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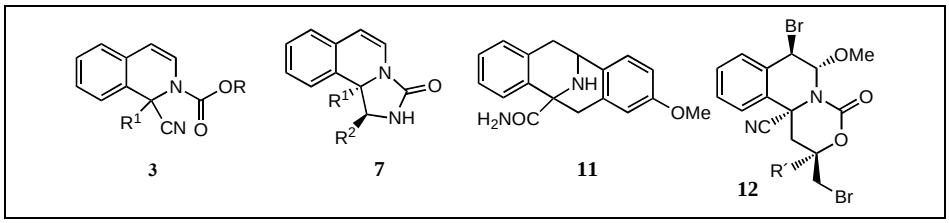
Received April 14, 2008



Reissert compounds **2** derived from isoquinoline, chloroformates and TMS-cyanide were alkylated in position 1. The resulting alkylation products **3** as well as the precursors **2** reacted with Grignard reagents affording imidazoisoquinolines **4**, **5**, **7** and **8** by addition to the cyano group and Grignard reduction or by twofold addition to the cyano group, respectively. In both cases the alcohol of the 2-alkoxycarbonyl moiety was eliminated by attack of the N-atom at the carbonyl carbon atom. Under acid conditions, 1-benzylated Reissert compound **3h** cyclised by attack of the resulting N-acyliminium C-atom at the *o*-position of the benzyl ring to form tetracyclic 1,3-bridged tetrahydroisoquinolines **10** and **11**. Bromocyclisation of 1-allyl-2-menthyloxycarbonyl-substituted Reissert compounds **3b, c** led to tricyclic dibromo products **12,** in which the menthol moiety was split off and addition to the enamine double bond occurred. A 2-menthyloxycarbonyl group in Reissert compounds **2a** and **3** failed to exert an asymmetric induction in all cases.

J. Heterocyclic Chem., **45**, 1651 (2008).

INTRODUCTION

Reissert compounds, *i.e.* *N*-acyl-1-cyano-1,2-dihydroisoquinolines, have been known for more than 100 years [1]. They are formed from isoquinolines or similar N-6-ring-heterocycles, acyl chlorides or acid anhydrides and cyanide *via* intermediate N-acyliminium salts. This reaction was originally used to transform acyl chlorides into aldehydes by final acid hydrolysis of the Reissert compounds. Following this, Reissert compounds were also recognized as useful intermediates for cyclic amino acids (benzo-annellated pipecolinic acids). Because of their acidity in position 1, Reissert compounds can be deprotonated and finally alkylated establishing a quaternary C-centre. Furthermore, they can serve as intermediates in the synthesis of condensed isoquinolines [2]. Asymmetric routes to condensed isoquinolines are interesting in the synthesis of natural products [3]. We became interested to apply such 1-alkylated 2-acyl-1-cyano-1,2-dihydroisoquinolines in intramolecular cyclisations in order to establish annellated dihydroisoquinolines. As one option, the chiral Reissert compound **2a** (R = (*R*)-menthyl) was chosen, which we recently made available by reaction of isoquinoline with chloro (-)-menthylformate and trimethylsilyl cyanide in the presence of $AlCl_3$ [4]. We expected that alkylation of such Reissert compounds could be stereoselective because of the presence of the menthyloxycarbonyl substituent. Recently, chiral 1-alkylated Reissert compounds became available by Shibasaki *et al.* carrying out asymmetric Reissert reactions of 1-alkylisoquinolines using BINOL-phosphineoxide-derived Lewis acids as chiral catalyst [5,6]. As 1-alkylisoquinolines are difficult to obtain and mainly commercially unavailable, the reversed synthetic sequence, *i.e.* firstly to transforming isoquinoline into Reissert compounds and then introducing the alkyl substituent by stereoselective alkylation would be a useful alternative. We further sought to introduce substituents in position 1 of Reissert compounds which allow fused isoquinolines to be established, such as imidazo[5,1-*a*]-isoquinolines, 1,4-oxazino[5,1-*a*]isoquinolines and 1,3-bridged isoquinolines.

RESULTS AND DISCUSSION

The 2-(*R*)-menthyloxycarbonyl Reissert compound **2a** (R = (*R*)-menthyl) was previously assigned by us to exist as a pure 1-(*S*)-diastereomer by comparison of measured data of optical rotation with calculated values [4]. However, as we achieved only modest asymmetric inductions when isoquinolinium salts derived from menthyloxycarbonyl chloride and isoquinoline were reacted with nucleophiles other than cyanide [7], investigation of the configuration of the Reissert compound **2a** was revisited. H^1 NMR spectrum of **2a** (R = (*R*)-menthyl) in DMSO-d_6, rather than chloroform as in our original publication, showed two sets of signal at 25 °C, 40 °C and 70 °C, *i.e.* no coalescence occurred. Furthermore, HPLC at a chiral phase revealed two peaks of identical integration. Finally, we succeeded in obtaining single crystals from the Reissert compound **2a** (R = (*R*)-menthyl) useful for X-ray crystal analysis. As

can be seen (Fig. 1), the compound exists as a 1:1 mixture of epimers even in the single crystal. All of these results request that our original configurational assignment [4] of the Reissert compound **2a** has to be revised. Instead of being a single 1-(*S*)-isomer, the compound is in fact a 1:1 mixture of 1-(*S*)/1(*R*) epimers (Fig. 1), *i.e.* the menthyloxycarbonyl group does not give any asymmetric induction in the addition of the cyanide to position 1 of isoquinoline in the formation of the Reissert product **2a**. This information was recently confirmed by Gibson *et al.* by NMR-investigations [8].

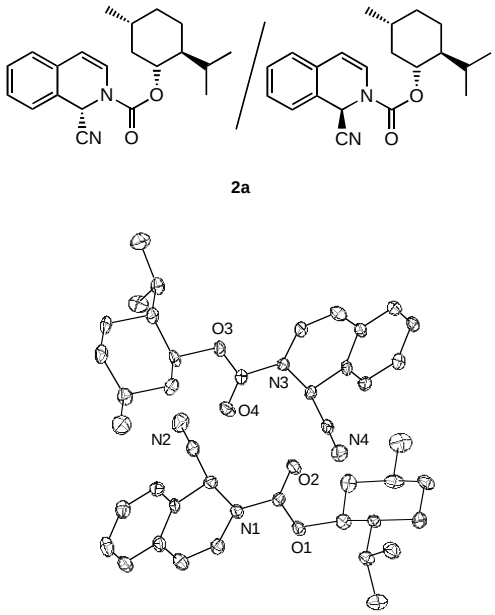
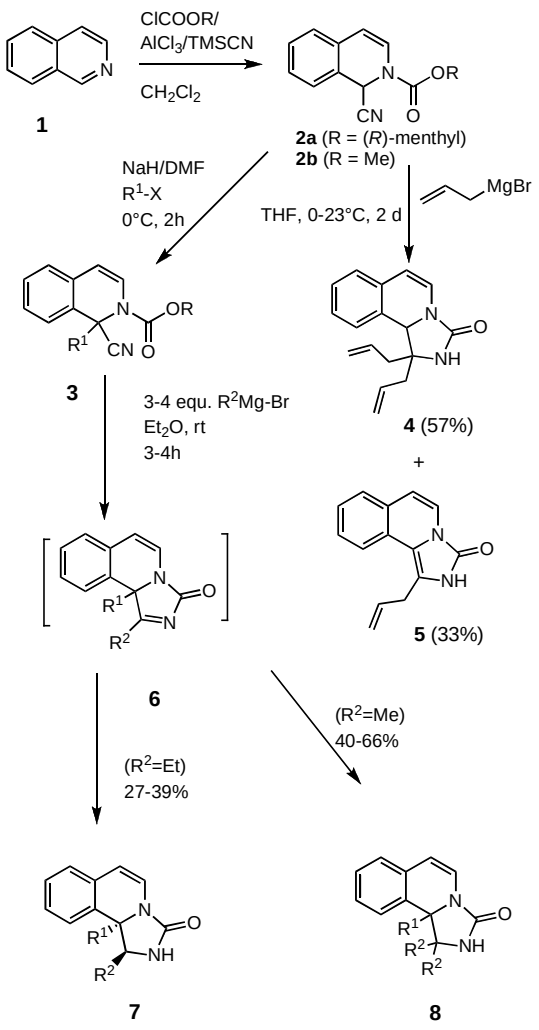


Figure 1. X-ray crystal analysis of Reissert product **2a** [23].

Regardless of this fact, we employed Reissert compound **2a** (R = (*R*)-menthyl) in alkylation reactions at position 1, taking into consideration that the possibility of the chiral auxiliary eventually giving an asymmetric induction in the reaction, when the site of attack is more congested. This is somewhat similar to the known reaction of **2a** with pivalaldehyde affording stereoselective formation of 1-(1-hydroxyalkyl)-1,2-isoquinolines [8]. Several bases, such as phenyl-Li [9], *n*Bu-Li [10], Na in xylene [11], KOH or NaOH under PTC [12], NaH [13], LDA [12,14], or *t*BuOK [15] were reported to achieve deprotonation of Reissert compounds at position 1 of the isoquinoline. Deprotonation-alkylation under phase transfer catalysis with chiral quaternary ammonium salts allowed stereoselective introduction of alkyl groups [16]. We deprotonated Reissert compounds **2a** with LDA in THF at -78 °C, similar to a previously used methylation protocol [4] or with NaH in DMF at 0 °C, and treated the resulting benzyl anions with alkylating reagents.

Scheme 1



The expected alkylation products **3** were obtained in both procedures, althoug NaH in DMF at 0 °C gave much better yields (Table 1). Two sets of signals were found in the NMR spectra of compounds **3** which gave coalescence upon heating to 50 °C, suggesting the existence of rotamers, as found before with 2-methoxycarbonyl-tetrahydroisoquinolines [17]. However, an almost racemic product was found when the (*R*)-menthyloxycarbonyl moiety was split off in a later transformation (*v. s.* formation of **8b**). Thus, unlike previous claims (the compound **13** of reference [4] was erroneously assigned as a single diastereomer) the alkylation of the Reissert compounds **2** did not occur stereoselectively, *i.e.* the products **3** are 1:1 epimers as their precursors **2**. Regardless of the non-stereoselective formation of alkylation products **3**, we tried to explore their synthetic potential at the functionality in the 1-alkyl group for building up more complex fused isoquinoline systems.

Table 1

1-Alkyl-1-cyano-2-(*R*)-menthyloxycarbonyl)-1,2-dihydroisoquinolines **3a-f** (R = (*R*)-menthyl) and corresponding 2-methoxcarbonyl compounds **3g, h** (R = Me).

3	R	R^1	X	Yield (%)
a	(*R*)-Menthyl	*n*-Bu	I	95
b	(*R*)-Menthyl	Allyl	Br	97
c	(*R*)-Menthyl	Methallyl	Cl	99
d	(*R*)-Menthyl	Bn	Cl	90[a]
			NEt_3^+ Cl^-	69[a, b]
e	(*R*)-Menthyl	2-BrBn	Cl	82
f	(*R*)-Menthyl	3-MeOBn	Br	89
g	Me	Allyl	Br	82
h	Me	Bn	Cl	86

[a] equimolar quantities of **2** and alkylating reagent were used [b] product contained 28 % of reactant **2**

For convenience, 1-alkylated Reissert compounds **3h** and **3g** bearing a non-chiral methoxycarbonyl moiety at the N-atom were also included.

Treatment of **3** with Grignard reagents showed an interesting dependence of the outcome of the reaction on the type of incoming substituent. Methyl and allyl magnesium bromide gave the racemic trisubstituted imidazo[5,1-*a*]isoquinolinone **8** by incorporating two allyl or methyl groups into the product. On the other hand, only one ethyl group was introduced when **3** were reacted with ethyl magnesium bromide and a further Grignard reduction took place rather than a Grignard addition. Thus a corresponding diethyl product **8** (R^2 = Et) was only found in traces (3 % yield) while **7** was obtained as major product. In both cases it can be assumed that the Reissert compounds **3** react primarily by addition of the Grignard reagent to the cyano group. This is followed by the resulting imine anion attacking the carbamate moiety at position 2 by cyclisation and elimination of menthol or methanol, affording imidazo[5,1-*a*]isoquinolinones **6**. The imine moiety of intermediate imidazoisoquinolinone **6** seems to be sterically shielded as a result of the occurrence of a Grignard reduction to **7** rather than a 1,2-addition taking place with ethyl magnesium bromide. If methyl or allyl magnesium bromide were used, no Grignard reduction was possible *per se*, and thus a second addition of the Grignard reagent occurred affording trialkyl products **8**. The structures of the imidazo[5,1-*a*]-isoquinolinones **7** and **8** were confirmed by several X-ray crystal analyses (see Figures 2-5). The *trans*-configuration of the alkyl substituents in compounds **7** can be understood by an attack of the Grignard-reagent in the Grignard-reduction of the intermediate **6** from the convex side of the bicyclic system.

Table 2

Imidazoisoquinolines **7** and **8**

Product	R^1	R^2	R in reactant **3**	yield (%)
7a	Allyl	Et	(R)-menthyl	39%
7b	Bn	Et	Me	27%
8a	*n*-Bu	Me	(R)-menthyl	66%
8b	Bn	Me	(R)-menthyl	40%[a]
			Me	65%
8c	Bn	Allyl	Me	51%

[a] 14 % ee, could be increased by recrystallisation, where the racemate crystallized preferably, thus increasing the ee in the mother liquor.

Non-alkylated Reissert compounds **2** can undergo a similar transformation into imidazo[5,1-*a*]isoquinolin-3-ones, as shown in the formation of the diallyl product **4** (55 % yield) upon treatment of **2a** with allyl magnesium

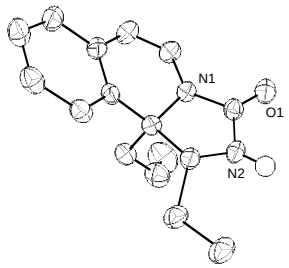


Figure 2. X-ray structure of imidazoisoquinoline **7a** [23].

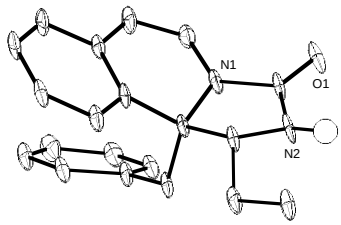


Figure 3. X-ray structure of imidazoisoquinoline **7b** [23].

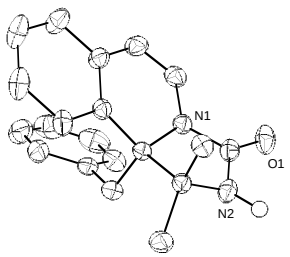


Figure 4. X-ray structure of imidazoisoquinoline **8b** [23].

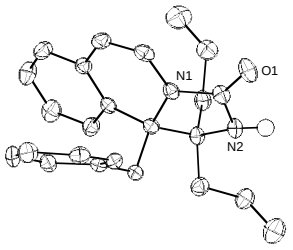
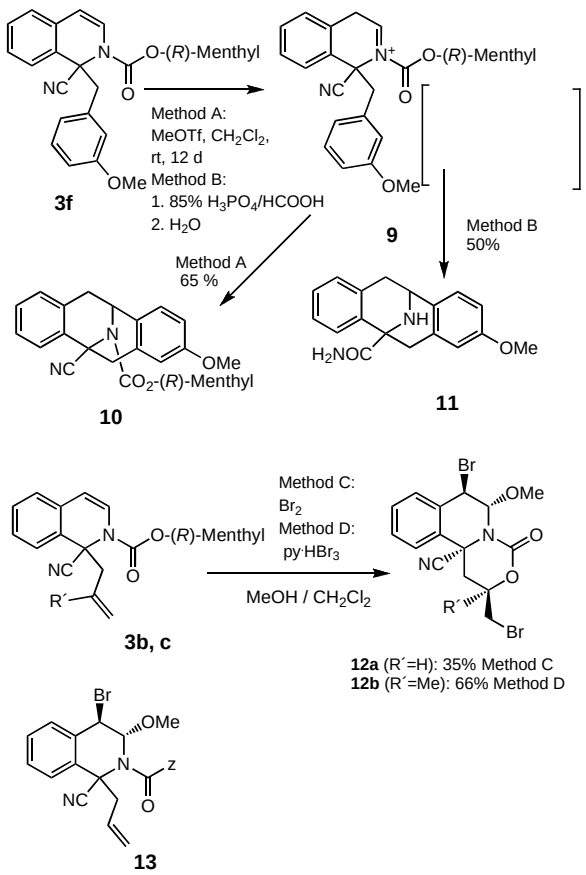


Figure 5. X-ray structure of imidazoisoquinoline **8c** [23].

bromide. Interestingly, the 1-allyl imidazo[5,1-*a*]iso-quinolin-3(2*H*)-one **5** was obtained as a by-product in 30 % yield, which was obviously formed by 1,3-H shift in the intermediate cyclisation product **6** (R^1 = H, R^2 = allyl). The Grignard reagent-mediated formation of imidazo[5,1-*a*]-isoquinolin-3-ones **4**, **5**, **7** and **8** represents a new access to this ring system. So far, cyclisation of Reissert compounds to imidazo[5,1-*a*]isoquinolines was implemented by the application of hydrogen peroxide, giving corresponding 1,3-diones [6]. A Reissert compound derived from *N*,*N*-dimethyl nicotinamide could be transformed to a hexahydroimidazo[1,5-*a*]pyridine by reduction with Mg in methanol [18].

Scheme 2



1-Benzylisoquinolines can be used to establish 1,3-bridged isoquinolines by intramolecular Mannich-type reaction [19]. This cyclisation however, has rarely been applied to Reissert compounds until now [20]. We treated the 1-(3-methoxybenzyl)-substituted Reissert compound **3f** with methyl triflate in dichloromethane (Method A). Our aim was the introduction of a methyl group in position 6 and subsequent cyclisation, but instead we obtained the dibenzo-9-azabicyclo[3.3.1]nonane **10**, which lacked a methyl group. Presumably the enamine moiety of **3h** was protonated by catalytic traces of triflic acid, followed by the resulting N-acyliminium salt **9** undergoing an intramolecular Mannich reaction at position 4 of the 3-methoxybenzyl substituent, thus giving product **10**. When the Reissert compound **3f** was treated with phosphoric acid in formic acid (Method B) and the resulting mixture worked up under aqueous conditions, hydrolysis of the cyano group and the carbamate took place resulting in the formation of dibenzo-9-azabicyclo-[3.3.1]nonane **11**. The structure of the cyclisation product **11** was unambiguously assigned by X-crystal structure analysis (as hydrochloride, see Fig. 6)

In order to verify a novel access to 1,4-oxazino[5,1-*a*]-isoquinolines we submitted 1-allyl and 1-methallyl-substituted Reissert compounds **3b** and **3c** to bromo cyclisation in methanol/dichloromethane as solvent. The 1,4-oxazino[5,1-*a*]isoquinolines **12** were formed where bromine and methoxide were also added to the acyl enamine moiety. The latter addition was previously observed with Reissert compounds which could not undergo cyclisation [21]. The application of yridinium tribromide (Method C) turned out to be advantageous

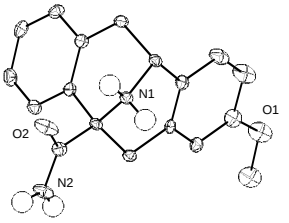


Figure 6 X-ray structure of **11** (as hydrochloride, anion not shown) [23]

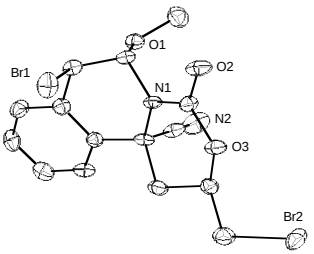


Figure 7 X-ray structure of oxazinoisoquinoline **12a** [23]

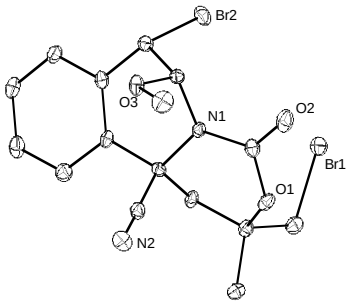


Figure 8 X-ray structure of oxazinoisoquinoline **12b** [23].

over elemental bromine (Method D) in this synthesis. A plausible explanation of this reaction outcome could be the transformation of the alkene double bond of the allyl moiety of **3** into a bromonium ion. Subsequent intramolecular attack at the carbonyl oxygen (rather than at the cyano nitrogen atom – Ritter-type reaction) atom would follow forming the oxazino ring, while the menthyloxy moiety is split off. The structure of the 1,4-oxazino[5,1-*a*]isoquinolines **12** were proved by X-ray crystal analysis (see Figures 7, 8). It reveals that the bromine atom is found at the concave side of the bowl shaped 1,4-oxazino[5,1-*a*]isoquinoline ring system. Since attack at bowl shaped ring systems occurs preferably from the convex side, it can be assumed that the bromo alkoxide addition to the enamine moiety occurred prior to the formation of the oxazine ring. This assumption is supported by the fact that we were able to isolate small quantities of the non-cyclised addition product **13**. Syntheses of the 1,4-oxazino[5,1-*a*]isoquinoline system are rare and so far this heterocycle has been obtained starting from 1-(2-hydroxyalkyl)-tetrahydroisoquinolines and chloroformate [22].

In summary, we revised configurational assignment of the Reissert compound **2a** obtained from (-)-(*R*)-menthylchloroformate and isoquinoline as a 1:1 epimeric mixture. Alkylation of this Reissert compound at position 1 gave products **3** with no or marginal diastereoselectivities. Reissert compounds **2** and **3** could be used to establish a number of new condensed isoquinolines, thus reaction with Grignard-reagents has afforded imidazoisoquinolines **4**, **7**, **8** in a new connective scheme. Under acid conditions, 1-(3-methoxybenzyl)-substituted Reissert compound **2f** underwent intramolecular Mannich reactions to tetracyclic isoquinolines similar to naturally occurring alkaloids. Bromocyclisation of 1-allyl-substituted Reissert compounds in methanol incorporated two bromo atoms and methoxide, affording new oxazinoisoquinolins **12** in a novel synthetic scheme.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively, on a Bruker AC-300 with TMS as internal standard. ESI-mass spectra were measured with Varian CH-7a MAT (EI 70 eV) LDQ FT Finnigan ESI with MeOH as solvent. Silica gel 60 (0.04-0.063 mm, Merck) was used for preparative column chromatography and a Chiracel-OD-column for chiral HPLC. Unless otherwise mentioned, chemicals were purchased. Compounds **2** (R = Me, (*R*)-menthyl) were obtained adopting reported procedures [4,24] (*v. i.*). Compound **2b** was reported before [24], but higher yields were obtained using the $AlCl_3$-assisted method with TMSCN.

General Procedure for the Synthesis of Alkylated Reissert Compounds 3. Reissert compound **2** (339 mg, 1.00 mmol) and alkylating reagent R^1-X (1.10 mmol) were dissolved in dry DMF (1 mL) and stirred under argon in an ice-bath. NaH (48 mg of a 60% suspension in mineral oil, 1.20 mmol) was added. Equimolar quantities of R^1-X led to incomplete conversion, *i.e.* products **3** contained starting materials **2**, which could not be removed by chromatography. The mixture became slightly brown, while a gas (H_2) evolved. After 2 h, excess of NaH was destroyed by addition of MeOH. After dilution with DCM (5 mL), the DMF was extracted by washing twice with water (5 mL). The DCM layer was dried with $MgSO_4$ and evaporated to dryness under reduced pressure. If necessary, the product can be purified by column chromatography with silica gel and DCM or cyclohexane/EtOAc (7:3). The substances are slightly coloured oils.

1-(*n*-Butyl)-1-cyano-2-[(*R*)-menthyloxycarbonyl]-1,2-dihydroisoquinoline (3a). The product was obtained in 95% yield following the general procedure using *n*-butyl iodide. ^{1}H-NMR ($CDCl_3$): δ = 0.60-2.20 (m, 27 H, menthyl + butyl); 2.53 (m, 1 H, butyl); 4.84 (m, 1 H, CH-O); 5.63 (t, 1 H, J = 6.89 Hz, CHCH-N); 6.97 (m, 2 H); 7.23 (m, 2 H); 7.52 ppm (m, 1 H). ^{13}C-NMR ($CDCl_3$): δ = 13.7; 16.1; 20.7; 21.9; 22.0; 23.2; 25.0; 26.3; 31.4; 34.0; 40.9; 47.1; 59.9; 77.8; 105.2 (CH-CH-N); 119.1 (CN); 124.6-129.1 (aromatic C and CH); 151.8 ppm (CO). *Anal*. Calcd. for $C_{25}H_{34}N_2O_2$ (394.55): C, 76.10; H, 8.69; N, 7.10. Found: C, 75.81; H, 8.96; N, 6.92.

1-Allyl-1-cyano-2-[(*R*)-menthyloxycarbonyl]-1,2-dihydroisoquinoline (3b). The product was obtained in 97 % yield following the general procedure using allyl bromide. ^{1}H-NMR ($CDCl_3$): δ = 0.6-2.3 (m, 18 H, menthyl); 2.70-2.85 (m, 1 H, $=CHCH_2$); 3.15-3.35 (m, 1 H, $=CHCH_2$); 4.75-4.95 (m, 1 H, CH-O); 4.95-5.15 (m, 2 H); 5.64 (m, 2 H); 6.80-7.60 ppm (m, 5H, $4CH_{ar}$ + CHCH-N). ^{13}C-NMR ($CDCl_3$): δ = 16.3; 20.8; 22.0; 23.4; 26.5; 31.6; 34.2; 41.1; 45.7 ($=CHCH_2$); 47.3; 59.8 (C_q); 78.2 (CHO); 105.4 (CH-CH-N); 118.6 (CN); 121.5 ($=CH_2$); 125-130 (aromatic C and CH); 152.0 ppm (C=O). HRMS (ESI) m/z: Calc. for $C_{24}H_{30}N_2O_2+H^+$ 379.2380, found 379.2380. *Anal*. Calcd. for $C_{24}H_{30}N_2O_2$ (378.51): C, 76.10; H, 8.69; N, 7.10. Found: C, 75.81; H, 8.96; N, 6.92.

1-Cyano-1-(2-methylallyl)-2-[(*R*)-menthyloxycarbonyl]-1,2-dihydroisoquinoline (3c). The product was obtained in 99 % yield following the general procedure using methallyl chloride. ^{1}H-NMR ($CDCl_3$): δ = 0.6-2.2 (m, 21H), menthyl + methyl), 2.71 (d, 1 H, J = 13.0 Hz, CH_2), 3.06 (d, 1 H, J = 13.0 Hz, CH_2), 4.53 (s, 1 H, $=CH_2$), 4.80(m, 2 H, $=CH_2$, CH-O), 5.63 (d, 1 H, J = 8.1 Hz, CHCH-N), 6.84 (d, 1 H, J = 7.9 Hz, CH_{ar}), 6.96 (m, 1H, CH_{ar}), 7.18 (m, 2 H, CH_{ar}), 7.54 ppm (m, 1H, CH_{ar}). ^{13}C-NMR ($CDCl_3$): δ = 15.6; 20.6; 21.8; 23.0; 23.3; 26.2; 31.3; 33.9; 40.8; 46.9; 47.6; 59.4 (C_q); 77.8 (CHO); 105.5 (CH-CH-N); 117.9 (CN); 118.9 ($=CH_2$);

124.4; 124.8; 126.7; 127.2 ; 128.7; 128.9; 129.2; 138.2; 151.7 ppm (CO). HRMS (EI) m/z: Calc. for $C_{25}H_{32}N_2O_2$: 392.2464, found 392.2465. *Anal*. Calcd. for $C_{25}H_{32}N_2O_2$ (392.53): C, 76.49; H, 8.22; N, 7.14. Found: C, 76.21; H, 8.41; N, 7.33.

1-Benzyl-1-cyano-2-[(*R*)-menthyloxycarbonyl]-1,2-dihydroisoquinoline (3d). The product was obtained in 74 % yield following the general procedure but using equimolar quantities of reactant 2 and benzyl chloride. If benzyltriethylammonium chloride was used under the same conditions 69 % of 3d was obtained together with 28 % of starting material 2. ^{1}H-NMR ($CDCl_3$): δ = 0.6-2.3 (m, 18 H, menthyl); 3.31 (t, 1 H, J = 12.6 Hz, ArCH); 3.60-3.95 (m, 1 H, ArCH); 4.70-5.00 (m, 1 H, CH-O); 5.42 (d, d, 1 H, J_1 = 7.18 Hz, J_2 = 8.12 Hz); 6.60-7.50 ppm (m, 9H, CH_{ar}). ^{13}C-NMR ($CDCl_3$): δ = 16.2; 20.9; 22.0; 23.2; 26.5; 31.5; 34.1; 41.0; 46.0 (CH_2Ph); 47.1; 60.8 (C-CN); 78.1; 105.4 (CH-CH-N); 118.8 (CN); 124.3; 124.7; 127.0; 127.2; 127.3; 127.6; 127.9; 128.0; 129.4; 130.8; 132.9; 152.0 ppm (CO). HRMS (EI): Calc. for $C_{28}H_{32}N_2O_2$: 428.2464, found: 428.2465. *Anal*. Calcd. for $C_{28}H_{32}N_2O_2$ (428.57): C, 78.47; H, 7.53; N, 6.54. Found: C, 78.27; H, 7.80; N, 6.33.

1-(2-Bromobenzyl)-1-cyano-2-[(*R*)-menthyloxycarbonyl]-1, 2-dihydroisoquinoline (3e). The product was obtained in 82 % yield following the general procedure using 2-bromobenzyl bromide. ^{1}H-NMR ($CDCl_3$): δ = 0.6-2.3 (m, 18 H, menthyl); 3.46 (m, 1 H, ArCH); 3.95 (m, 1 H, ArCH); 4.86 (m, 1 H, CH-O); 5.56 (d, 1 H, J = 7.93 Hz); 6.70-7.50 ppm (m, 9H, CH_{ar}). ^{13}C-NMR ($CDCl_3$): δ = 16.1; 20.9; 22.0; 23.1; 26.4; 31.5; 34.0; 41.0; 43.8; 47.0; 47.1; 53.5; 60.9; 78.2; 105.9 (CH-CH-N); 118.4 (CN); 124.5-132.9 (aromatic C and CH); 151.9 ppm (CO). HRMS (EI): Calc. for $C_{28}H_{31}BrN_2O_2$: 506.1569, found: 506.1569. *Anal*. Calcd. for $C_{28}H_{31}BrN_2O_2$ (507.46): C, 66.27; H, 6.16; N, 5.52. Found: C, 66.02; H, 6.38; N, 5.29.

1-Cyano-1-(3-methoxybenzyl)-2-[(*R*)-menthyloxycarbonyl]-1,2-dihydroisoquinoline (3f). The product was obtained in 89 % yield following the general procedure using 3-methoxybenzyl bromide. ^{1}H-NMR ($CDCl_3$): δ = 0.7-2.3 (m, 18 H, menthyl); 3.28 (m, 1 H, ArCH); 3.61 (d, 3 H, OCH_3); 3.65-3.90 (m, 1 H, ArCH); 4.92 (m, 1 H, CH-O); 5.43 (dd, 1 H, J_1 = 7.74 Hz, J_2 = 8.12 Hz); 6.20+6.26 (s+s, 1H, CH_{ar}); 6.42 (d, J = 7.36 Hz, CH_{ar}); 6.65-6.85 (m, 2H, CH_{ar}); 6.94 (m, 1H, CH_{ar}); 7.0-7.5 ppm (m, 4H, CH_{ar}). ^{13}C-NMR ($CDCl_3$): δ = 16.2; 20.9; 22.9; 23.2; 26.5; 31.5; 34.1; 41.0; 46.0 (CH_2Ph); 47.1; 54.9 (OCH_3); 60.8 (C1); 78.1; 105.3 (CH-CH-N); 113.7; 115.7; 118.8 (CN); 123.1; 124.4; 124.7; 127.2; 128.0; 128.8; 128.9; 129.4; 129.6; 134.3; 152.0 ppm (CO). HRMS (EI) m/z: Calc. for $C_{29}H_{34}N_2O_3$ 458.2569, found 458.2570. *Anal.* Calcd. for $C_{29}H_{34}N_2O_3$ (458.59): C, 75.95; H, 7.47; N, 6.11. Found: C, 75.77; H, 7.68; N, 5.87.

1-Allyl-1-cyano-1-2-methoxycarbonyl-1,2-dihydroisoquinoline (3g). The product was obtained in 82 % yield following the general procedure using 1-cyano-2-methoxycarbonyl-1,2-dihydroquinoline and allyl bromide. ^{1}H-NMR ($CDCl_3$): δ = 3.00 (dd, J_1 = 1.38 Hz, J_2 = 178.0 Hz, 1 H, $PhCH_2$), 3.02 (dd, J_1 = 1.38 Hz, J_2 = 178.0 Hz, 1 H, $PhCH_2$) 3.92 (s, 3 H, MeO); 4.97 - 5.16 (2 H, m, $=CH_2$), 5.50 – 5.62 (m, 1 H, CH=), 5.65 (d, J = 11.2 Hz, 1H, Ph-CH), 6.88 (d, J = 11.2 Hz, 1 H, =CHN); 6.98 – 7.03, m, 1H, ArH); 7.20 – 7.32 (m, 2 H, ArH); 7.52 – 7.59 ppm (m, 1 H, ArH). *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$ (254.28): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.76; H, 5.68; N, 10.96.

1-Benzyl-1-cyano-2-methoxycarbonyl-1,2-dihydroisoquinoline (3h). The product was obtained in 86 % yield following the general procedure using 1-cyano-2-methoxycarbonyl-1,2-dihydroquinoline and benzyl chloride. ^{1}H-NMR ($CDCl_3$): δ = 3.32 (d, J = 13.20 Hz, 1.4 H, $PhCH_2$); 3.61 – 3.76 (m, 1.6 H, $PhCH_2$); 3.91 (s, 3 H, MeO); 5.46 (d, J = 8.43 Hz,1 H, PhCH); 6.92 (d, J = 9.35 Hz, 1H, CHN), 6.62 – 7.34 ppm (m, 9 H, aryl). ^{13}C-NMR ($CDCl_3$): δ = 45.5 (CH_2Ph); 54.1 (OCH_3); 61.1 (C1); 78.1; 105.7 (CH=CH-N); 118.5 (CN); 124.2; 124.9; 127.3; 127.7, 128.1, 129.2; 129.5, 130.8, 132.8, 152.9 ppm (CO). *Anal*. Calcd. for $C_{19}H_{16}N_2O_2$ (304.34): C, 74.98; H, 5.30; N, 9.20. Found: C, 75.07; H, 5.28; N, 9.04.

Imidazo[5,1-*a*]isoquinolines 4 and 5 by Reaction of Reissert Compounds 2b with Allyl Magnesium Bromide. Reissert compound **2b** (1.00 mmol) was dissolved in dry THF (20 mL) and cooled to 0°C. Allylmagnesium chloride solution (2.0 M in THF, 5 mL, 10 eq.) was added drop by drop under stirring. The solution became turbid. After stirring for 2 days, excess of Grignard reagent was destroyed by cautious addition of saturated aq. NH_4Cl solution (20 mL). The phases were separated, and the aqueous phase extracted three times with EtOAc (50 mL). The combined organic layers were dried over $MgSO_4$. The solution was then evaporated to dryness under reduced pressure. Separation of by-products by column-chromatography DCM/acetone 8:2) yielded 4 (120 mg, 0.568 mmol, 57%) as a yellow-brown oil and 5 (75 mg, 0.33 mmol, 33%) as a brown oil. **4** R_f: 0.44 (DCM/acetone 8:2), **5** R_f: 0.09 (DCM/(acetone 8:2)

1,1-Diallyl-1,2-dihydroimidazo[5,1-*a*]isoquinolin-3(10bH)-one (4). ^{1}H-NMR ($CDCl_3$): δ = 2.20-2.30 (m, 1H); 2.45-2.60 (m, 2H); 2.65-2.75 (m, 1H); 4.60-5.00 (m, 2 H); 5.11 (d, 1 H); 5.16 (d, 1H, J = 4.49 Hz); 5.85-6.00 (m, 1 H); 6.68 (d, 1H, J = 4.49 Hz); 6.88-6.95 (m, 1H); 6.98-7.15 ppm (m, 3H). ^{13}C-NMR ($CDCl_3$): δ = 40.6 (CH_2); 43.2 (CH_2); 60.4 (CH); 64.7 (C_q); 105.8; 119.6 ($=CH_2$); 120.2 ($=CH_2$); 122.9; 124.5; 125.8; 126.4; 128.1; 131.3; 132.6; 132.9; 156.9 ppm (CO). *Anal*. Cald. For $C_{17}H_{18}N_2O$ (266.34): C: 76.66, H: 6.81, N: 10.52. Found: C: 76.41, H. 6.97, N: 10.66.

1-Allylimidazo[5,1-*a*]isoquinolin-3(2H)-one (5). ^{1}H-NMR ($CDCl_3$): δ = 3.59 (m, 2 H, CH_2-CH=CH_2); 5.05-5.20 (m, 2 H, $=CH_2$); 5.85-6.00 (m, 1 H, -CH=CH_2); 6.19 (d, 1 H, J = 7.61 Hz, CH); 7.11-7.27 (m, 3 H, ArH); 7.30 (d, 1 H, J = 7.61 Hz, CH); 7.50-7.55 (m, 1H, ArH); 11.26 ppm (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ = 30.4 (CH_2); 110.4 (C_q-NH); 111.8; 115.4; 117.3 ($=CH_2$); 120.3; 122.5; 125.9; 126.7; 127.0; 127.8; 129.0; 132.8; 148.9 ppm (CO). *Anal*. Calcd. for $C_{14}H_{12}N_2O$ (224.26): C: 74.98, H: 5.39, N: 12.49. Found: C: 74.72, H. 5.53, N: 12.36.

Imidazo[5,1-*a*]isoquinolines 7 and 8 by Reaction of Alkylated Reissert Compounds 3 with Grignard Reagents. Alkylated Reissert compound **3** (1.00 mmol) was dissolved in dry Et_2O (5 mL). Grignard reagent (3.00 mmol for single addition, 4.00 mmol for double addition, as solution in Et_2O or THF) was added drop by drop under stirring. The solution became turbid. After 3 h, excess of Grignard reagent was destroyed by cautious addition of MeOH. The reaction mixture was evaporated to dryness under reduced pressure, taken up in EtOAc and the product was separated from by-products by column chromatography (EtOAc/cyclohexane 1:1). Final purification was done by crystallization from EtOAc by evaporation to yield colourless crystals.

Allyl-1-ethyl-1,2-dihydroimidazo[5,1-*a*]isoquinolin-3(10bH)-one (7a). Following the general procedure 39 % yield was obtained starting from the methyl carbamate (R = Me). ^{1}H-NMR ($CDCl_3$): δ = 1.18 (t, 3H, J = 7.41 Hz, CH_3); 1.90-2.20 (m, 2H, ethyl); 2.39 (dq, 2H, J_1 = 14.36 Hz, J_2 = 7.19 Hz); 4.09 (m, 1H); 4.88-5.02 (m, 2H, $=CH_2$); 5.66-5.82 (m, 2H, =CH-, NH);

5.86 (d, 1H, J = 7.43 Hz, 1H); 6.87 (d, 1H, J = 7.42 Hz); 7.06-7.14 (m, 2H, ArH); 7.15-7.26 ppm (m, 2H, ArH). ^{13}C-NMR ($CDCl_3$): δ = 12.2 (CH_3); 24.1 (CH_2); 39.7 (CH_2); 63.5 (Cq); 64.3 (CH); 107.7 (CH); 118.7 (CH_2); 122.2 (CH); 122.5 (CH); 125.1 (CH); 126.7 (CH); 127.7 (CH); 131.1 (Cq); 132.6 (CH); 134.8 (Cq); 157.1 ppm (CO). Mp: 168-171 °C. HRMS (ESI) m/z: Calcd. for $C_{16}H_{19}N_2O$ [M + H]$^+$: 255.1492, found 255.1497. *Anal*. Calcd. for $C_{16}H_{18}N_2O$ (254.33): C, 75.56; H, 7.13; N, 11.01. Found: C, 75.48; H, 7.33; N, 10.95.

Benzyl-1-ethyl-1,2-dihydroimidazo[5,1-*a*]isoquinolin-3-(10bH)-one (7b). Following the general procedure 27 % yield were obtained starting from the methyl carbamate (R = Me). ^{1}H-NMR ($CDCl_3$): δ = 1.19 (t, 3H, J = 7.39 Hz, CH_3); 2.00-2.30 (m, 2H, ethyl CH_2); 2.69 (d,1H, J = 13.12 Hz, ArCH_2); 3.06 (d, 1H, J = 13.13 Hz, ArCH_2); 4.14 (dd, J_1 = 10.82 Hz, J_2 = 2.30 Hz, 1H); 5.23 (d, 1H, J = 7.48 Hz), 6.57 (d, 1H, J = 7.47 Hz); 4.60-6.20 (br s, 1H, NH); 6.63-6.70 (m, 2H, ArH); 6.81-6.89 (m, 1H, ArH); 6.98-7.06 (m, 2H, ArH); 7.09-7.17 (m, 1H, ArH); 7.17-7.26 ppm (m, 3H, ArH). ^{13}C-NMR ($CDCl_3$): δ = 12.4 (CH_3); 24.0 (CH_2); 43.0 (ArCH_2); 64.6 (Cq); 66.0 (CH); 106.7 (CH); 123.1 (ArH); 123.1 (ArH); 124.8 (ArH); 126.3 (ArH); 126.8 (ArH); 127.3 (ArH); 127.9 (ArH); 130.7 (ArH); 132.3 (Cq); 133.5 (Cq); 135.5 (Cq); 157.6 ppm (CO). Mp: 224-226 °C. HRMS (ESI) m/z: Calcd. for $C_{20}H_{21}N_2O$ [M + H]$^+$: 305.1648, found 305.1655. *Anal*. Calcd. for $C_{20}H_{20}N_2N_2O$ (304.39): C, 78.92; H, 6.62; N, 9.20. Found: C, 78.77; H, 6.73; N, 9.02.

10b-(*n*-Butyl)-1,1-dimethyl-1,2-dihydroimidazo[5,1-*a*]-isoquinolin-3(10b*H*)-one (8a). Following the general procedure 66 % yield were obtained starting from the (*R*)-menthyl carbamate [R = (R)-menthyl)]. ^{1}H-NMR ($CDCl_3$): δ = 0.76 (t, 3 H, J = 7,22 Hz, CH_3); 0.95-1.25 (m, 3 H, Butyl); 1,21 (s, 3 H, CH_3); 1.35-1.70 (m, 2 H, Butyl); 1.61 (s, 3 H, CH_3); 1.90-2.10 (m, 1 H, Butyl); 5.56 (d, 1 H, J = 7.58 Hz); 5.60-6.00 (br s, 1H, NH); 6.86 (d, 1 H, J = 7.56 Hz); 6.92-7.04 (m, 2H, ArH); 7.04-7.18 ppm (m, 2H, ArH). ^{13}C-NMR ($CDCl_3$): δ = 13.9 (CH_3); 22.8 (CH_3); 23.1 (CH_2); 25.6 (CH_2); 27.6 (CH_3); 40.1 (CH_2); 63.8 (Cq); 67.9 (Cq); 105.3 (CH); 123.6 (CH); 124.4 (CH); 125.0 (CH); 126.1 (CH); 127.4 (CH); 132.2 (Cq); 132.3 (Cq); 157.6 ppm (CO). Oil. HRMS (ESI) m/z: Calcd. for $C_{17}H_{23}N_2O$ [M + H]$^+$: 271.1805, found 271.1807. *Anal*. Calcd. for $C_{17}H_{22}N_2O$ (270.37): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.27; H, 8.43; N, 10.08.

10b-Benzyl-1,1-dimethyl-1,10b-dihydro-2*H*-imidazo[5,1-*a*]-isoquinolin-3-one (8b). Following the general procedure 40 % yield of optically active product (ee = 14 %) were obtained starting from the menthyl carbamate (R = (*R*) menthyl). 65 % of racemic material was obtained, when the non-chiral starting material (R = Me) was used. ^{1}H-NMR ($CDCl_3$): δ = 1.32 (s, 3 H, CH_3); 1.77 (s, 3 H, CH_3); 2.77 (d, 1H, J = 12.65 Hz, ArCH_2); 3.34 (d, 1H, J = 12.66 Hz, ArCH_2); 4.40-5.60 (br s, 1H, NH); 4.93 (d, 1H, J = 7.57 Hz); 6.44 (d, 1H, J = 7.56 Hz); 6.60-6.67 (m, 2H, ArH); 6.69-6.75 (m, 1H, ArH); 6.95-7.05 (m, 2H, ArH); 7.08-7.25 ppm (m, 4H, ArH). ^{13}C-NMR ($CDCl_3$): δ = 22.9 (CH_3); 27.6 (CH_3); 45.2 (CH_2); 64.2 (Cq); 69.1 (Cq); 104.8 (CH); 123.3 (CH); 124.8 (CH); 125.1 (CH); 126.1 (CH); 126.2 (CH); 127.3; 127.9; 130.8; 131.0; 133.2; 135.9; 157.1 ppm (CO). Mp: 231.0-234 °C. HRMS (ESI) m/z: Calcd. for $C_{20}H_{20}N_2ONa$ [M + Na]$^+$: 327.1468, found 327.14.77. *Anal*. Calcd. for $C_{20}H_{20}N_2O$ (304.39): C, 78.92; H, 6.62; N, 9.20. Found: C, 79.07; H, 6.53; N, 9.09.

1,1-Diallyl-10b-benzyl-1,2-dihydroimidazo[5,1-*a*]isoquinolin-3(10bH)-one (8c). Following the general procedure using the achiral starting material (R = Me) provided 51 % yield of the racemic product. ^{1}H-NMR ($CDCl_3$): δ = 2.32-2.44 (m, 1 H); 2.45-2.56 (m, 1 H); 2.73-86 (m, 1H); 2.77 (d, J = 12.29 Hz, 1H, ArCH_2); 3.00-3.11 (m, 1H); 3.31 (d, J = 12.41 Hz, 1H, ArCH_2); 4.77-4.86 (m, 1H); 4.88-4.98 (m, 2H); 5.30-5.41 (m, 2H); 5.41-5.58 (m, 1H); 5.93-6.15 (m, 2H); 6.39 (d, 1H, J = 7.59 Hz); 6.59-6.65 (m, 2H); 6.67-6.73 (m, 1H); 6.96-7.05 (m, 2H); 7.09-7.25 (m, 3H); 7.29-7,35 ppm (m, 1H). ^{13}C-NMR ($CDCl_3$): δ = 39.5 (CH_2); 41.9 (CH_2); 46.3 (CH_2); 68.3 (Cq); 68.9 (Cq); 104.4 (CH); 119.3 (CH_2); 120.1 (CH_2); 123.0 (CH); 124.9 (CH); 125.2 (CH); 125.9 (CH); 126.2 (CH); 127.1 (CH); 127.8 (CH); 130.4 (Cq); 131.0 (CH); 131.2 (CH); 133.2 (CH); 133.5 (Cq); 135.2 (Cq); 157.3 ppm (CO). Mp: 162-164 °C. *Anal*. Calcd. for $C_{24}H_{24}N_2O$ (356.46): C, 80.87; H, 6.79; N, 7.86. Found: C, 81.01; H, 6.71; N, 7.65.

***N*-[(*R*)-Menthyloxycarbonyl]-2-methoxy-5,6,11,12-tetrahydro-dibenzo[*a,e*]cyclooctene-5,11-imin-11-carbonitrile (10) (Method A)**. To a solution of **3f** (235 mg, 0.51 mmol) in DCM (10 mL) methyl triflate (60 μL, 0.53 mmol) was added. After 12 days at rt some colourless solid separated which was dissolved by addition of some MeOH. The solution was washed with aqueous saturated solution of $NaHCO_3$ (5 mL). The solvent was distilled off, the remaining slightly yellow foam (201 mg) was purified by column chromatography (DCM) yielding 152 mg (65%) product **10**. Almost colourless oil, R_f = 0.70 (DCM). ^{1}H-NMR ($CDCl_3$): δ = 0.5 – 2.3 (m, 18H, menthyl); 2.91 (d, 1 H, J = 16.5 Hz, ArCH); 3.21 (m, 1 H, ArCH); 3.58 (m, 1 H, ArCH); 3.72 (s, 3 H, OCH_3); 4.07 (m, 1 H, ArCH); 4.76 (m, 1 H, CH-O); 5.75 (m, 1H, CH-N); 6.50 (s, 1H); 6.76 (m, 1 H, CH_{ar}); 7.00-7.15 (m, 2H, CH_{ar}); 7.22 (m, 1H, CH_{ar}); 7.30 (m, 1H,); 7.70-7.80 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ = 15.9; 20.6; 22.0; 23.2; 26.1; 31.4; 34.1; 36.5; 41.1; 47.1; 51.8; 55.1 (OCH_3); 77.5; 113.1; 113.5; 120.6 (CN); 126.7-133.6 (aromatic C and CH); 154.8; 155.6. HRMS (EI) m/z: Calcd. for $C_{29}H_{35}N_2O_3$ [M + H]$^+$: 459.2642, found 459.2649. *Anal*. Calcd. for $C_{29}H_{34}N_2O_3$ (458.59): C, 75.95; H, 7.47; N, 6.11. Found: C, 76.02; H, 7.70; N, 6.03.

2-Methoxy-5,6,11,12-tetrahydro-dibenzo[a,e]cyclooctene-5,11-imin-11-carbamide (11). (Method B). 85% H_3PO_4 (2 mL) was added to a solution of **3g** (235 mg, 0.51 mmol) in 99% AcOH (6 mL). The solution was heated to 100°C for 15 h. After dilution with water (10 mL), the solution was stirred in an ice-bath and 3 *M* aqueous NaOH (60 mL) added dropwise. The pH rose to about 14. A colourless substance separated and disappeared after extraction with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness with a rotary evaporator. A slightly yellow solid (109 mg, 73%) remained. It was dissolved in MeOH (about 5 mL) by boiling, filtered hot and cooled to -24 °C. A white solid substance seperated, which was centrifuged off, washed with MeOH and dried. Yield 31 mg (21%) of a white powder, mp = 249-251 °C (MeOH). ^{1}H-NMR ($CDCl_3$): δ = 2.65 (d, 1 H, J = 15.86 Hz); 3.11 (m, 2 H); 3.38 (dd, 1 H, J_1 = 16.06 Hz, J_2 = 5.29 Hz); 3.60 (s, 3 H, OCH_3); 4.40 (d, 1 H, J = 4.53 Hz); 6.51 (d, 1 H, J = 2.26 Hz); 6.65 (dd, 1H, J_1 = 8.31 Hz; J_2 = 2.64 Hz); 6.92 (m, 1 H); 7.04 (m, 2H); 7.09 (d, 1H, J = 8.50 Hz); 7.15 (m, 1H, NH); 7.32 (m, 1H, NH); 7.44 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ = 38.2 (CH_2); 40.5 (CH_2); 50.2 (CH); 55.3 (OCH_3); 59.4 (C_q); 112.8 ($CCONH_2$); 113.8 ($CCONH_2$); 125.0 ($C_{ar}H$); 126.3 ($C_{ar}H$); 127.3 ($C_{ar}H$); 127.7 ($C_{ar}H$); 129.7; 131.5 (C_q); 133.6 (C_q); 135.6 (C_q); 138.2 (C_q); 177.1 ($CONH_2$). HRMS (ESI) m/z: Calcd. for $C_{18}H_{19}N_2O_2$ [M + H]$^+$: 295.1441, found 295.1444. *Anal*. Calcd. for $C_{18}H_{18}N_2O_2$ (294.14): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.22; N, 9.33.

7-Bromo-2-bromomethyl-6-methoxy-1,6,7,11b-tetrahydro-2*H*[1,3]oxazino[4,3-*a*]isoquinoline-4-on-11b-carbonitrile (12a) (Method C). A solution of the allyl-substituted Reissert compound **3a** (385 mg, 1.0 mmol) in CH_2Cl_2 (7 mL) and methanol (0.5 mL, 12 mmol) was stirred under argon in an ice bath. A solution of bromine (332 mg, 2.1 mmol) in CH_2Cl_2 (2 mL) was added dropwise over a period of 15 min. After stirring for 15 min, the solution was washed with water (3 x 10 mL) and satd. aqu. $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4) and the solvent distilled off. The remaining light yellow oil was purified by column chromatography (AcOEt/cyclohexane 3:7) and the resulting colorless foam was recrystallized from ethyl acetate. Yield 35 %. Clear colourless crystals, mp = 207-209 °C (decomposition), R_f = 0.46 (cyclohexane/EtOAc 7:3), chiral HPLC: 28.1 min (100%, isopropanol/hexane 20:80). ^{1}H-NMR (DMSO-d_6): δ = 2.27 (m, 1 H, CH_2CN); 3.35 (m, 1 H, CH_2CN); 3.43 (s, 3 H, OCH_3); 3.81-4.01 (m, 2 H, CH_2Br); 5.11 (m, 1 H); 5.65 (d, 1 H, J = 2.26 Hz, CHOMe); 6.07 (d, 1H, J = 2.26 Hz, CHBr); 7.50-7.71 ppm (m, 4H, CH_{ar}). ^{13}C-NMR (DMSO-d_6): δ = 36.0 (CH_2); 38.8 (CH_2); 45.8 (CHBr); 52.9 (C_q); 57.7 (OCH_3); 74.6 (CH-O); 84.9 (C-O CH_3); 120.5 (CN); 127.3 ($C_{ar}H$); 130.5 ($C_{ar,\ q}$); 131.2 ($C_{ar}H$); 131.6 ($C_{ar}H$); 131.9 ($C_{ar}H$); 132.7 ($C_{ar,\ q}$); 151.7 ppm (CO). *Anal*. Calcd. for $C_{15}H_{14}Br_2N_2O_3$ (430.09): C: 41.89, H: 3.23, N: 6.51. Found: C: 41.77, H: 3.48, N: 6.31

7-Bromo-2-bromomethyl-2-methyl-6-methoxy-1,6,7,11b-tetrahydro-2*H*[1,3]oxazino[4,3-*a*]isoquinoline-4-on-11b-carbonitrile (12b) (Method D). To a solution of the Reissert compound **3** (1.00 mmol) in DCM (5 mL) and MeOH (0.4 mL; 10 mmol) solid pyridiumhydrobromide-perbromide (3.00 mmol, 90% techn.) was added at 0°C and the solution was stirred at 0°C for 1 h. After washing with sat. aq. $NaHCO_3$ (5 mL), 5% $Na_2S_2O_3$ (5 mL), and sat. aq. NaCl (5 mL), the solution was dried with $MgSO_4$ and evaporated to dryness under reduced pressure. Purification by column chromatography (DCM or EtOAc/cyclohexane 1:3) yielded white foams, which could be crystallized from EtOAc. Yield 66 %. White crystals, mp = 160-162 °C, $[\alpha]^{20}_D$ = +21.5° (c = 1, CH_2Cl_2), R_f = 0.31 (CH_2Cl_2). Chiral HPLC: 22.5 min (100%, isopropanol/hexane 20:80). ^{1}H-NMR ($CDCl_3$): δ = 1.99 (s, 1 H, CH_3); 2.72 (m, 2 H, CH_2); 3.51 (m, 2 H, CH_2Br); 3.53 (s, 3 H, OCH_3); 5.21 (d, 1 H, J = 2.27 Hz, CHOMe); 6.08 (d, 1 H, J = 2.27 Hz, CHBr); 7.35-7.55 ppm (m, 4H, CH_{ar}). ^{13}C-NMR ($CDCl_3$): δ = 25.8 (CH_3); 41.3 (CH_2); 44.0 (CH_2Br); 44.4 (CHBr); 50.6 (C_q); 57.5 (OCH_3); 79.1 (C-O); 83.9 (C-O); 119.3 (CN); 126.1; 130.0; 130.2; 130.3; 130.8; 131.2; 152.0 ppm (CO). *Anal*. Calcd. for $C_{16}H_{16}Br_2N_2O_3$ (444.12): C: 43.27, H: 3.63, N: 6.31. Found: C: 43.28, H: 3.78, N: 6.20.

1-Allyl-4-bromo-1-cyano-2-[(*R*)-menthyloxycarbonyl]-3-methoxy-1,2,3,4-tetrahydroisoquinoline (13). Small quantities of the product (yield not determined) were obtained, when only one equivalent of bromine was used in Method C. ^{1}H-NMR ($CDCl_3$): δ = 0.60-2.30 (m, 18 H, menthyl), 3.10-3.70 (m, 5 H, OCH_3, CH_2), 4.76-5.02 (m, 2 H), 5.02-5.13 (m, 1 H), 5.14-5.20 (m, 1 H), 5.40-5.70 (m, 1 H, OCH), 5.85-6.00 (br s, 1H); 7.28-7.44 (m, 3 H, CH_{ar}); 7.48-7.58 ppm (m, 1 H, CH_{ar}). ^{13}C-NMR ($CDCl_3$): δ = 15.5; 20.6; 20.9; 21.9; 22.6: 26.0; 31.4; 33.9; 34.0; 40.6; 41.0; 44.1; 46.8; 47.3; 56.1; 77.9 (CHO); 85.2 (NCHO); 119.3; 120.8; 127.0; 125-130 (aromatic C and CH); 154.8 ppm (C=O). HRMS (ESI) m/z: Calcd. for $C_{25}H_{33}BrN_2O_3K$ $[M + K]^+$: 527.1306, found 527.1321. *Anal*. Calcd. for $C_{25}H_{33}BrN_2O_3$ (489.44): C, 61.35; H, 6.80; N, 5.72. Found: C: 61.18, H: 6.78, N: 5.56.

Acknowledgement. Donations of chemicals by Bayer Services GmbH & Co. OHG, BASF AG, Sasol GmbH is gratefully acknowledged.

REFERENCES

[1] Reissert, A., *Ber. Dtsch. Chem. Ges.*, **1905**, *38*, 1603; Mosettig, E. and Mozingo, R., *Organic Reactions*, **1947**, *4*, 362; Mcewen, W. E. and Cobb, R. L., *Chem. Rev.*, **1955**, *55*, 511.

[2] Langer, P., *Eur. J. Org. Chem.*, **2007**, 2233; Schöpf, C. and Thierfelder, K., *Liebigs Ann. Chem.*, **1932**, *497*, 22.

[3] Munchhof, M. J. and Meyers, A. I., *J. Org. Chem.*, **1996**, *61*, 4607.

[4] Sieck, O., Schaller, S., Grimme, S. and Liebscher, J., *Synlett*, **2003**, 337.

[5] Takamura, M., Funabashi, K., Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.*, **2000**, *122*, 6327.

[6] Funabashi, K., Ratni, H., Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.*, **2001**, *123*, 10784.

[7] Bender, C., *PhD-Thesis, Humboldt-University Berlin*, **2007**.

[8] Gibson, H. W., Berg, M. A. G., Dickson, J. C., Lecavalier, P. R., Wang, H. and Merola, J. S., *J. Org. Chem.*, **2007**, *72*, 5759.

[9] Popp, F. D. and Gibson, H. W., *J. Heterocycl. Chem.*, **1964**, *1*, 51; Walters, L. R., Iver, N. T. and McEven, W. E., *J. Am. Chem. Soc.*, **1958**, *80*, 1177; Boekelheide, V. and Godfrey, J. C., *J. Amer. Chem. Soc.*, **1953**, *75*, 3679.

[10] Kubo, A., Nakahara, S., Inaba, K. and Kitahara, Y., *Chem. Pharm. Bull.*, **1986**, *34*, 4056; Kant, J. and Popp, F. D., *J. Heterocycl. Chem.*, **1985**, *22*, 1065.

[11] Boekelheide, V. and Ainsworth, C., *J. Amer. Chem. Soc.*, **1950**, *72*, 2134.

[12] Skiles, J. W. and Cava, M. P., *Heterocycles*, **1978**, *9*, 653.

[13] Kovacs, L. and Kerekes, P., *Acta Chim. Hungarica*, **1985**, *120*, 103; Popp, F. D. and Wefer, J. M., *J. Heterocycl. Chem.*, **1967**, *4*, 183; Reimann, E., Grasberger, F. and Polborn, K., *Monatsh. Chem.*, **2003**, *134*, 991.

[14] Lorsbach, B. A., Bagdanoff, J. T., Miller, R. B. and Kurth, M. J., *J. Org. Chem.*, **1998**, *63*, 2244.

[15] Uff, B. C., Budhram, R. S., Consterdine, M. F., Hicks, J. K., Slingsby, B. P. and Pemblington, J. A., *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2018.

[16] Brozda, D., Hoffman, K. and Rozwadowska, M. D., *Heterocycles*, **2006**, *67*, 119.

[17] Ullah, E., Rotzoll, S., Schmidt, A., Michalik, D. and Langer, P., *Tetrahedron Lett.*, **2005**, *46*, 8997.

[18] Ichikawa, E., Suzuki, M., Yabu, K., Albert, M., Kanai, M. and Shibasaki, M., *J. Am. Chem. Soc.*, **2004**, *126*, 11808.

[19] Wanner, K. T., Beer, H., Hofner, G. and Ludwig, M., *Eur. J. Org. Chem.*, **1998**, 2019; Youte, J. J., Barbier, D., Al-Mourabit, A., Gnecco, D. and Marazano, C., *J. Org. Chem.*, **2004**, *69*, 2737; Battersby, A. R. and Binks, R., *J. Chem. Soc.*, **1955**, 2888; Lee, K. H. and Soine, T. O., *J. Pharm. Sci.*, **1968**, *57*, 1922.

[20] Dyke, S. F., White, A. W. C. and Hartley, D., *Tetrahedron*, **1973**, *29*, 857; Yamada, K., Takeda, M., Itoh, N., Ohtsuka, H., Tsunashima, A. and Iwakuma, T., *Chem. Pharm. Bull.*, **1982**, *30*, 3197.

[21] Sugiura, M., Asai, K., Hamada, Y., Hatano, K., Kurono, Y., Suezawa, H. and Hirota, M., *Chem. Pharm. Bull.*, **1997**, *45*, 928.

[22] Sohár, P., Lázár, L., Fülöp, F., Bernáth, G. and Kóbor, J., *Tetrahedron*, **1992**, *48*, 4937; Lázár, L., Fülöp, F., Dombi, G., Bernáth, G., Argay, G. and Kálmán, A., *Tetrahedron*, **1990**, *46*, 4039.

[23] Full details have ben deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 653654 for **2a,** CCDC 653660 for **7a,** CCDC 653659 for **7b**, CCDC 653656 for **8b**,CCDC 653661 for **8c,** CCDC 653657 for **11**, CCDC 653655 for **12a**, CCDC for **12b**.

[24] Popp, F. D., Katz, L. E., Klinowski, C. W. and Wefer, J. M., *J. Org. Chem.*, **1968**, *33*, 4447.