 7.0 Hz, 1H, H-7), 7.28 (d, ^3J = 7.9 Hz, 1H, H-8), 7.17 (virt. t, $^3J \approx$ 7.1 Hz, 1H, H-6), 5.89 (s, 1H, H-3), 4.17 (t, ^3J = 5.9 Hz, 2H, H-1′), 3.46 (t, ^3J = 6.9 Hz, 2H, H-3′), 2.30 (*virt.* quint, $^3J \approx$ 6.5 Hz, 2H, H-2′); ^{13}C-NMR (90.6 MHz, DMSO-d_6). δ (ppm) = 164.0 (s, C-4), 163.0 (s, C-2), 139.5 (s, C-8a), 131.9 (d, C-7), 123.3 (d, C-5), 122.2 (d, C-6), 116.0 (s, C-4a), 115.4 (d, C-8), 98.0 (d, C-3), 69.0 (t, C-1′), 32.8 (1, C-2′), 4.7 (t, C-3′); MS (EI, 70 eV): *m/z*

(%) = 329 (4) [M^+], 312 (1), 279 (2), 237 (5), 201 (100), 186 (69), 172 (11), 161 (23) [$C_9H_7NO_2^+$], 146 (19), 132 (11), 119 (33), 93 (12), 77 (11) [$C_6H_5^+$], 65 (6), 51 (5), 41 (50); HRMS (EI) ($C_{12}H_{12}INO_2$): required: 328.99127, found: 328.99077.

4-(3-Iodopropylthio)-2-quinolone (8a). To a suspension of 100 mg (425 µmol) alcohol **14c** in 5 mL THF 122 mg (467 µmol) triphenylphosphane and 61 mg (892 µmol) imidazole were added at ambient temperature. Within five minutes 124 mg (489 µmol) iodine were added portionwise to the stirred reaction mixture. Stirring was continued for two hours and the reaction was quenched by addition of silica gel. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (1.5 × 20 cm, P/EtOAc 70/30 → 0/100, EtOAc/MeOH 80/20) and subsequent recrystallisation from acetonitrile. Compound **8a** was obtained as a colourless solid: 90.0 mg (261 µmol, 61%). TLC: R_f = 0.30 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2832 cm^{-1} (m, CH), 2740 (m, CH), 1640 (vs, C═O), 1567 (s, NH), 1500 (m), 1434 (m), 1366 (s), 1159 (m), 962 (w), 909 (w), 746 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.58 (s, 1H, NH), 7.72 (dd, ^3J = 8.3 Hz,^4J = 1.3 Hz, 1H, H-5), 7.53 (ddd, ^3J = 8.2 Hz,^3J = 7.2 Hz, ^4J = 1.3 Hz, 1H, H-7), 7.33 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, H-8), 7.20 (ddd,^3J = 8.3 Hz,^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, H-6), 6.34 (s, 1H, H-3), 3.41 (t, ^3J = 6.9 Hz, 2H, H-3′), 3.18 (t, ^3J = 7.2 Hz, 2H, H-1′), 2.17 (*virt.* quin.,$^3J \approx$ 7.1 Hz, 2H, H-2′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.1 (s, C-2), 149.0 (s, C-4), 137.8 (s, C-8a), 130.8 (d, C-7), 123.3 (d, C-5), 121.7 (d, C-6), 117.4 (s, C-4a), 115.7 (d, C-8), 114.2 (d, C-3), 31.2 (t, C-2′), 30.2 (t, C-1′), 5.9 (t, C-3′); MS (EI, 70 eV), *m/z* (%): 345 (81) [M^+], 218 (100) [M^+-IH], 190 (21) [$C_{10}H_8NOS^+$], 177 (29) [$C_9H_7NOS^+$], 156 (7), 148 (17) [$C_8H_6NS^+$], 116 (14) [$C_8H_6N^+$], 89 (15), 44 (30); HRMS (EI) ($C_{12}H_{12}INOS$): required: 344.9684, found: 344.9683.

General procedure III. Synthesis of mesylates **15**. The corresponding alcohol (1.0 equiv.) was dissolved in anhydrous DMF and the solution was cooled to 0 °C. Upon addition of 1.5 equiv. NEt_3, methanesulfonyl chloride (1.1 equiv.) was added dropwise at 0 °C to the stirred solution. The reaction was monitored by TLC. Upon complete conversion water (5 mL $mmol^{-1}$ alcohol) and ethyl acetate (10 mL $mmol^{-1}$ alcohol) were added. The layers were separated and the organic layer was washed with water (5 × 5 mL $mmol^{-1}$ alcohol). The combined aqueous layers were extracted with ethyl acetate (2 × 10 mL $mmol^{-1}$ alcohol). The combined organic layers were washed with brine (10 mL $mmol^{-1}$ alcohol), dried over Na_2SO_4 and filtered. After removal of the solvents *in vacuo* the crude product was of sufficient purity for the subsequent transformation into the corresponding iodide.

4-(2,2-Dimethyl-3-(methanesulfonyloxy)-propyloxy)-2-quinolone (15a). According to general procedure III, 300 mg (1.21 mmol) alcohol **14b**, 252 µL (184 mg, 1.82 mmol) NEt_3 and 103 µL (152 mg, 1.33 mmol) methanesulfonyl chloride were reacted in 12 mL anhydrous DMF. The reaction went to completion in four hours. After work-up 371 mg (1.05 mmol, 94%) compound **15a** was obtained as a colourless solid. TLC: R_f = 0.19 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 3157 cm^{-1} (w, NH), 2933 (w, CH), 2856 (w, CH), 1692 (s, C═O), 1630 (s, NH), 1436 (m), 1317 (w), 1337 (m), 1217 (s), 1188 (s), 1159 (s), 960 (m), 829 (s), 767 (s, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.34 (s, 1H, NH), 7.86 (dd, ^3J = 8.0 Hz,^4J = 1.3 Hz, 1H, H-5), 7.51 (ddd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.3 Hz, 1H, H-7), 7.28 (d, ^3J = 8.3 Hz, 1H, H-8), 7.17 (dd,^3J = 8.0 Hz, ^3J = 7.2 Hz, 1H, H-6), 5.89 (s, 1H, H-3), 4.19 (s, 2H, H-12), 3.92 (s, 2H, H-10), 3.16 (s, 3H, H-14), 1.11 (s, 6H, H-13); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 163.0 (s, C-2), 162.1 (s, C-4), 138.5 (s, C-8a), 130.9 (d, C-7), 122.2 (d, C-5), 121.3 (d, C-6), 115.1 (s, C-4a), 114.4 (d, C-8), 97.1 (d, C-3), 74.4 (t, C-10), 72.5 (t, C-12), 36.2 (q, C-14), 35.2 (s, C-11), 20.9 (q, C-13); MS (EI, 70 eV), *m/z* (%): 325 (9) [M^+], 275 (30), 247 (10) [M^+-SO_2CH_3) + H], 161 (100) [$C_9H_7NO_2^+$], 133 (15), 119 (22) [$C_7H_5NO^+$], 105 (9), 77 (8), 69 (67), 55 (10), 41 (38); HRMS (EI) ($C_{15}H_{19}NO_5S$): required: 325.0984, found: 325.0983.

4-(2,2-Dimethyl-3-(methanesulfonyloxy)-propylthio)-2-quinolone (15b). According to general procedure III, 300 mg (1.14 mmol) alcohol **14d**, 238 µL (173 mg, 1.71 mmol) NEt_3 and 97.1 µL (144 mg, 1.26 mmol) methanesulfonyl chloride were reacted in 12 mL anhydrous DMF. The reaction went to completion in three hours. After work-up 358 mg (1.05 mmol, 92%) compound **15b** was obtained as a colourless solid. TLC: R_f = 0.15 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2919 cm^{-1} (w, CH), 2837 (w, CH), 1644 (vs, C═O), 1586 (s, NH), 1503 (w), 1426 (w), 1367 (m), 1338 (m), 1178 (m), 956 (s), 844 (s), 752 (m, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.57 (s, 1H, NH), 7.81 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 1H, H-5), 7.54 (ddd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-7), 7.32 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1H, H-8), 7.21 (ddd, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, H-6), 6.42 (s, 1H, H-3), 4.11 (s, 2H, H-3′), 3.21 (s, 3H, H-14), 3.14 (s, 2H, H-1′), 1.12 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.1 (s, C-2), 149.7 (s, C-4), 137.7 (s, C-8a), 130.8 (d, C-7), 123.4 (d, C-5), 121.6 (d, C-6), 117.5 (s, C-4a), 115.7 (d, C-8), 114.6 (d, C-3), 75.9 (t, C-3′), 38.4 (t, C-1′), 36.3 (q, O_2SCH_3), 35.2 (s, C-2′), 23.1 (q, C-4′); MS (EI, 70 eV), *m/z* (%): 341 (90) [M^+], 262 (100) [M^+-SO_2CH_3)], 232 (21) [$C_{13}H_{14}NOS^+$], 216 (12), 190 (77) [$C_{10}H_8NOS^+$], 159 (16), 148 (17) [$C_8H_6NS^+$], 116 (11) [$C_8H_6N^+$], 89 (11), 79 (13), 55 (24), 41 (24); HRMS (EI) ($C_{15}H_{19}NO_4S_2$): required: 341.0756, found: 341.0750.

General procedure IV. Iodo-de-mesylation of mesylates **15**. The mesylate (1.0 equiv.) was dissolved in anhydrous DMF. NaI (4.0 equiv.) was added and the reaction mixture was heated to 140 °C for 12 hours. Upon cooling to room temperature, water (5 mL $mmol^{-1}$ mesylate) and ethyl acetate (10 mL $mmol^{-1}$ mesylate) were added. The layers were separated and the organic layer was washed with brine (5 × 5 mL $mmol^{-1}$ mesylate). The combined aqueous layers were extracted with ethyl acetate (2 × 10 mL $mmol^{-1}$ mesylate). The combined organic layers were dried over Na_2SO_4 and filtered. After removal of the solvents *in vacuo* the crude product was purified by flash column chromatograpy on silica gel (2.5 g $mmol^{-1}$ mesylate).

4-(2,2-Dimethyl-3-iodopropyloxy)-2-quinolone (7b). According to general procedure IV, 300 mg (922 µmol) mesylate **15a** and 551 mg (3.69 mmol) NaI were reacted in 15 mL anhydrous DMF. After work-up and purification by flash column chromatography on silica gel (2 × 20 cm, P/EtOAc 50/50 → 0/100) compound **7b** was obtained as a colourless solid; 131 mg (367 µmol, 40%). TLC: R_f = 0.26 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2948 cm^{-1} (w, CH), 2861 (w, CH), 1615 (vs, C═O), 1596 (s, NH), 1498 (m), 1406 (m), 1252 (w), 1169 (m), 1105 (s), 747 (vs, C_{ar}).;

^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.36 (s, 1H, NH), 7.85 (dd, ^3J = 8.3 Hz, ^4J = 1.4 Hz, 1H, H-5), 7.52 (ddd, ^3J = 8.7 Hz, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H-7), 7.28 (dd, ^3J = 8.7 Hz, ^4J = 1.1 Hz, 1H, H-8), 7.18 (ddd,^3J = 8.3 Hz,^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, H-6), 5.88 (s, 1H, H-3), 3.93 (s, 2H, H-3′), 3.48 (s, 2H, H-1′), 1.17 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 163.0 (s, C-2), 162.1 (s, C-4), 138.5 (s, C-8a), 130.9 (d, C-7), 122.2 (d, C-5), 121.3 (d, C-6), 115.1 (s, C-4a), 114.4 (d, C-8), 97.0 (d, C-3), 74.4 (t, C-1′), 35.5 (s, C-2′), 23.7 (t, C-3′), 20.3 (q, C-4′); MS (EI, 70 eV), *m/z* (%): 357 (13) [M$^+$], 229 (55), 214 (100), 186 (11) [$C_{11}H_8NO_2^+$], 172 (24), 119 (7) [$C_7H_5NO^+$], 69 (67), 41 (12); HRMS (EI) ($C_{14}H_{16}INO_2$): required: 357.0226, found: 357.0221.

4-(2,2-Dimethyl-3-iodopropylthio)-2-quinolone (8b). According to general procedure IV, 300 mg (879 µmol) mesylate **15b** and 525 mg (3.51 mmol) NaI were reacted in 15 mL anhydrous DMF. After work-up and purification by flash column chromatography on silica gel (2 × 20 cm, P/EtOAc 50/50 → 0/100) compound **8b** was obtained as a colourless solid; 166mg (445 µmol, 51%). TLC: R_f = 0.31 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2962 cm^{-1} (w, CH), 2827 (w, CH), 1639 (vs, C═O), 1586 (m, NH), 1503 (m), 1426 (w), 1367 (m), 1372 (m), 1207 (w), 956 (w), 829 (w), 762 (w), 742 (s, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.58 (s, 1H, NH), 7.81 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 1H, H-5), 7.53 (ddd, ^3J = 8.2 Hz, ^3J = 7.3 Hz, ^4J = 1.2 Hz, 1H, H-7), 7.32 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, H-8), 7.20 (ddd, ^3J = 8.1 Hz, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1H, H-6), 6.41 (s, 1H, H-3), 3.45 (s, 2H, H-3′), 3.17 (s, 2H, H-1′), 1.19 (s, 6H, H-4′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.1 (s, C-2), 149.7 (s, C-4), 137.7 (s, C-8a), 130.8 (d, C-7), 123.5 (d, C-5), 121.7 (d, C-6), 117.5 (s, C-4a), 115.7 (d, C-8), 114.6 (d, C-3), 40.8 (t, C-1′), 34.5 (s, C-2′), 25.9 (q, C-4′), 22.8 (t, C-3′); MS (EI, 70 eV), *m/z* (%): 373 (100) [M$^+$], 246 (31) [M$^+$-I], 190 (98) [$C_{10}H_8NOS^+$], 172 (25), 148 (14) [$C_8H_6NS^+$], 116 (10) [$C_8H_6N^+$], 89 (15), 77 (10), 69 (42), 41 (33); HRMS (EI) ($C_{14}H_{16}INOS$): required: 372.9997, found: 372.9990.

Cyclisation Experiments

4-Propyloxy-2-quinolone (19a). 30.0 mg (9.00 µmol) of compound **7a** were dissolved under argon in 6 mL toluene. After addition of 2.44 µL (2.93 mg, 9.00 µmol) Bu_3SnCl, 11.3 mg (18.0 µmol) $NaCNBH_3$ and 45.0 µL (45.0 µmol, 1.00 M in hexane) triethylborane the reaction mixture was saturated with oxygen and stirred for three days. Silica gel was added and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatograpy on silica gel (2 × 6 cm, EtOAc/EtOH 75/25). The deiodinated product **19a** was obtained as a colourless, crystalline solid: 18.3 mg (9.00 µmol, 100%). mp.: 171-173 °C; TLC R_f = 0.64 (EtOAc/EtOH 75/25) [UV]; ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.30 (s, 1H, NH), 7.79–7.76 (m, 1H, H-5), 7.50 (virt. t, $^3J \approx$ 6.9 Hz, 1H, H-7), 7.28 (d, ^3J = 8.2 Hz, 1H, H-8), 7.16 (virt. t, $^3J \approx$ 8.1 Hz, 1H, H-6), 5.86 (s, 1H, H-3), 4.33 (t, ^3J = 5.1 Hz, 2H, H-1′), 1.35–1.23 (m, 2H, H-2′), 1.06 (t, ^3J = 7.0 Hz, 3H, H-3′); ^{13}C-NMR: (90.6 MHz, DMSO-d_6): δ (ppm) = 167.0 (s, C-4), 163.2 (s, C-2), 138.5 (s, C-8a), 131.4 (d, C-7), 128.5 (d, C-5), 122.2 (d, C-6), 121.1 (s, C-4a), 115.0 (d, C-8), 96.8 (d, C-3), 67.7 (t, C-1′), 29.7 (1, C-2′), 13.8 (t, C-1′). The analytical data were in accord with literature values.[31]

General procedure V. Successful and attempted radical cyclisation reactions of substrates **7–8**. Under argon a solution of the respective iodide (1.0 equiv.) in anhydrous toluene or trifluorotoluene was brought to the temperature indicated in Table 1 or 2. For the entries in Table 2, template (+)-**1** (2.5 equiv.) was also dissolved in reaction mixture. Triethylborane (0.25–0.50 equiv., 1 M in hexane) and the hydride source (2.0 equiv.) were added. Upon saturation with oxygen, the reaction was stirred until the reaction was complete. In some cases a second addition of triethylborane was required to achieve a complete conversion. In this case, the flask was purged with argon, triethylborane (0.25–0.50 equiv., 1 M in hexane) was added and the solution was again saturated with oxygen (CAUTION: The triethylborane must always be added under inert gas atmosphere directly into the solution. The syringe needle should be below the solvent surface. In an oxygen atmosphere even a 1 molar solution of triethyl borane is highly pyrophoric). The reaction was quenched by addition of silica gel (2.5 g mmol^{-1} iodide) and the solvents were removed *in vacuo*. The crude product was purified by flash column chromatograpy on silica gel. The results of the individual reactions are listed in Tables 1 and 2. The reactions of substrates **6** and the analytical data of products **16a** and **17** have been reported previously.[22] Representative examples and analytical data for yet unreported compounds are given below.

4-(2,2-Dimethylpropyloxy)-2-quinolone (19b). According to general procedure V (Table 1, entry 4), 30.0 mg (84.0 µmol) iodide **7b**, 21.0 µL (21.0 µmol) triethylborane (1 M in hexane) and 44.5 µL (49.0 mg, 168 µmol) Bu_3SnH were reacted in 9 mL anhydrous toluene (c = 7.5 mM) at ambient temperature. After 24 hours 21.0 µL (21.0 µmol) triethylborane (1 M in hexane) were added. The reaction was complete after 48 hours. Purification by flash column chromatography on silica gel (1 × 15 cm, P/EtOAc 50/50 → 0/100, EtOAc/MeOH 80/20) gave 18.3 mg (79.1 µmol, 94%) of compound **19b** as a colourless solid. TLC: R_f = 0.18 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2851 cm^{-1} (w, CH), 1640 (vs, C═O), 1606 (s, NH), 1500 (w), 1434 (m), 1395 (m), 1227 (vs), 1112 (m), 996 (m), 819 (m), 746 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.30 (s, 1H, NH), 7.82 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz 1H, H-5), 7.51 (ddd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, ^4J = 1.5 Hz, 1H, H-7), 7.28 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1H, H-8), 7.18 (ddd,^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-6), 5.84 (s, 1H, H-3), 3.78 (s, 2H, H-1′), 1.07 (s, 9H, H-3′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 163.1 (s, C-2), 162.4 (s, C-4), 138.5 (s, C-8a), 130.8 (d, C-7), 122.0 (d, C-5), 121.3 (d, C-6), 115.1 (s, C-4a), 114.6 (d, C-8), 96.7 (d, C-3), 77.4 (t, C-1′), 31.4 (s, C-2′), 26.2 (q, C-3′); MS (EI, 70 eV), *m/z* (%): 231 (64) [M$^+$], 214 (16), 161 (100) [$C_9H_7NO_2^+$], 133 (12), 119 (20) [$C_7H_5NO^+$], 71 (20), 55 (13), 43 (45); HRMS (EI) ($C_{14}H_{17}NO_2$): required: 231.1259, found: 231.1252.

3,3-Dimethyl-2*H*,4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one (21b). According to general procedure V (Table 1, entry 5), 30.0 mg (84.0 µmol) iodide **7b**, 21.0 µL (21.0 µmol) triethylborane (1 M in hexane) and 51.8 µL (41.9 mg, 116 µmol) TMS_3SiH were reacted in 9 mL anhydrous toluene (c = 7.5 mM) at ambient temperature. After 24 hours 21.0 µL (21.0 µmol) triethylborane (1 M in hexane) were added. The reaction was complete after 48 hours. Purification by flash column chromatography on silica gel (1 × 15 cm, P/EtOAc 50/50 → 0/100, EtOAc/MeOH 80/20) gave 3.72 mg (14.3 µmol, 17%) of compound **21b** and 12.8 mg

(55.4 µmol, 66%) of compound **19b** as colourless solids. TLC: R_f = 0.28 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2967 cm^{-1} (w, CH), 1634 (br m, C═O), 1566 (m, NH), 1387 (m), 1281 (w), 1212 (m), 1087 (w), 970 (m), 824 (w), 762 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.41 (s, 1H, NH), 7.73 (dd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, 1H, H-10), 7.46 (ddd, ^3J = 8.3 Hz, ^3J = 7.1 Hz, ^4J = 1.3 Hz, 1H, H-8), 7.27 (dd, ^3J = 8.3 Hz, ^4J = 1.0 Hz, 1H, H-7), 7.15 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.0 Hz, 1H, H-9), 3.92 (s, 2H, H-2), 2.24 (s, 2H, H-4), 1.00 (s, 6H, CH_3); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 162.7 (s, C-5), 155.5 (s, C-10b), 137.0 (s, C-6a), 129.8 (d, C-8), 121.5 (d, C-10), 121.1 (d, C-9), 114.9 (d, C-7), 114.0 (s, C-10a), 105.9 (s, C-4a), 75.0 (t, C-2), 32.8 (t, C-4), 27.5 (s, C-3), 24.4 (q, CH_3); MS (EI, 70 eV), *m/z* (%): 229 (50) [M^+], 214 (100) [M^+-CH_3], 186 (9) [$C_{11}H_8NO_2^+$], 172 (25), 43 (13); HRMS (EI) ($C_{14}H_{15}NO_2$): required: 229.1103, found: 229.1101.

4-Propylthio-2-quinolone (20a). According to general procedure V (Table 1, entry 6), 50.0 mg (145 µmol) iodide **8a**, 72.5 µL (72.5 µmol) triethylborane (1 M in hexane) and 76.7 µL (84.4 mg, 290 µmol) Bu_3SnH were reacted in 20 mL anhydrous toluene (c = 7.5 mM) at ambient temperature. After 24 hours 72.5 µL (72.5 µmol) triethylborane (1 M in hexane) were added. The reaction was complete after 48 hours. Purification by flash column chromatography on silica gel (1 × 18 cm, P/Et_2O 70/30 → 0/100, EtOAc/MeOH 100/0 → 80/20) gave 18.0 mg (82.0 mmol, 57%) of compound **20a** and 9.00 mg (41.0 µmol, 28%) of compound **18** (91/9 mixture of racemic diastereomers *trans*-**18** and *cis*-**18**; analytical data for compound *trans*-**18** are provided further below) as colourless solids. TLC: R_f = 0.30 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2837 cm^{-1} (w, CH), 1639 (vs, C═O), 1591 (s, NH), 1498 (m), 1431 (m), 1367 (m), 1178 (w), 955 (w), 829 (m), 738 (vs, C_{ar}); ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.57 (s, 1H, NH), 7.74 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1H, H-5), 7.53 (ddd, ^3J = 8.2 Hz, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, H-7), 7.31 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1H, H-8), 7.19 (ddd, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-6), 6.31 (s, 1H, H-3), 3.08 (t, ^3J = 7.2 Hz, 2H, H-1′), 1.73 (*virt.* sext., $^3J \approx$ 7.3 Hz, 2H, H-2′), 1.04 (t, ^3J = 7.3 Hz, 3H, H-3′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.1 (s, C-2), 149.8 (s, C-4), 137.8 (s, C-8a), 130.7 (d, C-7), 123.3 (d, C-5), 121.6 (d, C-6), 117.5 (s, C-4a), 115.7 (d, C-8), 114.0 (d, C-3), 31.6 (t, C-2′), 20.9 (t, C-1′), 13.2 (q, C-3′); MS (EI, 70 eV), *m/z* (%): 219 (46) [M^+], 202 (26), 177 (100) [$C_9H_7NOS^+$], 172 (7), 149 (33), 117 (7), 89 (7), 77 (7) [$C_6H_4^+$], 43 (12); HRMS (EI) ($C_{12}H_{13}NOS$): required: 219.0718, found: 219.0713.

4-(2,2-Dimethylpropylthio)-2-quinolone (20b). According to general procedure V (Table 1, entry 8), 20.0 mg (53.6 µmol) iodide **8b**, 26.8 µL (26.8 µmol) triethylborane (1 M in hexane) and 28.3 µL (31.1 mg, 107 µmol) Bu_3SnH were reacted in 7 mL anhydrous toluene (c = 7.5 mM) at ambient temperature. After 24 hours 26.8 µL (26.8 µmol) triethylborane (1 M in hexane) were added. The reaction was complete after 48 hours. Purification by flash column chromatography on silica gel (1 × 18 cm, P/Et_2O 70/30 → 0/100, EtOAc/MeOH 100/0 → 80/20) gave 3.80 mg (15.5 µmol, 29%) of compound **20b** and 5.90 mg (24.1 µmol, 45%) of compound **22b** as colourless solids. TLC: R_f = 0.31 (EtOAc) [UV]; ^{1}H-NMR (360 MHz, DMSO-d_6): δ (ppm) = 11.54 (s, 1H, NH), 7.81 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1H, H-5), 7.52 (ddd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, H-7), 7.31 (dd, ^3J = 8.4 Hz, ^4J = 1.3 Hz, 1H, H-8), 7.19 (ddd, ^3J = 8.2 Hz, ^3J = 7.2 Hz, ^4J = 1.3 Hz, 1H, H-6), 6.37 (s, 1H, H-3), 3.03 (s, 2H, H-1′), 1.09 (s, 9H, H-3′); ^{13}C-NMR (90.6 MHz, DMSO-d_6): δ (ppm) = 160.1 (s, C-2), 150.4 (s, C-4), 137.6 (s, C-8a), 130.7 (d, C-7), 123.4 (d, C-5), 121.6 (d, C-6), 117.6 (s, C-4a), 115.6 (d, C-8), 114.2 (d, C-3), 43.7 (t, C-1′), 31.5 (s, C-2′), 28.7 (q, C-3′).

***trans*-2,3,4a,10b-Tetrahydro-1-thiapyrano[3,2-*c*]quinolin-5(6*H*)-one (18).** According to general procedure V (Table 2, entry 8), 20.0 mg (58.0 µmol) iodide **8a**, 51.1 mg (145 µmol) template (+)-**1**, 29.0 µL (29.0 µmol) triethylborane (1 M in hexane) and 35.8 µL (28.9 mg, 116 µmol) TMS_3SiH were reacted in 8 mL anhydrous trifluorotoluene (*c* = 7.5 mM) at 0 °C. After 24 hours 21.0 µL (21.0 µmol) triethylborane (1 M in hexane) were added. The reaction was complete after 48 hours. Purification by flash column chromatography on silica gel (1 × 18 cm, P/Et_2O 70/30 → 0/100, EtOAc/MeOH 100/0 → 80/20) gave 9.80 mg (44.7 µmol, 77%) of compound *trans*-**18** (99% *ee*) and 2.80 mg (12.8 µmol, 22%) of compound **20a** as colourless solids. TLC: R_f = 0.46 (EtOAc) [UV]; IR (ATR): $\tilde{\nu}$ = 2914 cm^{-1} (w, CH), 1674 (vs, C═O), 1592 (m, NH), 1486 (m), 1376 (m), 1246 (m), 1035 (m), 838 (s), 746 (vs, C_{ar}). ^{1}H-NMR (360 MHz, $CDCl_3$): δ (ppm) = 7.84 (s, 1H, NH), 7.42 (d, ^3J = 7.7 Hz, 1H, H-10), 7.26–7.20 (m, 1H, H-8), 7.07 (*virt.* t, $^3J \approx$ 7.7 Hz, 1H, H-9), 6.75 (d, ^3J = 7.8 Hz, 1H, H-7), 4.02 (d, ^3J = 13.2 Hz, 1H, H-10b), 2.82–2.78 (m, 2H, H-2), 2.67 (*virt.* dq, ^2J = 14.2 Hz, $^3J \approx$ 3.4 Hz, 1H, H-4), 2.54 (dt, ^3J = 13.2 Hz, ^3J = 3.4 Hz, 1H, H-4a), 2.17 (*virt.* dquin., ^2J = 13.6 Hz, $^3J \approx$ 3.3 Hz, 1H, H-3), 1.80–1.67 (m, 1H, H-3), 1.49–1.35 (m, 1H, H-4); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 170.5 (s, C-5), 135.5 (s, C-6a), 128.4 (d, C-8), 125.8 (d, C-10), 124.0 (s, C-10a), 123.4 (d, C-9), 115.0 (d, C-7), 44.7 (d, C-10b), 42.3 (d, C-4a), 29.1 (t, C-2), 27.2 (t, C-3), 26.7 (t, C-4). MS (EI, 70 eV), *m/z* (%): 219 (67) [M^+], 186 (24), 172 (33), 159 (100) [$C_{10}H_9NO^+$], 146 (11), 129 (13) [$C_9H_7N^+$], 77 (6) [$C_6H_5^+$], 40 (8); HRMS (EI) ($C_{12}H_{13}NOS$): required: 219.0718, found: 219.0711. HPLC: t_R = 11.1 min, 13.2 min (AS-H, 1-hexane:isopropanol = 20:80, 1.0 mL/Min.).

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