Towards a Total Synthesis of Quinocarcin: Diastereoselective Synthesis of Functionalized Azepino[1,2-*b*]isoquinolines

Oliver Koepler,[a] Sabine Laschat,*[b] Angelika Baro,[b] Peter Fischer,[b] Burkhard Miehlich,[b] Marc Hotfilder,[c] and Christoph le Viseur[c]

Dedicated to Professor Johann Mulzer on the occasion of his 60th birthday

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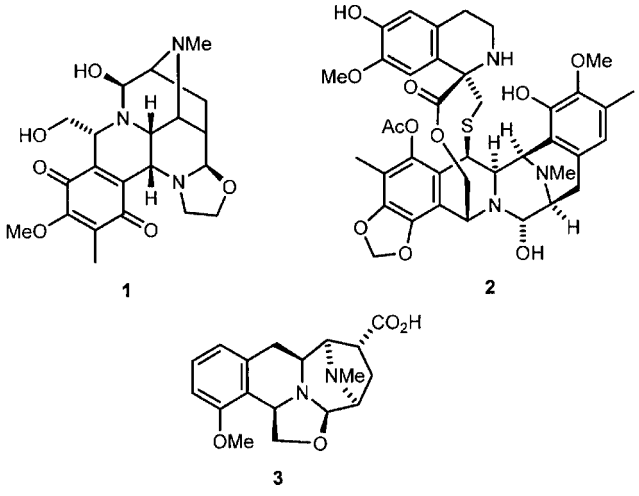
1,3-Disubstituted tetrahydro-oxazolo-isoquinolinones **19a**,**b** were obtained from phenylalanine in seven steps and 42% overall yield by Katritzky's benzotriazole method. The tricyclic oxazolidinone **19a** was further converted into amino alcohol **10** by employing a chemoselective reduction of the ester group with $LiBH_4$/MeOH. Compound **10** and the corresponding 1-unsubstituted tetrahydroisoquinoline alcohol **11** were converted into aldehydes **27** and **33**, which cyclized in the presence of different Lewis acids to give the substituted azepino[1,2-*b*]isoquinolines **34** and **35**, respectively, which are key structural features of the alkaloid quinocarcin. The stereoselectivities of the Lewis-acid-catalyzed hetero-ene reaction are highly dependent on the substitution pattern and the type of Lewis acid.

Introduction

Among the class of tetrahydroisoquinoline alkaloids, various members such as naphthyridinomycin (**1**),[1] ecteinascidin 743 (**2**),[2] and quinocarcin (**3**)[3] (Scheme 1) have received increasing interest due to their potent cytotoxic properties. Ecteinascidin 743, for example, is currently undergoing phase II/III clinical trials.[2d] Although quinocarcin (**3**) seems to be the structurally simplest representative, the two known enantioselective total syntheses require up to 28 steps to establish the molecular skeleton.[4,5] Thus, during our ongoing efforts in the field of alkaloid synthesis we were interested in developing a general strategy which would allow not only the total synthesis of (−)-quinocarcin (**3**) itself, but also derivatives thereof.

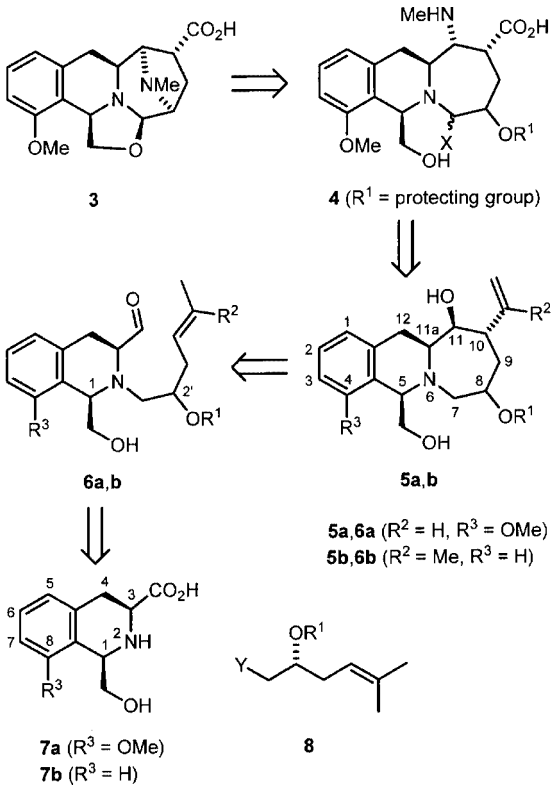
According to the retrosynthetic analysis (Scheme 2) we envisioned the cleavage of the hemiaminal in target compound **3** followed by a retro S_N2 reaction to afford the tricyclic azepino[1,2-*b*]isoquinoline **4**. The amino group and the carboxylic acid in **4** may be traced back to an alcohol and an alkene, respectively, in **5**. As a key step for the formation of the azepino[1,2-*b*]isoquinoline skeleton we decided to use a Lewis-acid-catalyzed hetero-ene reaction of precursor **6**. Former results from our laboratory have shown the synthetic utility of the Lewis-acid-catalyzed hetero-ene reaction of amino acid derivatives for the diastereoselective synthesis of various nitrogen-containing heterocycles.[6,7] The cyclization precursor **6** may be available from the tetrahydroisoquinoline derivative **7** and a functionalized alkene **8**.



Scheme 1. Tetrahydroisoquinoline alkaloid derivatives **1**−**3**

Therefore, the current aim was to elaborate concise synthetic routes to the building blocks **7** and **8** and, further-

[a] Institut für Organische Chemie der Technischen Universität Braunschweig,
Hagenring 30, 38106 Braunschweig, Germany
[b] Institut für Organische Chemie der Universität Stuttgart,
Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: (internat.) + 49-711-685-4285
E-mail: sabine.laschat@oc.uni-stuttgart.de
[c] Klinik und Poliklinik für Kinderheilkunde, Pädiatrische Hämatologie/Onkologie,
Domagkstr. 9a, 48149 Münster, Germany



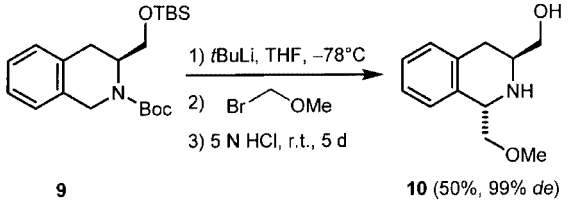
Scheme 2. Retrosynthetic pathway

more, to investigate the scope and limitations of the Lewis-acid-catalyzed hetero-ene cyclization of derivatives **6**. In particular, it was of interest to see whether the Lewis acid would interfere with additional coordinating groups at C-1 and C-2′ of the tetrahydroisoquinolinecarbaldehyde **6** with regard to diastereoselectivity. The results towards this goal are discussed below.

Results and Discussion

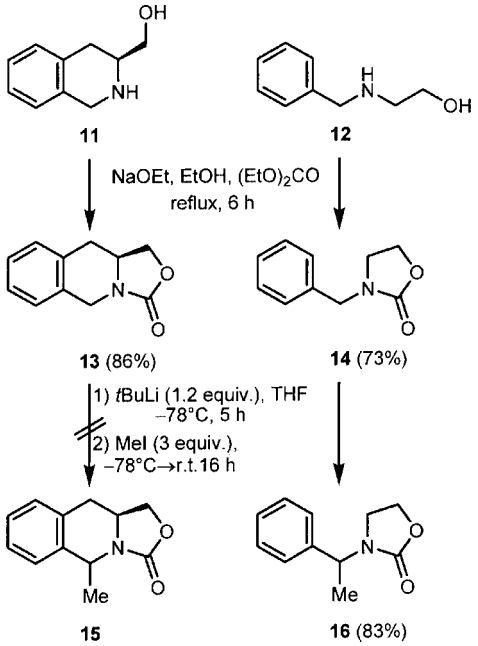
Synthesis of 1,3-Disubstituted Tetrahydroisoquinolines

Previously we have reported the synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines such as **10** by deprotonation of compound **9** with *t*BuLi at −78 °C, followed by alkylation and subsequent two-step deprotection using HF/pyridine and TFA, respectively.[8] Although the diastereoselectivities were high for various electrophiles, the yields were low. When using 5 N HCl for the deprotection of both the TBS ether and carbamate the yield of amino alcohol **10** could be improved to 50% starting from **9** (Scheme 3).



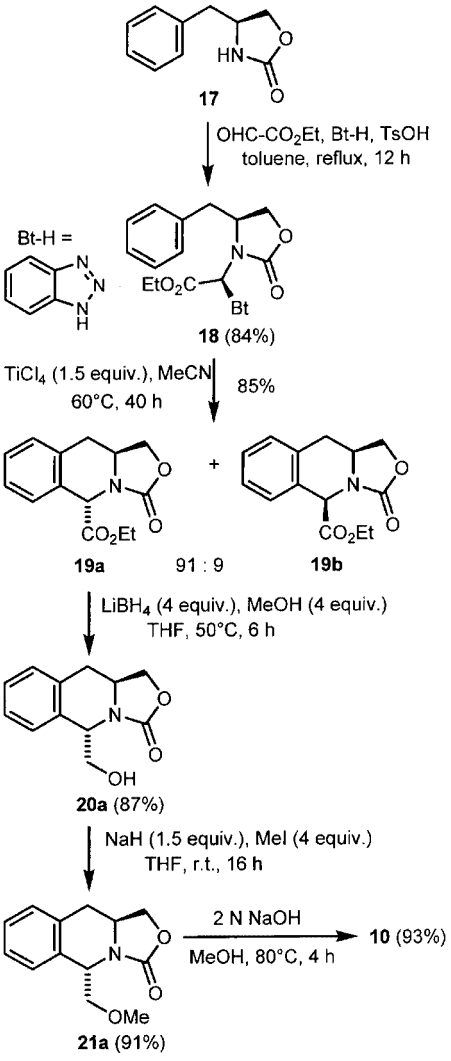
Scheme 3. Preparation of *trans*-1,3-disubstituted tetrahydroisoquinoline **10**; for other electrophiles see ref.[8]

Nevertheless, the moderate yield prompted us to investigate alternative routes towards compound **10**. Beak,[9] Meyers,[10] and Gawley[11] have reported that carbamates or formamidines are suitable precursors for alkylation of tetrahydroisoquinolines because these protecting groups on the nitrogen atom are capable of stabilizing the intermediate benzylic carbanion by a dipole-dipole interaction. Based on these findings we chose the tricyclic oxazolidinone **13** as a suitable alkylation precursor hoping that the carbamate moiety would act both as protecting and activating group (Scheme 4). According to a known procedure,[12] compound **13** was obtained by treatment of (*S*)-3-(hydroxymethyl)tetrahydroisoquinoline (**11**) with NaOEt and diethyl carbonate in refluxing EtOH in 86% yield. However, upon deprotonation of tricyclic oxazolidinone **13** with *t*BuLi at −78 °C in THF, and quenching with an excess of methyl iodide, no trace of the desired alkylation product **15** was found. Neither variation of base, reaction time or electrophile nor addition of TMEDA or (−)-sparteine resulted in any conversion of **13**. In contrast, the structurally closely related oxazolidinone **14** (Scheme 4), which is available from 2-(benzylamino)ethanol (**12**) in 73% yield,[13] was cleanly methylated under similar conditions to give product **16** in 83% yield. Presumably, the low reactivity of the tricyclic oxazolidinone **13** as compared to **15** is caused by the restricted conformation, which does not allow sufficient stabilization of the intermediate carbanion. This observation is in good agreement with the results of Beak, showing that an orthogonal position of the lithiated carbanion relative to the amide π-system is absolutely necessary for an optimum stabilization;[13] in the case of **13** this geometry is obviously not possible.



Scheme 4. Alkylation of tricyclic oxazolidinone **13** and structurally related compound **14**

The alternative route to 1,3-disubstituted tetrahydroisoquinoline via Katritzky's benzotriazole methodology[14] is shown in Scheme 5. L-Phenylalaninol-derived oxazolidinone **17** was condensed with ethyl glyoxylate and benzotriazole in refluxing toluene in the presence of TsOH to give the Mannich-type adduct **18** in 84% yield. Treatment of compound **18** with $TiCl_4$ in MeCN at 60 °C resulted in the formation of the iminium ion, which cyclized to the tricyclic oxo-oxazolidine-carboxylate **19**. In contrast to Katritzky's results, ester **19** was obtained as a diastereomeric mixture of *trans*- and *cis*-configured products **19a** and **19b** (*dr* = 91:9), respectively. This diastereomeric ratio could not be changed by using other Lewis acids. However, partial epimerization of **19a**,**b** was possible by deprotonation of *trans*-ester **19a** with BuLi (1.2 equiv.) in THF at −78 °C followed by hydrolysis with 2,4,6-tri-*tert*-butylphenol (2 equiv.) as a bulky proton source, giving 86% of a diastereomeric mixture of **19a** and **19b** (66:34). Despite these limitations it should be noted that both the Katritzky cyclization and the epimerization can be performed easily on a multi-gram scale.

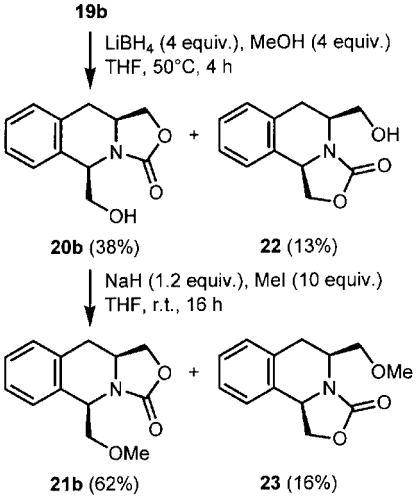


Scheme 5. Synthesis of 1,3-disubstituted tetrahydroisoquinoline **10** by benzotriazole methodology

In the conversion of *trans*-ester **19a** to tetrahydroisoquinoline derivative **10** (Scheme 5) we first had to tackle the chemoselective reduction of the ester moiety while keeping the oxazolidinone ring intact. Whereas $LiAlH_4$ resulted in cleavage and reduction of the oxazolidinone, the reduction of **19a** with $LiBH_4$ in the presence of equimolar amounts of MeOH in THF at 50 °C[15] proceeded cleanly to give alcohol **20a**.

Alcohol **20a** was methylated with MeI in the presence of NaH in THF at room temperature to give methyl ether **21a** in 91% yield. Subsequent basic hydrolysis yielded the amino alcohol **10** in 93% yield.

Surprisingly, *cis*-oxazolidinone ester **19b** displayed a different behavior when a similar reaction sequence was applied (Scheme 6). Upon treatment of **19b** with $LiBH_4$ and equimolar amounts of MeOH in THF a mixture of the desired alcohol **20b** (38%) and the rearranged oxazolidinone **22** (13%) was isolated. After separation of compounds **20b** and **22** by flash chromatography, alcohol **20b** was treated with NaH and MeI, resulting in the formation of **21b** (62%) and the rearranged by-product **23** (16%). Due to the *cis*-1,3-disubstitution pattern at the tetrahydroisoquinoline, under basic conditions the hydroxymethylene group at C-1 can easily undergo rearrangement by nucleophilic addition at the oxazolidinone carbonyl group, followed by elimination.[16]

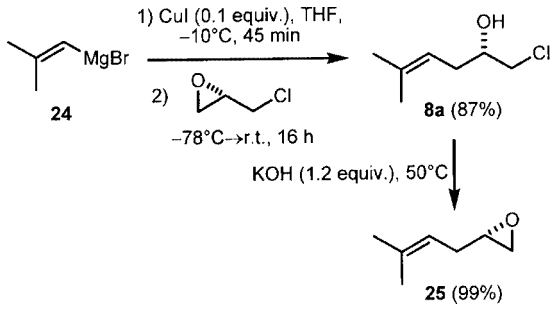


Scheme 6. Conversion of *cis*-ester **19b**

It is surprising that the corresponding *trans*-ester **19a** and alcohol **20a** did not undergo a similar rearrangement because they should be even more prone to such nucleophilic displacement by the pendent hydroxy group. Rearrangement occurs via tetrahedral tricyclic intermediates, as calculated by molecular modelling.[17] Due to a higher small-angle strain, the *trans* intermediate derived from alcohol **20a** is less stable (ca. 2.5 kcal·mol^{-1}) than the *cis* intermediate from **20b**, leading to a higher activation barrier and thus lower tendency to undergo nucleophilic displacement.

Synthesis of the Side-Chain Precursor

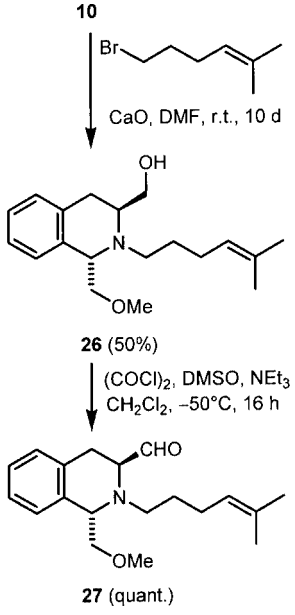
According to a modified procedure by Mazzocchi,[18] 2-methyl-1-propenylmagnesium bromide (**24**) was treated with CuI (0.1 equiv.) in THF at −10 °C, then (*S*)-epichlorohydrin was added at −78 °C and, after hydrolysis, aqueous workup and distillation, the chlorohydrin **8a** was isolated in 87% yield (Scheme 7). Upon addition of powdered KOH and heating the mixture at 50 °C the desired epoxide **25** was obtained almost quantitatively by distillation from the reaction mixture.



Scheme 7. Synthesis of side-chain precursor **25**

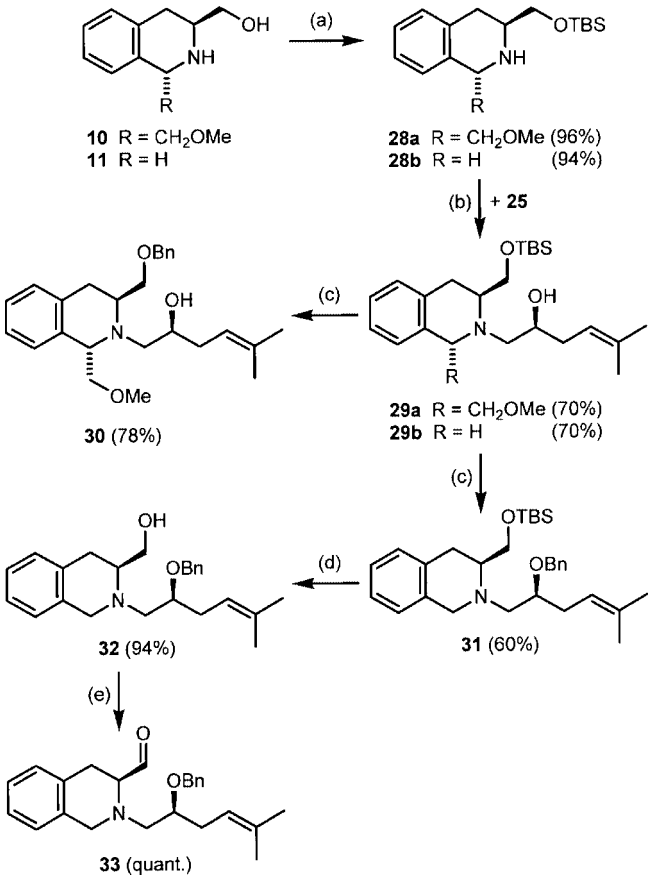
Synthesis of the Cyclization Precursors

The tetrahydroisoquinoline-carbaldehyde **27** with an unfunctionalized side chain and a methoxymethylene group at C-1 was easily accessible from amino alcohol **10** by *N*-alkylation with 5-methyl-4-hexenyl bromide in the presence of CaO in DMF at room temperature[7] to give alcohol **26**, which was submitted to Swern oxidation,[19] yielding the desired aldehyde **27**[19d] (Scheme 8).



Scheme 8. Synthesis of unfunctionalized cyclization precursor **27**

Cyclization precursors with a functionalized side chain were prepared as shown in Scheme 9. The amino alcohols **10** and **11** were cleanly converted into the respective TBS ethers **28a**,**b** in good yields. According to a procedure by Overman[20] the side chain was introduced by nucleophilic ring-opening of the chiral epoxide **25** with tetrahydroisoquinolines **28** in the presence of Et_3Al, giving the corresponding secondary alcohols **29a**,**b** in 70% yield each.



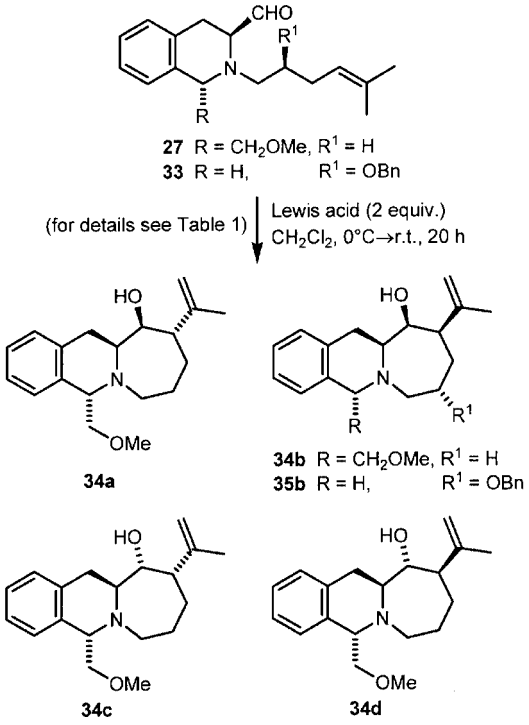
Scheme 9. Introduction of a chiral side chain; reagents and conditions: (a) TBSCl, imidazole, DMAP, CH_2Cl_2, room temp., 16 h; (b) $AlEt_3$ (1.3 equiv.), **25**, CH_2Cl_2, room temp., 16 h; (c) 1) NaO*t*Bu (1.2 equiv.), BnBr (1.5 equiv.), THF, room temp., 16 h; (d) TBAF (3 equiv.), THF, room temp., 24 h; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −50 °C, 16 h

With regard to the Lewis-acid-catalyzed hetero-ene cyclization a suitable protecting group for the alcohol moiety was required. Preliminary studies revealed that benzyl-protected tetrahydroisoquinoline alcohols survived even a large excess of strong Lewis acids. Thus, the secondary alcohols **29** were deprotonated with NaO*t*Bu and protected with benzyl bromide. Surprisingly, the benzylation reaction depended strongly on the substitution pattern of the tetrahydroisoquinoline **29**. Methoxymethylene-substituted **29a** underwent desilylation and subsequent benzylation of the primary hydroxy group to yield benzyl ether **30** in 78%. Replacing the base by NaH and a TBS ether by a TIPS ether again led to benzyl ether **30**. In contrast, the unsubstituted **29b** gave the desired benzyl ether **31** in 60% yield with-

out any difficulty. We therefore focussed our further work on the 1-unsubstituted series. Swern oxidation of the primary alcohol **32**, derived from the TBS ether **31** by deprotection with TBAF in 94% yield, provided aldehyde **33**.[19d]

Lewis-Acid-Catalyzed Cyclizations

When methoxymethylene-substituted aldehyde **27** was treated with Lewis acid (2 equiv.) in CH_2Cl_2 for 20 h, a mixture of diastereomeric azepino[1,2-*b*]isoquinolines **34a**−**d** was obtained (Scheme 10, Table 1).



Scheme 10. Lewis-acid-catalyzed cyclization of derivatives **27** and **33**[19d] to diastereomers **34a**−**d** and **35b**, respectively; 40 h reaction time in the conversion of **33**

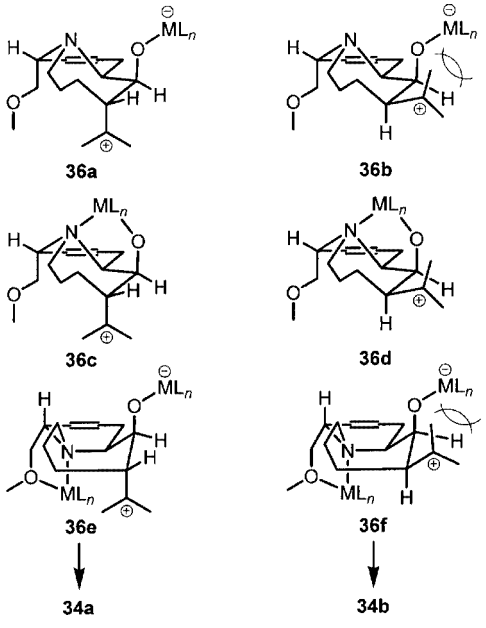
Table 1. Diastereoselective cyclization of tetrahydroisoquinolinecarbaldehyde **27** in the presence of various Lewis acids

Entry[a][b]	Lewis acid	Diastereomeric ratio (%)				Yield
		34a	**34b**	**34c**	**34d**	(%)
1	$BF_3{\cdot}OEt_2$	10.0	90.0	< 0.1	< 0.1	78
2	$SnCl_4$	92.0	5.1	2.9	< 0.1	90
3	$TiCl_4$	88.9	4.7	0.7	5.8	60
4	$ZnCl_2$	89.4	9.8	< 0.1	0.8	89
5	$EtAlCl_2$	88.0	8.3	< 0.1	3.7	90

[a] For reaction conditions see Scheme 10. [b] Diastereomeric ratios were obtained by capillary GC and GC-MS of the crude products. Yields refer to isolated yields.

As summarized in Table 1, the diastereomeric ratio was strongly dependent on the Lewis acid. Whereas diastereomer **34a**, with a *cis*,*trans* configuration at C-11a, C-11 and C-10, was obtained as the major product with chelating Lewis acids $SnCl_4$, $TiCl_4$, $ZnCl_2$ and $EtAlCl_2$ (Entries 2−5), the use of $BF_3{\cdot}OEt_2$ resulted in the formation of compound **34b** as the major diastereomer (Entry 1). In contrast, Lewis-acid-catalyzed cyclization of aldehyde **33** with a benzyl ether in the side chain proceeded in favor of diastereomer **35b** (Scheme 10) regardless of the Lewis acid. For example, use of $SnCl_4$ resulted in the formation of a diastereomeric mixture (*dr* = 83:17) in 88% yield, from which the major diastereomer **35b** was isolated in pure form after preparative HPLC in 30% yield. It should be noted that determination of the diastereomeric ratios of **35** was severely hampered by decomposition during chromatography (GC and HPLC). Therefore, the minor diastereomer of the $SnCl_4$ cyclization could not be isolated and characterized. Similar results were observed for other Lewis acids. One possible reason for the lability of the secondary alcohol **35** might be an acid-promoted elimination of water leading to the conjugated diene. The stereochemical assignment of the cyclization products is based on 2D NOE experiments of all isolated diastereomers **34a**,**b** and **35b**.

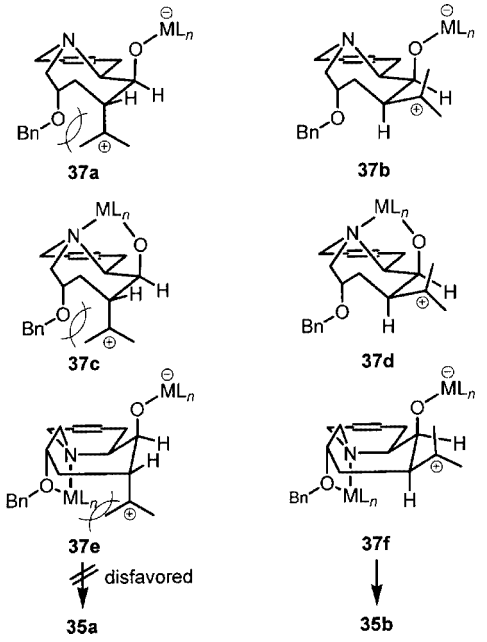
In order to explain the stereochemical outcome of the cyclization the following mechanistic rationale may be drawn. As shown in Scheme 11, in the case of the stepwise cyclization[6c−6e] of aldehyde **27** six different transition-state geometries **36a**−**f** have to be considered: two half-chair geometries with a monodentate Lewis acid (**36a**,**b**), two half-chairs with a chelating Lewis acid (**36c**,**d**), and two half-boat geometries with a monodentate and a bidentate Lewis acid (**36e**,**f**). In this respect it should be noted that cyclizations were incomplete when less than 2 equiv. of Lewis acid were used. The only transition state which can be ruled out first seems to be **36e** as a result of steric interactions between the chelated Lewis acid and the axial isopropenyl substituent. For small, nonchelating Lewis acids such as $BF_3{\cdot}OEt_2$ with a tetrahedral coordination sphere, transition



Scheme 11. Assumed transition state geometries **36a**−**f** in the Lewis-acid-catalyzed cyclization of aldehyde **27** to products **34**

state **36b** with the isopropenyl group in the equatorial position is probably favored rather than **36a**, resulting in product **34b** as the major diastereomer. However, in the case of larger chelating Lewis acids, transition state **36b** is disfavored relative to **36a** due to steric interactions between the Lewis acid and the equatorial substituent. In addition, transition states **36c**,**d** must be considered as well. For steric reasons, transition states **36a**,**c** seem to be most favorable, both leading to diastereomer **34a**.

For aldehyde **33**, with a benzyloxy group in the side chain, transition-state geometries **37a**−**f** are conceivable (Scheme 12). Independent of the conformation of the transition state, all geometries **37a**,**c**,**e** with a 1,3-diaxial interaction between the benzyl ether and the isopropenyl group should be strongly disfavored (Scheme 12). Thus, the remaining geometries **37b**,**d**,**f** with an equatorial isopropenyl substituent lead to the major diastereomer **35b**. This means that the preference of different Lewis acids for different transition states, for example nonchelating (**37b**) or chelating (**37d** or **37f**), always gives the same stereochemical result.



Scheme 12. Assumed transition state geometries **37a**−**f** in the Lewis-acid-catalyzed cyclization of aldehyde **33** to product **35b**

Biological Assays

In vitro cytotoxicity studies against two different human tumor cell lines RD-ES and CAD-ES1 (Ewing's sarcoma)[21] reveal that azepino[1,2-*b*]isoquinolines **34a**,**b** and **35b** are weakly active, displaying similar cytotoxicities against both cell lines. The activity decreases in the order **35b** > **34a** > **34b** (RD-ES) and **35b** > **34b** > **34a** (CAD-ES1).[22]

Conclusion

We have shown that functionalized azepino[1,2-*b*]isoquinolines **34** and **35** can be prepared stereoselectively from suitable tetrahydroisoquinoline-carbaldehydes **27** and **33** by a Lewis-acid-catalyzed hetero-ene cyclization. Whereas for 1-methoxymethylene-substituted derivative **27**, with an unfunctionalized side chain, the major effect on stereoselectivity is caused by the Lewis acid, the opposite result was obtained for aldehyde **33** with R = H at C-1 and a benzyl ether substituent in the side chain. In the latter case, the substituent dominates the stereochemistry regardless of the Lewis acid. Unfortunately, due to synthetic difficulties both substituents in the same precursor could not be studied. With regard to application in the quinocarcin synthesis further work on these functionalized azepino[1,2-*b*]isoquinolines **34** and **35** is necessary, in particular inversion of the stereochemistry at C-5. Studies towards this goal are currently underway.

Experimental Section

General: The following compounds were prepared according to literature procedures: **9**, **10**,[8] **11**,[7] **12**,[12] **17** and **18**.[14] Flash chromatography was carried out using Merck SiO_2 60 (particle size 230−400 mesh) with pentane and ethyl acetate (EtOAc) as eluents. HPLC was performed using an MZ Analysetechnik silica gel-NH_2 10-μm column (250 mm × 32 mm). GC was carried out with a Hewlett−Packard HP 6890 using an Agilent Technologies HP-5 column (30 m) and helium as the carrier gas.

(10a*S*)-1,5,10,10a-Tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one (13): A solution of NaOEt (1 M, 36.8 mL, 36.8 mmol) and diethyl carbonate (22.3 mL, 184 mmol) was added dropwise to a solution of **11** (3.00 g, 18.4 mmol) in abs. EtOH (150 mL), and the reaction mixture was heated at reflux for 6 h. After cooling to room temp. and hydrolysis with HOAc (20 mL), the solution was concentrated, taken up in 10% HCl/H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. Chromatography (SiO_2; pentane/EtOAc = 3:1) gave **13** as a colorless solid (2.98 g, 15.8 mmol, 86%), m.p. 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27−7.13 (m, 4 H, 6-H, 7-H, 8-H, 9-H), 4.82 (d, J = 16.7 Hz, 1 H, 5-H_a), 4.58 (t, J = 8.5 Hz, 1 H, 1-H_a), 4.37 (d, J = 16.7 Hz, 1 H, 5-H_b), 4.14 (dd, J = 8.5, J = 5.1 Hz, 1 H, 1-H_b), 4.00−3.93 (m, 1 H, 10a-H), 2.94 (dd, J = 15.3, J = 4.4 Hz, 1 H, 10-H_a), 2.86 (dd, J = 15.3, J = 10.8 Hz, 1 H, 10-H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (C=O), 131.6 (C-9a), 131.4 (C-5a), 129.4 (C-9), 127.0 (C-6), 126.8 (C-7), 126.4 (C-8), 68.4 (C-1), 51.1 (C-10a), 43.0 (C-5), 34.0 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3021, 3005 (m, C-H aromat.), 2958, 2946, 2912 (m, C−H aliphat.), 1747 (s, C=O), 1455, 1436 (s, C=C aromat.), 1077, 1011 (s, C−O), 780, 762 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 189 (54) [M^+], 144 (15) [$C_{10}H_{10}N^+$], 116 (27), 104 (100) [$C_8H_8^+$], 91 (16) [$C_7H_7^+$].

3-Benzyl-1,3-oxazolidin-2-one (14): A solution of NaOEt (1 M, 39.7 mL, 39.7 mmol) and diethyl carbonate (24.0 mL, 198 mmol) was added dropwise to a solution of **12** (3.0 g, 19.8 mmol) in abs. EtOH (150 mL), and the reaction mixture was heated at reflux for 6 h.The reaction was quenched with HOAc (50 mL) and the solvents were evaporated. The residue was taken up in 2 N HCl (15 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to give **14** as a colorless solid (2.56 g, 14 mmol, 73%), m.p. 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.27 (m, 5 H, 7-H, 8-H, 9-H, 10-H, 11-H), 5.23 (s, 2 H, 5-H), 4.29 (t, J = 8.1 Hz, 2 H, 1-

H), 3.42 (t, J = 8.1 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (C=O), 135.7 (C-6), 128.7 (C-7, C-11), 128.0 (C-8, C-10), 127.9 (C-9), 61.7 (C-1), 48.3 (C-5), 43.6 (C-4) ppm.

3-(1-Phenylethyl)-1,3-oxazolidin-2-one (16): A solution of *t*BuLi (1.6 M, 0.85 mL, 1.4 mmol) was added dropwise to a solution of **14** (177 mg, 1 mmol) in abs. THF (5 mL) in a Schlenk flask, and the reaction mixture stirred at −78 °C for 5 h. After addition of MeI (0.19 mL, 3 mmol), the reaction mixture was allowed to warm up to room temp. (16 h), hydrolyzed with satd. $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and the residue purified by flash chromatography (SiO_2; pentane/EtOAc = 2:1) to give **16** as a light-yellow oil (159 mg, 0.83 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.27 (m, 5 H, 7-H, 8-H, 9-H, 10-H, 11-H), 5.21 (q, J = 7.1 Hz, 1 H, 5-H), 4.29 (ddd, J = 9.2, J = 8.5, J = 6.8 Hz, 1 H, 1-H$_a$), 4.21 (ddd, J = 9.2, J = 8.5, J = 6.8 Hz, 1 H, 1-H$_b$), 3.51 (ddd, J = 9.2, J = 8.5, J = 6.8 Hz, 1 H, 4-H$_a$), 3.05 (ddd, J = 9.2, J = 8.5, J = 6.8 Hz, 1 H, 4-H$_b$), 1.58 (d, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9 (C=O), 139.4 (C-6), 128.7 (C-7, C-11), 127.8 (C-9), 126.9 (C-8, C-10), 61.8 (C-1), 51.3 (C-5), 39.9 (C-4), 16.2 (CH_3) ppm.

Ethyl (5*S*,10a*S*)-3-Oxo-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinoline-5-carboxylate (19a): $TiCl_4$ (10.8 mL, 98.5 mmol) was added dropwise over 30 min to a solution of **18** (25.0 g, 65.7 mmol) in MeCN (375 mL), and the reaction mixture heated at 60 °C for 40 h. After hydrolysis with water (150 mL) with ice cooling, the layers were separated and the aqueous layer was extracted with Et_2O (4 × 150 mL). The combined organic layers were washed successively with 2 N NaOH solution (2 × 100 mL) and satd. NH_4Cl solution (2 × 100 mL), and dried ($MgSO_4$). The solvent was removed under vacuum, and the residue chromatographed (SiO_2; pentane/EtOAc = 2:1). In a first fraction (R_f = 0.25) **19a** was isolated as a colorless solid (13.6 g, 52.1 mmol, 79%), m.p. 61 °C, $[\alpha]_D^{22}$ = −126.5 (c = 1.1, $CHCl_3$). In a second fraction (R_f = 0.17) its diastereomer **19b** was obtained as a yellow oil (850 mg, 3.25 mmol, 5%), $[\alpha]_D^{22}$ = −135.5 (c = 1.08, $CHCl_3$).

19a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, J = 5.4, J = 3.6 Hz, 1 H, 6-H), 7.29−7.25 (m, 2 H, 7-H, 8-H), 7.17 (dd, J = 5.4, J = 3.8 Hz, 1 H, 9-H), 5.45 (s, 1 H, 5-H), 4.70 (t, J = 8.3 Hz, 1 H, 1-H$_a$), 4.48 (dddd, J = 11.3, J = 8.3, J = 6.4, J = 4.3 Hz, 1 H, 10a-H), 4.21 (q, J = 7.1 Hz, 2 H, 11-H), 4.14 (dd, J = 8.3, J = 6.3 Hz, 1 H, 1-H$_b$), 3.03 (dd, J = 15.7, J = 4.3 Hz, 1 H, 10-H$_a$), 2.88 (dd, J = 15.7, J = 11.1 Hz, 1 H, 10-H$_b$), 1.31 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (C=O, ester), 156.9 (C-3), 131.8 (C-9a), 129.7 (C-9), 128.7 (C-5a), 128.1 (C-7), 127.4 (C-6), 127.1 (C-8), 69.2 (C-1), 61.9 (C-11), 54.9 (C-5), 49.2 (C-10a), 33.6 (C-10), 14.0 (C-12) ppm. IR (KBr): $\tilde{\nu}$ = 3068 (m, C−H aromat.), 2991, 2936, 2905 (m, C−H aliphat.), 1758, 1725 (s, C=O, ester, oxazolidinone), 1477, 1408 (s, C=C aromat.), 1068, 1016 (s, C−O), 759, 715 (m) cm^{-1}. MS (EI): m/z (%) = 188 (100) [M^+ − $CH_2COOC_2H_5$], 144 (21) [$C_{11}H_{10}N^+$], 117 (23), 44 (36). GC: HP-5, temperature program: 16 °C min^{-1} gradient from 80 to 300 °C, t_R = 12.36 min.

19b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (dd, J = 5.4, J = 3.6 Hz, 1 H, 6-H), 7.31−7.26 (m, 2 H, 7-H, 8-H), 7.19 (dd, J = 4.9, J = 3.6 Hz, 1 H, 9-H), 5.29 (s, 1 H, 5-H), 4.68 (t, J = 8.4 Hz, 1 H, 1-H$_a$), 4.25 (dd, J = 9.6, J = 8.4 Hz, 1 H, 1-H$_b$), 4.16 (q, J = 7.1 Hz, 2 H, 11-H), 4.20−4.01 (m, 1 H, 10a-H), 3.14 (dd, J = 14.4, J = 11.4 Hz, 1 H, 10-H$_a$), 2.97 (dd, J = 14.4, J = 3.2 Hz, 1 H, 10-H$_b$), 1.22 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8 (C=O, ester), 157.1 (C-3), 133.3 (C-9a), 129.9 (C-5a), 129.1 (C-6), 128.5 (C-8), 127.8 (C-9), 127.6 (C-7), 69.7 (C-1), 62.0 (C-11), 57.7 (C-5), 52.4 (C-10a), 34.5 (C-10), 13.9 (C-12) ppm. IR (film): $\tilde{\nu}$ = 3029 (m, C−H aromat.), 2979, 2904 (m, C−H aliphat.), 1755, 1736 (s, C=O, ester, oxazolidinone), 1490, 1415 (s, C=C aromat.), 1188, 1023 (s, C−O), 755, 738 (m) cm^{-1}. MS (EI): m/z (%) = 188 (100) [M^+ − $CH_2COOC_2H_5$], 144 (22) [$C_{11}H_{10}N^+$], 117 (24), 115 (17), 43 (66). $C_{14}H_{15}NO_4$ (261.27): calcd. C 64.36, H 5.79, N 5.36; found C 63.94, H 5.99, N 5.02. GC: t_R = 12.26 min.

(5*S*,10a*S*)-5-(Hydroxymethyl)-1,5,10,10a-tetrahydro[1,3]oxazolo-[3,4-*b*]isoquinolin-3-one (20a): MeOH (4.70 mL, 385 mmol) was added dropwise to a solution of $LiBH_4$ (8.39 g, 385 mmol) in abs. THF (270 mL). After stirring for 30 min, a solution of **19a** (25.1 g, 96.1 mmol) in abs. THF (50 mL) was added, and the reaction mixture was heated at 50 °C for 6 h, and then hydrolyzed with 3 N HCl (80 mL) with ice cooling. The organic solvent was removed under vacuum, and the precipitate filtered off, washed with Et_2O and dried over P_2O_5 under high vacuum to give **20a** as a colorless solid (18.3 g, 83.5 mmol, 87%), m.p. 200 °C, $[\alpha]_D^{22}$ = −68.3 (c = 1.04, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.35−7.33 (m, 1 H, 6-H), 7.26−7.16 (m, 3 H, 7-H, 8-H, 9-H), 5.00 (t, J = 6.0 Hz, 1 H, OH), 4.70 (dd, J = 5.9, J = 4.4 Hz, 1 H, 5-H), 4.50 (t, J = 8.2 Hz, 1 H, 1-H$_a$), 4.25−4.18 (m, 1 H, 10a-H), 4.14 (dd, J = 8.2, J = 3.8 Hz, 1 H, 1-H$_b$), 3.76 (ddd, J = 11.3, J = 6.0, J = 4.4 Hz, 1 H, 1′-H$_a$), 3.68 (ddd, J = 11.3, J = 5.8, J = 5.8 Hz, 1 H, 1′-H$_b$), 2.96 (dd, J = 16.4, J = 4.6 Hz, 1 H, 10-H$_a$), 2.77 (dd, J = 16.4, J = 11.0 Hz, 1 H, 10-H$_b$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.6 (C=O), 133.2 (C-9a), 133.0 (C-5a), 129.3 (C-9), 126.9 (C-8), 126.8 (C-7), 126.3 (C-6), 68.0 (C-1), 64.4 (C-1′), 54.3 (C-5), 48.3 (C-10a), 33.0 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3331 (br., O−H), 2475 (s, O−H, intramolecular H bond), 3063, 3032 (m, C−H aromat.), 2941, 2920, 2853 (m, C−H aliphat.), 1715 (s, C=O), 1605, 1484, 1455, 1433 (s, C=C aromat.), 1064 (s, C−O), 759, 718 (m) cm^{-1}. MS (EI): m/z (%) = 218 (8) [M^+ − H], 188 (100) [M^+ − CH_2OH], 144 (44) [$C_{11}H_{10}N^+$], 117 (59), 115 (49). $C_{12}H_{13}NO_3$ (219.24): calcd. C 65.74, H 5.98, N 6.39; found C 65.34, H 6.26, N 6.22.

(5*S*,10a*S*)-5-(Methoxymethyl)-1,5,10,10a-tetrahydro[1,3]oxazolo-[3,4-*b*]isoquinolin-3-one (21a): With ice cooling, MeI (19.6 mL, 314 mmol) and a solution of **20a** (17.4 g, 78.6 mmol) in abs. THF (45 mL) was added dropwise to a suspension of NaH (4.77 g, 121 mmol) in abs. THF (230 mL). The reaction mixture was stirred at room temp. for 16 h prior to hydrolysis with satd. NH_4Cl solution (30 mL). The organic solvent was removed, and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2; pentane/EtOAc = 5:1) to give **21a** as a colorless solid (16.7 g, 71.6 mmol, 91%), m.p. 72.5 °C, $[\alpha]_D^{22}$ = −188.5 (c = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26−7.21 (m, 3 H, 7-H, 8-H, 9-H), 7.14 (d, J = 7.1 Hz, 1 H, 6-H), 5.02 (t, J = 4.3 Hz, 1 H, 5-H), 4.60 (t, J = 8.6 Hz, 1 H, 1-H$_a$), 4.25 (dddd, J = 10.8, J = 8.6, J = 4.5, J = 4.2 Hz, 1 H, 10a-H), 4.13 (dd, J = 8.6, J = 4.2 Hz, 1 H, 1-H$_b$), 3.81 (dd, J = 10.1, J = 4.3 Hz, 1 H, 1′-H$_a$), 3.78 (dd, J = 10.1, J = 4.3 Hz, 1 H, 1′-H$_b$), 3.33 (s, 3 H, OCH_3), 2.95 (dd, J = 15.6, J = 4.3 Hz, 1 H, 10-H$_a$), 2.87 (dd, J = 15.6, J = 10.8 Hz, 1 H, 10-H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0 (C=O), 132.6 (C-5a), 132.5 (C-9a), 129.5 (C-6), 127.3 (C-9), 126.9 (C-8), 126.5 (C-7), 75.9 (C-1′), 68.5 (C-1), 59.2 (O*C*H$_3$), 52.3 (C-5), 49.4 (C-10a), 34.1 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3065, 3035, 3024 (m, C−H aromat.), 2992, 2967, 2931, 2897 (m, C−H aliphat.), 1745 (s, C=O), 1435, 1417 (s, C=C aromat.), 1103, 1020 (s, C−O), 761, 750 (m) cm^{-1}. MS (EI): m/z (%) =

234 (2) [$M^+ + H$], 233 (1) [M^+], 188 (100) [$M^+ - CH_2OCH_3$], 144 (27) [$C_{11}H_{10}N^+$], 117 (32), 115 (24). $C_{13}H_{15}NO_3$ (233.26): calcd. C 66.94, H 6.48, N 6.00; found C 66.63, H 6.55, N 5.67. GC: HP-5, temperature program: 16 °C min^{-1} gradient from 80 to 300 °C, t_R = 11.7 min.

[(1*S*,3*S*)-1-(Methoxymethyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]-methanol (10): A 2 N NaOH solution (200 mL) was added to a solution of **21a** (16.6 g, 71.0 mmol) in MeOH (200 mL), and the reaction mixture heated at 80 °C for 4 h. The organic solvent was removed, and the remaining aqueous layer extracted with CH_2Cl_2 (3 × 80 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give **10** as a light-yellow solid (13.6 g, 67.5 mmol, 93%), m.p. 122 °C, $[\alpha]_D^{22} = -26.7$ (c = 1.0, $CHCl_3$). NMR spectroscopic data are in accordance with those in ref.[23]

(5*R*,10a*S*)-5-(Hydroxymethyl)-1,5,10,10a-tetrahydro[1,3]oxazolo-[3,4-*b*]isoquinolin-3-one (20b): As described above for **20a**, from **19b** (300 mg, 1.15 mmol) in abs. THF (5 mL), $LiBH_4$ (100 mg, 4.60 mmol) in abs. THF (5 mL), MeOH (186 μL, 4.60 mmol), hydrolysis with 3 N HCl (6 mL), and flash chromatography (SiO_2; pentane/EtOAc = 1:1) by-product **22** was obtained in a first fraction (R_f = 0.19) as a yellow oil (32 mg, 0.15 mmol, 13%), $[\alpha]_D^{22} = -202.2$ (c = 1.05, $CHCl_3$), and **20b** in a second fraction (R_f = 0.10) as a colorless solid (95 mg, 0.43 mmol, 38%), m.p. 178 °C, $[\alpha]_D^{22} = -174.5$ (c = 1.0, MeCN).

20b: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.36−7.22 (m, 4 H, 6-H, 7-H, 8-H, 9-H), 4.84 (dd, J = 6.7, J = 5.6 Hz, 1 H, OH), 4.66 (dd, J = 3.8, J = 2.5 Hz, 1 H, 5-H), 4.55 (t, J = 7.4 Hz, 1 H, 1-H$_a$), 4.10−4.04 (m, 1 H, CH_2OH), 4.03 (dd, J = 10.8, J = 7.4 Hz, 1 H, 1-H$_b$), 3.94 (dddd, J = 10.8, J = 10.6, J = 7.4, J = 3.7 Hz, 1 H, 10a-H), 3.63 (ddd, J = 10.8, J = 6.7, J = 2.5 Hz, 1 H, CH_2OH), 2.94 (dd, J = 14.2, J = 10.6 Hz, 1 H, 10-H$_a$), 2.88 (dd, J = 14.2, J = 3.7 Hz, 1 H, 10-H$_b$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.2 (C=O), 135.2 (C-9a), 134.6 (C-5a), 128.2 (C-6), 127.5 (C-9), 126.6 (C-8), 126.5 (C-7), 68.0 (C-1), 62.9 (C-1′), 56.4 (C-5), 53.6 (C-10a), 33.3 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3395 (br., O−H), 3067, 3020, 3006 (m, C−H aromat.), 2960, 2920, 2893 (m, C−H aliphat.), 1722 (s, C=O), 1479, 1428 (s, C=C aromat.), 1078 (m, C−O), 762, 754 (m) cm^{-1}. MS (EI): m/z (%) = 219 (5) [M^+], 188 (100) [$M^+ - CH_2OH$], 144 (57) [$C_{11}H_{10}N^+$], 130 (9) [$C_9H_8N^+$], 117 (17), 115 (19). $C_{12}H_{13}NO_3$ (219.24): calcd. C 65.74, H 5.98, N 6.39; found C 65.55, H 5.82, N 6.51.

22: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21−7.17 (m, 2 H, 7-H, 8-H), 7.14−7.10 (m, 1 H, 6-H), 6.92−6.88 (m, 1 H, 9-H), 5.02 (t, J = 8.3 Hz, 1 H, 5-H), 4.80 (t, J = 8.3 Hz, 1 H, 1-H$_a$), 4.17 (t, J = 8.3 Hz, 2 H, 1-H$_b$, OH), 3.96 (br. s, 2 H, CH_2OH), 3.60 (dddd, J = 11.1, J = 5.7, J = 4.0, J = 3.9 Hz, 1 H, 11-H), 3.08 (dd, J = 16.3, J = 11.1 Hz, 1 H, 10-H$_a$), 2.68 (dd, J = 16.3, J = 3.9 Hz, 1 H, 10-H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2 (C=O), 133.8 (C-5a), 133.5 (C-9a), 129.4 (C-6), 127.8 (C-7), 127.1 (C-8), 124.1 (C-9), 69.1 (C-1), 62.2 (*C*H_2OH), 56.7 (C-5), 55.0 (C-11), 30.3 (C-10) ppm. IR (film): $\tilde{\nu}$ = 3419 (br., O-H), 3066, 3028, (m, C−H aromat.), 2910 (m, C−H aliphat.), 1747 (s, C=O), 1476, 1457 (s, C=C aromat.), 1083 (m, C−O), 762, 746 (m) cm^{-1}. MS (EI): m/z (%) = 188 (100) [$M^+ - CH_2OCH_3$], 144 (23) [$C_{11}H_{10}N^+$], 117 (29), 115 (21). $C_{12}H_{13}NO_3$ (219.24): calcd. C 65.74, H 5.98, N 6.39; found C 65.46, H 5.92, N 6.11.

(5*R*,10a*S*)-5-(Methoxymethyl)-1,5,10,10a-tetrahydro[1,3]oxazolo-[3,4-*b*]isoquinolin-3-one (21b): As described above for **21a**, from MeI (0.29 mL, 4.56 mmol), **20b** (100 mg, 0.46 mmol) in abs. THF (5 mL), and NaH (27 mg, 0.69 mmol) in abs. THF (5 mL), hydrolysis with satd. NH_4Cl solution (8 mL) and flash chromatography (SiO_2; pentane/EtOAc = 2:1; R_f = 0.11) was obtained a mixture of **21b** and **23** in a ratio of 5:1 (83 mg, 0.36 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.21 (m, 3 H, 7-H, 8-H, 9-H), 7.17−7.14 (m, 1 H, 6-H), 4.79 (dd, J = 4.6, J = 2.4 Hz, 1 H, 5-H), 4.52 ('td', J = 6.6, J = 0.9 Hz, 1 H, 1-H$_a$), 4.06 (dd, J = 9.6, J = 4.6 Hz, 1 H, CH_2OCH$_3$), 4.06−4.02 (m, 1 H, 1-H$_b$), 4.02−3.94 (m, 1 H, 10a-H), 3.66 (dd, J = 9.6, J = 2.4 Hz, 1 H, CH_2OCH$_3$), 3.21 (s, 3 H, CH$_2$OCH_3), 2.97 (dd, J = 14.1, J = 10.0 Hz, 1 H, 10-H$_a$), 2.89 (dd, J = 14.1, J = 3.0 Hz, 1 H, 10-H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7 (C=O), 134.7 (C-5a), 133.8 (C-9a), 128.4 (C-6), 127.3 (C-9), 127.2 (C-8), 127.0 (C-7), 73.9 (C-1′), 68.4 (C-1), 59.2 (O*C*H$_3$), 55.0 (C-5), 54.2 (C-10a), 34.1 (C-10) ppm. IR (ATR): $\tilde{\nu}$ = 2995 (m, C−H aromat.), 2977, 2955, 2924, 2891 (m, C−H aliphat.), 1733 (s, C=O), 1491, 1474, 1407 (s, C=C aromat.), 1103, 1075 (s, C−O), 790, 760 (m) cm^{-1}. MS (EI): m/z (%) = 233 (1) [M^+], 201 (2) [$M^+ - 32$], 188 (100) [$M^+ - CH_2OCH_3$], 144 (25) [$C_{11}H_{10}N^+$], 117 (24), 115 (19).

(2*S*)-1-Chloro-5-methylhex-4-en-2-ol (8a): A solution of **24** (0.5 M, 21.6 mL, 10.8 mmol) in Et_2O was added dropwise to a suspension of CuI (206 mg, 1.08 mmol) in abs. THF (40 mL) at −10 °C in a Schlenk flask. After stirring at −10 °C for 45 min and then cooling to −78 °C, (*S*)-epichlorohydrin (1.00 g, 10.81 mmol) was slowly added. The reaction mixture was allowed to warm up to room temp. (16 h) and hydrolyzed with satd. NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was distilled under vacuum to give **8a** as a colorless liquid (1.39 g, 9.35 mmol, 87%), b.p. 82−85 °C/40 mbar, $[\alpha]_D^{22} = +8.3$ (c = 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (m, 1 H, 4-H), 3.82 (ddd, J = 13.0, J = 6.6, J = 3.7 Hz, 1 H, 2-H), 3.63 (dd, J = 11.1, J = 3.7 Hz, 1 H, 1-H$_a$), 3.50 (dd, J = 11.1, J = 6.6 Hz, 1 H, 1-H$_b$), 2.31−2.28 (m, 3 H, 3-H, OH), 1.73 (d, J = 1.1 Hz, 3 H, 6-H), 1.65 (s, 3 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7 (C-5), 118.5 (C-4), 71.4 (C-2), 49.6 (C-1), 33.0 (C-3), 25.8 (C-6), 17.9 (C-7) ppm. IR (film): $\tilde{\nu}$ = 3384 (br., OH), 3048 (C−H olefin), 2969, 2916, 2860, 2731 (s, C−H aliphat.), 1673, 1648 (C=C olefin), 1437 (O−H), 1053 (s, C−O) cm^{-1}. MS (EI): m/z (%) = 150 (12) [$C_7H_{13}ClO^+$], 148 (35) [M^+], 81 (47) [$C_6H_9^+$], 69 (100) [$C_5H_9^+$], 41 (94) [$C_3H_5^+$].

(2*S*)-2-(3-Methylbut-2-enyl)oxirane (25): A mixture of **8a** (1.24 g, 8.34 mmol) and powdered KOH (565 mg, 10.1 mmol) was heated in a distillation apparatus under vacuum until product **25** distilled off as a colorless liquid (934 mg, 8.33 mmol, 99%), b.p. 48−50 °C/140 mbar, $[\alpha]_D^{22} = +23.2$ (c = 1.31, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 5.14 (m, 1 H, 4-H), 2.65 (dddd, J = 5.4, J = 5.4, J = 3.8, J = 2.5 Hz, 1 H, 2-H), 2.33 (dd, J = 5.4, J = 3.8 Hz, 1 H, 1-H$_a$), 2.18−2.11 (m, 1 H, 3-H$_a$), 2.14 (dd, J = 5.4, J = 2.5 Hz, 1 H, 1-H$_b$), 2.06−1.99 (m, 1 H, 3-H$_b$), 1.59 (d, J = 1.0 Hz, 3 H, 6-H), 1.43 (s, 3 H, 7-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 134.1 (C-5), 119.2 (C-4), 51.4 (C-2), 45.9 (C-1), 31.4 (C-3), 25.7 (C-6), 17.7 (C-7) ppm. IR (film): $\tilde{\nu}$ = 3048 (C−H olefin), 2981, 2918, 2859, 2734 (s, C−H aliphat.), 1675 (C=C olefin), 1111 (s, C−O), 836 (C−H olefin) cm^{-1}. MS (EI): m/z (%) = 112 (29) [M^+], 97 (50) [$C_6H_9O^+$], 81 (42) [$C_5H_5O^+$], 79 (83) [$C_6H_7^+$], 69 (93) [$C_5H_9^+$], 67 (92) [$C_5H_7^+$], 41 (100) [$C_3H_5^+$].

[(1*S*,3*S*)-1-(Methoxymethyl)-2-(5-methyl-4-hexenyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (26): CaO (1.00 g, 18.1 mmol) was added to a solution of **10** (1.50 g, 7.24 mmol) in DMF (12 mL) in a Schlenk flask, followed by addition of 6-bromo-2-methylhex-2-ene (1.39 g, 7.83 mmol) over 5 min, and the reaction mixture stirred at room temp. for 3 d. Additional CaO (1.00 g, 18.1 mmol) was then added, and the reaction mixture stirred for a further 7 d. After

dilution with CH_2Cl_2 and filtration through Celite, the solvent was removed under vacuum, and remaining DMF by azeotropic distillation with toluene. The residue was purified by flash chromatography (SiO_2; pentane/EtOAc = 5:1 and 3:1) to give **26** as a yellow oil (1.23 g, 4.05 mmol, 56%). NMR spectroscopic data are in accordance with those in ref.[23]

(1*S*,3*S*)-1-(Methoxymethyl)-2-(5-methyl-4-hexenyl)-1,2,3,4-tetrahydroisoquinoline-3-carbaldehyde (27): DMSO (0.82 mL, 11.55 mmol) in abs. CH_2Cl_2 (4 mL) was added dropwise over 30 min to a solution of $(COCl)_2$ (0.52 mL, 5.94 mmol) in abs. CH_2Cl_2 (15 mL) at −50 °C. After stirring for 15 min, a solution of **26** (700 mg, 2.31 mmol) in abs. CH_2Cl_2 (10 mL) was added dropwise over 45 min, and the reaction mixture was stirred at −50 °C for 16 h. Et_3N (1.7 mL) was added dropwise over 30 min, the reaction mixture stirred for a further 15 min and then allowed to warm up to room temp. The organic layer was washed with water (3 × 50 mL) and dried ($MgSO_4$). The solvent was removed under vacuum to give **27** (699 mg, quant.). NMR spectroscopic data are in accordance with those in ref.[23]

Silylation of Compounds 10 and 11. General Procedure: TBSCl (26.0 mmol) was added to a solution of **10** or **11** (24.0 mmol), imidazole (60.0 mmol) and DMAP (1.23 mmol) in abs. CH_2Cl_2 (40 mL), and the reaction mixture stirred at room temp. for 16 h. After hydrolysis with satd. NH_4Cl solution (100 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed successively with satd. $NaHCO_3$ solution (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (SiO_2; pentane/EtOAc = 15:1) to give products **28**.

(1*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxymethyl)-1-(methoxymethyl)-1,2,3,4-tetrahydroisoquinoline (28a): From **10** (1.2 g, 5.79 mmol), imidazole (0.96 g, 14.12 mmol), DMAP (0.06 g, 0.43 mmol) and TBSCl (0.92 g, 6.12 mmol) **28a** was obtained as a colorless oil (1.78 g, 5.54 mmol, 96%), R_f = 0.20, $[\alpha]_D^{22}$ = −17.7 (*c* = 1.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06−6.99 (m, 4 H, 5-H, 6-H, 7-H, 8-H), 4.17 (dd, *J* = 10.0, *J* = 3.8 Hz, 1 H, 1-H), 3.65 (dd, *J* = 9.6, *J* = 4.0 Hz, 1 H, 1′′-H_a), 3.48 (dd, *J* = 10.0, *J* = 9.8 Hz, 1 H, 1′-H_a), 3.43 (dd, *J* = 9.6, *J* = 8.3 Hz, 1 H, 1′′-H_b), 3.39 (dd, *J* = 9.8, *J* = 3.8 Hz, 1 H, 1′-H_b), 3.33 (s, 3 H, OCH_3), 3.18−3.11 (m, 1 H, 3-H), 2.65 (br. s, 1 H, NH), 2.56 (dd, *J* = 15.9, *J* = 3.9 Hz, 1 H, 4-H_a), 2.44 (dd, *J* = 15.9, *J* = 10.7 Hz, 1 H, 4-H_b), 0.84 [s, 9 H, C(CH_3)$_3$], 0.09 (s, 3 H, Si−CH_3), 0.01 (s, 3 H, Si−CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9 (C-4a), 134.8 (C-8a), 129.3 (C-8), 127.2 (C-5), 126.5 (C-6), 125.6 (C-7), 74.8 (C-1′), 67.1 (C-1′′), 58.9 (O-CH_3), 55.2 (C-1), 48.6 (C-3), 31.6 (C-4), 25.8 [C(CH_3)$_3$], 18.2 [C(CH_3)$_3$], −5.3 (Si−CH_3), −5.4 (Si−CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3335 (N−H), 3063, 3021 (m, C−H aromat.), 2954, 2926, 2885, 2854 (s, C−H aliphat.), 1675, 1492, 1454 (s, C=C aromat.), 1104, 1053 (s, C−O), 833 (s, C−H olefin), 773, 740 (s, 1,2-disubst. aromat.) cm^{-1}. MS (EI): *m*/*z* (%) = 276 (100) [M^+ − CH_2OCH_3], 260 (38) [M^+ − CH_2OCH_3 − CH_3], 218 (15) [$C_{12}H_{16}NOSi^+$], 176 (23) [M^+ − $CH_2OSi(CH_3)_2C(CH_3)_3$], 144 (29) [$C_{10}H_{10}N^+$]. $C_{18}H_{31}NO_2Si$ (321.50): calcd. C 68.89, H 9.85, N 3.34; found C 68.81, H 10.04, N 3.24.

(3*S*)-3-(*tert*-Butyldimethylsilyloxymethyl)-1,2,3,4-tetrahydroisoquinoline (28b): From **11** (2.00 g, 12.3 mmol), imidazole (2.04 g, 30.0 mmol), DMAP (0.08 g, 0.61 mmol) and TBSCl (1.96 g, 13.0 mmol) **28b** was obtained as a colorless oil (3.21 g, 11.6 mmol, 94%), R_f = 0.10, $[\alpha]_D^{22}$ = −47.3 (*c* = 1.00, CH_2Cl_2). NMR spectroscopic data are in accordance with those in ref.[23]

***N*-Alkylation of Compounds 28. General Procedure:** A solution of Et_3Al (2 M in toluene, 1.30 mmol) was added dropwise under an inert gas to a solution of the appropriate **28** (1.00 mmol) in abs. CH_2Cl_2 (10 mL), and the reaction mixture stirred for 30 min. After addition of **25** (1.00 mmol), the reaction mixture was stirred at room temp. for 16 h, and then hydrolyzed with 2 N NaOH solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and the residue was purified by flash chromatography on SiO_2 to give products **29**.

(1*S*,2′*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-(2′-hydroxy-5′-methylhex-4′-enyl)-1-(methoxymethyl)-1,2,3,4-tetrahydroisoquinoline (29a): From **28a** (1.00 g, 3.11 mmol), Et_3Al (2.1 mL, 4.04 mmol) and **25** (300 mg, 3.11 mmol), after flash chromatography with pentane/EtOAc (20:1), **29a** was obtained as a colorless oil (944 mg, 2.18 mmol, 70%), R_f = 0.19, $[\alpha]_D^{22}$ = +18.6 (*c* = 1.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18−7.15 (m, 3 H, 5-H, 6-H, 7-H), 7.14−7.11 (m, 1 H, 8-H), 5.19−5.15 (m, 1 H, 4′-H), 3.94 (dd, *J* = 8.6, *J* = 4.5 Hz, 1 H, 1-H), 3.82 (dd, *J* = 10.2, *J* = 6.2 Hz, 1 H, CH_2OSi), 3.72−3.67 (m, 2 H, 2′-H, CH_2OSi), 3.64 (dd, *J* = 10.2, *J* = 8.6 Hz, 1 H, CH_2OCH_3), 3.54 (dd, *J* = 10.2, *J* = 4.5 Hz, 1 H, CH_2OCH_3), 3.41 (s, 3 H, OCH_3), 3.35−3.28 (m, 1 H, 3-H), 2.66−2.64 (m, 2 H, 4-H), 2.42−2.32 (m, 2 H, 1′-H), 2.23−2.16 (m, 1 H, 3′-H_a), 2.07−2.00 (m, 1 H, 3′-H_b), 1.67 (d, *J* = 1.3 Hz, 3 H, 7′-H), 1.57 (d, *J* = 0.8 Hz, 3 H, 6′-H), 0.88 [s, 9 H, C(CH_3)$_3$], 0.10 [s, 3 H, Si-(CH_3)$_2$], 0.09 [s, 3 H, Si-(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1 (C-5′), 134.4 (C-4a), 133.5 (C-8a), 129.6 (C-8), 128.8 (C-5), 126.8 (C-7), 126.3 (C-5), 120.5 (C-4′), 76.2 (CH_2OCH_3), 67.2 (C-2′), 65.4 (CH_2OSi), 61.2 (C-1), 59.4 (OCH_3), 54.3 (C-3), 52.8 (C-1′), 33.6 (C-3′), 26.8 (C-4), 26.2 [C(CH_3)$_3$], 26.1 (C-6′), 18.5 [C(CH_3)$_3$], 18.2 (C-7′), −5.1 (Si-CH_3), −5.0 (Si-CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3540 (br., O−H), 2954, 2926, 2883 (m, C−H aliphat.), 1451 (s, C=C aromat.), 1100 (s), 1006 (m), 834 (s, C−H olefin), 775, 740 (s, 1,2-disubst. aromat.) cm^{-1}. MS (EI): *m*/*z* (%) = 388 (100) [M^+ − CH_2OCH_3], 334 (12) [$C_{19}H_{32}NO_2Si^+$], 288 (12) [M^+ − CH_2OCH_3 − $CH_2OSi(C_3H_7)_3$], 144 (23) [$C_{10}H_{10}N^+$], 130 (12) [$C_9H_8N^+$].$C_{23}H_{43}NO_3Si$ (433.70): calcd. C 68.89, H 9.85, N 3.34; found C 68.82, H 10.04, N 3.24.

(2′*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-(2′-hydroxy-5′-methylhex-4′-enyl)-1,2,3,4-tetrahydroisoquinoline (29b): From **28b** (247 mg, 0.89 mmol), Et_3Al (0.58 mL, 1.16 mmol) and **25** (100 mg, 0.89 mmol), after flash chromatography with pentane/EtOAc (10:1), **29b** was obtained as a colorless oil (243 mg, 0.62 mmol, 70%), R_f = 0.24, $[\alpha]_D^{22}$ = +23.2 (*c* = 1.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15−7.08 (m, 3 H, 5-H, 6-H, 7-H), 7.03−7.00 (m, 1 H, 8-H), 5.19 ('tq', *J* = 7.2, *J* = 1.0 Hz, 1 H, 4′-H), 3.89 (d, *J* = 15.9 Hz, 1 H, 1-H_a), 3.80 (d, *J* = 15.9 Hz, 1 H, 1-H_b), 3.77 (dd, *J* = 10.4, *J* = 6.8 Hz, 1 H, 1′′-H_a), 3.73−3.67 (m, 1 H, 2′-H), 3.18−3.12 (m, 1 H, 3-H), 3.55 (dd, *J* = 10.4, *J* = 6.3 Hz, 1 H, 1′′-H_b), 2.97 (dd, *J* = 16.5, *J* = 5.5 Hz, 1 H, 4-H_a), 2.78 (dd, *J* = 13.1, *J* = 3.0 Hz, 1 H, 1′-H_a), 2.67 (dd, *J* = 16.5, *J* = 5.1 Hz, 1 H, 4-H_b), 2.50 (dd, *J* = 13.1, *J* = 10.6 Hz, 1 H, 1′-H_b), 2.27−2.20 (m, 1 H, 3′-H_a), 2.13−2.04 (m, 1 H, 3′-H_b), 1.71 (d, *J* = 1.0 Hz, 3 H, 7′-H), 1.62 (s, 3 H, 6′-H), 0.88 [s, 9 H, C(CH_3)$_3$], 0.02 [s, 6 H, Si-(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.1 (C-5′), 133.7 (C-4a), 133.5 (C-8a), 129.1 (C-5), 126.5 (C-6), 126.3 (C-7), 125.7 (C-8), 119.9 (C-4′), 67.0 (C-2′), 62.7 (C-1′′), 59.8 (C-1′), 59.7 (C-3), 51.1 (C-1), 33.4 (C-3′), 29.3 (C-4), 25.8 [C(CH_3)$_3$], 25.8 (C-6′), 18.2 [C(CH_3)$_3$], 17.9 (C-7′), −5.4 (Si-CH_3), −5.5 (Si-CH_3) ppm. IR (film): $\tilde{\nu}$ = 3452 (br., OH), 3064, 3046, 3023 (m, C−H aromat.), 2954, 2928, 2905, 2897 (s, C−H aliphat.), 1496 (m), 1104 (s), 1036 (m), 836 (s, C−H olefin), 776 (s, 1,2-disubst. aromat.) cm^{-1}. MS (EI): *m*/*z* (%) = 374 (1) [M^+ − 15], 290 (30) [M^+ − $C_6H_{11}O$], 258 (25) [M^+ − $C_6H_{15}SiO$], 244 (100) [M^+ − $C_7H_{17}SiO$],

130 (24) [$C_9H_8N^+$]. $C_{23}H_{39}NO_2Si$ (389.65): calcd. C 70.90, H 10.09, N 3.59; found C 70.71, H 10.44, N 3.51.

(1*S*,2′*S*,3*S*)-3-(Benzyloxymethyl)-2-(2′-hydroxy-5′-methylhex-4′-enyl)-1-(methoxymethyl)-1,2,3,4-tetrahydroisoquinoline (30): A solution of **29a** (300 mg, 0.69 mmol) in abs. THF (5 mL) was added to a suspension of NaH (33 mg, 0.83 mmol) in abs. THF (5 mL) with ice cooling, and the reaction mixture stirred for 30 min. After addition of BnBr (90 μL, 0.76 mmol), the reaction mixture was stirred at room temp. for 16 h and then hydrolyzed with satd. NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2; pentane/EtOAc = 3:1) to give **30** as a colorless oil (221 mg, 0.54 mmol, 78%), R_f = 0.21, $[\alpha]_D^{22}$ = +16.5 (*c* = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.25 (m, 4 H, 3′′-H, 7′′-H, 4′′-H, 6′′-H), 7.23−7.18 (m, 1 H, 5′′-H), 7.11−7.05 (m, 3 H, 6-H, 7-H, 8-H), 7.04−7.00 (m, 1 H, 5-H), 5.12−5.07 (m, 1 H, 4′-H), 4.52 (d, *J* = 11.9 Hz, 1 H, 1′′-H_a), 4.48 (d, *J* = 11.9 Hz, 1′′-H_b), 3.88 (dd, *J* = 8.7, *J* = 4.5 Hz, 1 H, 1-H), 3.66−3.59 (m, 2 H, 2′-H, CH_2OH), 3.59 (dd, *J* = 10.1, *J* = 8.7 Hz, 1 H, CH_2OCH$_3$), 3.49−3.43 (m, 2 H, 3-H, CH_2OH), 3.45 (dd, *J* = 10.1, *J* = 4.5 Hz, 1 H, CH_2OCH$_3$), 3.33 (s, 3 H, OCH_3), 2.59−2.58 (m, 2 H, 4-H), 2.34−2.26 (m, 2 H, 1′-H), 2.16−2.08 (m, 1 H, 3′-H_a), 2.00−1.93 (m, 1 H, 3′-H_b), 1.59 (d, *J* = 1.0 Hz, 3 H, 7′-H), 1.50 (d, *J* = 1.0 Hz, 3 H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (C-2′′), 135.5 (C-5′), 133.9 (C-4a), 133.2 (C-8a), 129.2 (C-5), 128.5 (C-7), 128.4 (C-4′′, C-6′′), 127.7 (C-3′′, C-7′′), 127.6 (C-5′′), 126.5 (C-8), 126.0 (C-6), 120.1 (C-4′), 75.8 (*C*H_2OCH$_3$), 73.2 (C-1′′), 72.1 (CH_2OH), 66.9 (C-2′), 60.9 (C-1), 59.1 (OCH_3), 52.5 (C-1′), 51.8 (C-3), 33.2 (C-3′), 26.8 (C-4), 25.8 (C-7′), 17.9 (C-6′) ppm. IR (ATR): $\tilde{\nu}$ = 3453 (br., O-H), 3061, 3028 (m, C−H aromat.), 2963, 2913, 2856 (s, C−H aliphat.), 1492, 1451 (s, C=C aromat.), 1098, 1028 (s, C−O), 833 (s, C−H olefin) cm^{-1}. MS (EI): *m*/*z* (%) = 364 (100) [M^+ − CH_2OCH_3], 288 (20) [M^+ − CH_2OH − C_7H_7], 376 (10) [M^+ − CH_2OCH_3 − 54], 144 (13) [$C_{10}H_{10}N^+$], 130 (15) [$C_9H_8N^+$], 91 (56) [$C_7H_7^+$]. $C_{26}H_{35}NO_3$ (409.57): calcd. C 76.25, H 8.61, N 3.42; found C 76.39, H 8.58, N 3.33.

(2′*S*,3*S*)-2-(2′-Benzyloxy-5′-methylhex-4′-enyl)-3-(*tert*-butyldimethylsilyloxymethyl)-1,2,3,4-tetrahydroisoquinoline (31): As described above for **30**, from **29b** (500 mg, 1.28 mmol) in abs. THF (8 mL), NaO*t*Bu (148 mg, 1.54 mmol) in abs. THF (8 mL), BnBr (220 μL, 1.93 mmol), after chromatography with pentane/EtOAc (20:1), **31** was obtained as a colorless oil (221 mg, 0.46 mmol, 60% referred to reacted **29b**), R_f = 0.21, $[\alpha]_D^{22}$ = +57.6 (*c* = 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.34 (m, 2 H, 3′′-H, 7′′-H), 7.31−7.24 (m, 3 H, 4′′-H, 5′′-H, 6′′-H), 7.16−7.09 (m, 3 H, 5-H, 6-H, 7-H), 6.99−6.97 (m, 1 H, 8-H), 5.19 ('tq', *J* = 7.2, *J* = 1.2 Hz, 1 H, 4′-H), 4.63 (s, 2 H, 1′′-H), 3.84 (d, *J* = 15.4 Hz, 1 H, 1-H_a), 3.80−3.76 (m, 1 H, CH_2OSi), 3.78 (d, *J* = 15.4 Hz, 1 H, 1-H_b), 3.63−3.57 (m, 1 H, 2′-H), 3.48 (dd, *J* = 10.1, *J* = 7.5 Hz, 1 H, CH_2OSi), 3.08 (dddd, *J* = 7.5, *J* = 5.3, *J* = 5.1, *J* = 4.8 Hz, 1 H, 3-H), 2.98 (dd, *J* = 16.3, *J* = 5.5 Hz, 1 H, 4-H_a), 2.87 (dd, *J* = 13.7, *J* = 6.7 Hz, 1 H, 1′-H_a), 2.76 (dd, *J* = 13.7, *J* = 4.5 Hz, 1 H, 1′-H_b), 2.73 (dd, *J* = 16.3, *J* = 4.8 Hz, 1 H, 4-H_b), 2.35−2.23 (m, 2 H, 3′-H), 1.71 (d, *J* = 1.2 Hz, 3 H, 7′-H), 1.61 (d, *J* = 0.9 Hz, 3 H, 6′-H), 0.87 [s, 9 H, Si−C(CH_3)$_3$], 0.01 [s, 6 H, Si-(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2 (C-2′′), 135.0 (C-5′), 134.3 (C-8a), 133.2 (C-4a), 128.9 (C-5), 128.2 (C-4′′, C-6′′), 127.7 (C-3′′, C-7′′), 127.3 (C-4′′), 126.3 (C-8), 126.1 (C-6), 125.4 (C-7), 120.5 (C-4′), 78.2 (C-2′), 71.5 (C-1′′), 62.9 (*C*H_2OSi), 59.6 (C-3), 58.5 (C-1′), 52.2 (C-1), 31.4 (C-3′), 29.9 (C-4), 25.9 [C(*C*H_3)$_3$], 25.8 (C-7′), 18.2 [*C*(CH$_3$)$_3$], 17.9 (C-6′), −5.4 [Si(*C*H_3)$_2$] ppm. IR (ATR): $\tilde{\nu}$ = 3064, 3026 (m, C−H aromat.), 2954, 2927, 2882, 2855 (s, C−H aliphat.), 1675, 1496 (s, C=C aromat.), 1092, 1069 (s, C−O), 833 (s, C−H olefin), 773, 738 (s, 1,2-disubst. aromat.) cm^{-1}. MS (EI): *m*/*z* (%) = 334 (100) [M^+ − $C_7H_{16}SiO$], 290 (30) [M^+ − $C_6H_{11}O$], 91 (9) [$C_7H_7^+$]. $C_{23}H_{39}NO_2Si$ (479.8): calcd. C 75.10, H 9.45, N 2.92; found C 74.85, H 9.51, N 2.78.

[(2′*S*,3*S*)-2-(2′-Benzyloxy-5′-methylhex-4′-enyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (32): A solution of TBAF (1 M in THF/5% H_2O, 1.05 mL, 1.05 mmol) was added to a solution of **31** (170 mg, 0.35 mmol) in THF (5 mL), and the reaction mixture stirred at room temp. for 24 h. After hydrolysis with water (10 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (4 × 8 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The product **32** (122 mg, 0.33 mmol, 94%) was dried under high vacuum and used without further purification, $[\alpha]_D^{22}$ = +31.6 (*c* = 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.24 (m, 4 H, 3′′-H, 7′′-H, 4′′-H, 6′′-H), 7.22−7.18 (m, 1 H, 5′′-H), 7.08−7.05 (m, 2 H, 6-H, 7-H), 7.00−6.98 (m, 1 H, 5 H), 6.94−6.92 (m, 1 H, 8-H), 5.08−5.03 (m, 1 H, 4′-H), 4.59 (d, *J* = 11.7 Hz, 1 H, 1′′-H_a), 4.48 (d, *J* = 11.7 Hz, 1 H, 1′′-H_b), 3.81 (s, 2 H, 1-H), 3.58−3.52 (m, 2 H, 2′-H, OH), 3.48 (d, *J* = 2.4 Hz, 1 H, CH_2OH), 3.46 (d, *J* = 5.1 Hz, 1 H, CH_2OH), 3.15 (dddd, *J* = 8.3, *J* = 8.3, *J* = 5.7, *J* = 5.6 Hz, 1 H, 3-H), 2.67−2.64 (m, 1 H, 4-H_a), 2.61 (d, *J* = 5.9 Hz, 1 H, 1′-H_a), 2.42−2.40 (m, 1 H, 4-H_b), 2.38−2.36 (m, 1 H, 1′-H_b), 2.25−2.11 (m, 2 H, 3′-H), 1.60 (d, *J* = 1.0 Hz, 3 H, 7′-H), 1.50 (d, *J* = 1.0 Hz, 3 H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1 (C-2′′), 133.9 (C-4a), 133.7 (C-8a), 133.5 (C-5′), 128.6 (C-5), 128.0 (C-4′′, C-6′′), 127.6 (C-3′′, C-7′′), 127.3 (C-5′′), 126.7 (C-8), 126.1 (C-6), 125.7 (C-7), 119.3 (C-4′), 77.1 (C-2′), 71.2 (C-1′′), 62.0 (*C*H_2OH), 58.7 (C-3), 53.0 (C-1′), 51.9 (C-1), 30.5 (C-3′), 25.9 (C-4), 25.5 (C-7′), 17.6 (C-6′) ppm. IR (ATR): $\tilde{\nu}$ = 3486 (br., O−H), 3068, 3056, 3022 (m, C−H aromat.), 2976, 2953, 2886 (s, C−H aliphat.), 1500, 1471 (s, C=C aromat.), 1068 (s, C−O), 823 (s, C−H olefin) cm^{-1}. MS (EI): *m*/*z* (%) = 365 (1) [M^+], 334 (42) [M^+ − CH_2OH], 176 (100) [$C_{14}H_{10}NO^+$], 146 (10) [$C_{10}H_{12}N^+$], 132 (12) [$C_9H_{10}N^+$], 117 (10), 105 (10), 91 (26) [$C_7H_7^+$]. $C_{23}H_{39}NO_2Si$ (365.51): calcd. C 78.86, H 8.55, N 3.83; found C 78.68, H 8.64, N 3.78.

(2′*S*,3*S*)-2-(2′-Benzyloxy-5′-methylhex-4′-enyl)-1,2,3,4-tetrahydroisoquinoline-3-carbaldehyde (33): As described above for **27**, from **32** (120 mg, 0.33 mmol), DMSO (148 μL, 1.64 mmol), $(COCl)_2$ (57 μL, 0.84 mmol) and NEt_3 (250 μL) **33** was obtained (119 mg, quant.). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.65 (d, *J* = 1.1 Hz, 1 H, CHO), 7.43−7.41 (m, 2 H, 3′′-H, 7′′-H), 7.29−7.25 (m, 2 H, 4′′-H, 6′′-H), 7.21−7.17 (m, 1 H, 5-H), 7.10−7.07 (m, 2 H, 6-H, 7-H), 7.00−6.98 (m, 1 H, 8-H), 6.89−6.84 (m, 1 H, 8-H), 5.38−5.33 (m, 1 H, 4′-H), 4.58 (d, *J* = 12.0 Hz, 1 H, 1′′-H_a), 4.54 (d, *J* = 12.0 Hz, 1 H, 1′′-H_b), 4.06 (d, *J* = 16.0 Hz, 1 H, 1-H_a), 3.74 (d, *J* = 16.0 Hz, 1 H, 1-H_b), 3.59 (ddd, *J* = 6.3, *J* = 6.1, *J* = 4.5 Hz, 1 H, 2′-H), 3.26 (ddd, *J* = 6.0, *J* = 5.7, *J* = 1.1 Hz, 1 H, 3-H), 2.90 (dd, *J* = 16.6, *J* = 5.7 Hz, 1 H, 4-H_a), 2.84 (dd, *J* = 13.6, *J* = 4.5 Hz, 1 H, 1′-H_a), 2.77 (dd, *J* = 13.6, *J* = 6.1 Hz, 1 H, 1-H_b), 2.76 (dd, *J* = 16.6, *J* = 6.3 Hz, 1 H, 4-H_b), 2.42 (t, *J* = 6.3 Hz, 2 H, 3′-H), 1.75 (d, *J* = 0.9 Hz, 3 H, 7′-H), 1.63 (s, 3 H, 6′-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 202.6 (C=O), 139.9 (C-2′′), 134.9 (C-5′), 133.5 (C-4a), 132.9 (C-8a), 129.2 (C-5), 128.7 (C-4′′, C-6′′), 128.1 (C-5′′), 128.0 (C-3′′, C-7′′), 127.8 (C-4), 127.1 (C-8), 126.9 (C-6), 126.6 (C-7), 121.2 (C-4′), 78.9 (C-2′), 71.8 (C-1′′), 67.4 (C-3), 58.3 (C-1′), 53.4 (C-1), 31.7 (C-3′), 26.8 (C-4), 26.1 (C-7′), 18.2 (C-6′) ppm. MS (EI): *m*/*z* (%) = 361 (1) [M^+ − 2], 332 (25) [M^+ − 2 − CHO], 270 (30) [M^+ − 2 − C_7H_7], 172 (84) [$C_{11}H_{10}NO^+$], 144 (48) [$C_{10}H_{10}N^+$], 91 (100) [$C_7H_7^+$].

Cyclization of Compounds 27 and 33 to Azepine Derivatives 34 and 35. General Procedure: The appropriate Lewis acid (Table 1, 2 equiv.) was added over 45 min, with ice cooling, to a solution of **27** (270 mg, 0.90 mmol) or **33** (115 mg, 0.32 mmol) in abs. CH_2Cl_2 (10 mL), and the reaction mixture stirred at room temp. for 24 h. After hydrolysis with 2 N NaOH solution (10 mL), the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was filtered through basic Al_2O_3 with hexane/*i*PrOH (3:1) as eluent, chromatographed (SiO_2; hexane/*i*PrOH/NEt_3 = 17:1:1) and finally purified by HPLC with hexane/*i*PrOH (17:1) as eluent.

(5*S*,10*S*,11*S*,11a*S*)-10-Isopropenyl-5-(methoxymethyl)-5,7,8,9,10,11,11a,12-octahydroazepino[1,2-*b*]isoquinolin-11-ol (34a): Crude yield: 81%; yield after HPLC: 54 mg, 0.18 mmol, 20%, yellow oil; GC: HP-5, temperature program 8 °C min^{-1}, gradient from 80 to 300 °C, t_R = 17.00 min, $[\alpha]_D^{22}$ = −20.1 (*c* = 1.97, MeCN). ^1H NMR (400 MHz, C_6D_6): δ = 7.15−7.13 (m, 2 H, 3-H, 4-H), 7.06−7.03 (m, 1 H, 2-H), 6.99−6.97 (m, 1 H, 1-H), 4.79−4.80 (m, 1 H, 14-H_a), 4.75−4.76 (m, 1 H, 14-H_b), 4.02 (t, *J* = 5.6 Hz, 1 H, 5-H), 3.61 (dd, *J* = 9.6 , *J* = 5.6 Hz, 1 H, 16-H_a), 3.55 (d, *J* = 2.5 Hz, 1 H, 11-H), 3.31 (dd, *J* = 9.6, *J* = 5.6 Hz, 1 H, 16-H_b), 3.29 (ddd, *J* = 9.5, *J* = 4.3, *J* = 3.6 Hz, 1 H, 11a-H), 3.03 (s, 3 H, OCH_3), 2.93−2.99 (m, 2 H, 7-H_a, 7-H_b), 2.78 (dd, *J* = 15.9, *J* = 9.5 Hz, 1 H, 12-H_a), 2.53 (dd, *J* = 15.9, *J* = 4.3 Hz, 1 H, 12-H_b), 2.35 (d, *J* = 11.4 Hz, 1 H, 10-H), 2.08−1.97 (m, 1 H, 9-H_a), 1.63 (s, 3 H, CH_3), 1.69−1.50 (m, 2 H, 8-H_a, 8-H_b), 1.49−1.41 (m, 1 H, 9-H_b) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 150.8 (C-13), 137.9 (C-12a), 135.1 (C-4a), 129.1, 127.8, 126.6, 125.7 (C-1, C-2, C-3, C-4), 110.2 (C-14), 75.7 (C-16, C-11), 64.7 (C-5), 60.2 (C-11a), 58.7 (O*C*H_3), 52.7 (C-7), 47.2 (C-10), 32.9 (C-12), 30.3 (C-8), 25.9 (C-9), 22.2 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3416 (br., OH), 3065, 3022 (C-H aromat.), 2923 (C−H aliphat.), 1604, 1493 (s, C=C aromat.), 1111 (s, C−O), 750 (1,2-disubst. aromat.) cm^{-1}. MS (EI): *m*/*z* (%) = 256 (100) [$C_{17}H_{22}NO^+$], 146 (13) [$C_{10}H_{12}N^+$], 130 (12) [$C_9H_8N^+$], 115 (7) [$C_9H_7^+$], 55 (6) [$C_4H_7^+$]. MS (CI, CH_4): *m*/*z* (%) = 302 (85) [M^+ +1], 270 (14) [$C_{18}H_{24}NO^+$], 256 (100) [$C_{17}H_{22}NO^+$].

(5*S*,10*R*,11*S*,11a*S*)-10-Isopropenyl-5-(methoxymethyl)-5,7,8,9,10,11,11a,12-octahydroazepino[1,2-*b*]isoquinolin-11-ol (34b): From **27** and $BF_3{\cdot}OEt_2$; crude yield: 80%; yield after HPLC: 41 mg, 0.14 mmol, 12%, yellow oil, t_R = 17.54, $[\alpha]_D^{22}$ = +6.0 (*c* = 0.90, MeCN). ^1H NMR (400 MHz, C_6D_6): δ = 7.13−7.09 (m, 2 H, 3-H, 4-H), 7.05−7.02 (m, 1 H, 1-H), 7.02−6.99 (m, 1 H, 4-H), 4.92 (d, *J* = 1.4 Hz, 2 H, 14-H), 3.92 (t, *J* = 6.4 Hz, 1 H, 5-H), 3.67 (s, 1 H, 11-H), 3.56 (dd, *J* = 9.5, *J* = 6.4 Hz, 1 H, 16-H_a), 3.46 (dd, *J* = 9.5, *J* = 6.4 Hz, 1 H, 16-H_b), 3.06 (s, 3 H, OCH_3), 2.83 (dd, *J* = 14.8, *J* = 9.7 Hz, 1 H, 12-H_a), 2.70−2.62 (m, 2 H, 7-H_a, 11a-H), 2.45 (dd, *J* = 14.8, *J* = 5.5 Hz, 1 H, 12-H_b), 2.34 (ddd, *J* = 11.2, *J* = 6.3, *J* = 2.8 Hz, 1 H, 7-H_b), 1.90 (t, *J* = 1.4 Hz, 3 H, 15-H), 1.87−1.82 (m, 1 H, 9-H_a), 1.84 (s, 1 H, 10-H), 1.60−1.54 (m, 1 H, 8-H_a), 1.46−1.40 (m, 1 H, 9-H_b), 1.21−1.13 (m, 1 H, 8-H_b) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 149.6 (C-13), 137.6 (C-12a), 137.5 (C-4a), 127.6 (C-1), 127.1 (C-2), 125.9 (C-3), 125.1 (C-4), 110.5 (C-14), 75.4 (C-11), 72.6 (C-16), 60.3 (C-5), 58.7 (C-11a), 58.6 (O*C*H_3), 54.3 (C-10), 49.4 (C-7), 33.2 (C-12), 27.5 (C-8), 25.0 (C-9), 22.4 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3417 (br., OH), 3066, 3024 (C−H aromat.), 2922, 2871, 2808 (C−H aliphat.), 1644, 1603, 1491 (s, C=C aromat.), 1106 (s, C−O), 742 (1,2-disubst. aromat.) cm^{-1}. MS (EI): *m*/*z* (%) = 256 (100) [$C_{17}H_{22}NO^+$], 146 (27) [$C_{10}H_{12}N^+$], 130 (22) [$C_9H_8N^+$], 115 (8) [$C_9H_7^+$], 55 (8) [$C_4H_7^+$]. MS (CI, CH_4): *m*/*z* (%) = 302 (88) [M^+ +1], 270 (18) [$C_{18}H_{24}NO^+$], 256 (100) [$C_{17}H_{22}NO^+$].

(5*S*,8*S*,10*R*,11*S*,11a*S*)-8-Benzyloxy-10-isopropenyl-5,7,8,9,10,11,11a,12-octahydroazepino[1,2-*b*]isoquinolin-11-ol (35b): Crude yield: 88%; yield after HPLC: 35 mg, 0.10 mmol, 30%, yellow oil; GC: HP-5, temperature program 8 °C min^{-1}, gradient from 80 to 300 °C, t_R = 13.03 min, $[\alpha]_D^{22}$ = +37.3 (*c* = 2.18, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 7.16−7.01 (m, 7 H, 2-H, 3-H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H), 6.99−6.97 (m, 1 H, 1-H), 6.92−6.90 (m, 1 H, 4-H), 5.01−5.00 (m, 1 H, 14-H_a), 4.97−4.96 (m, 1 H, 14-H_b), 4.23 (d, *J* = 12.1 Hz, 1 H, 1′-H_a), 4.07 (d, *J* = 12.1 Hz, 1 H, 1′-H_b), 3.67 (d, *J* = 1.9 Hz, 1 H, 11-H), 3.59−3.54 (m, 1 H, 8-H), 3.58 (d, *J* = 14.4 Hz, 1 H, 5-H_a), 3.23 (d, *J* = 14.4 Hz, 1 H, 5-H_b), 2.81−2.72 (m, 2 H, 12-H_a, 11a-H), 2.74 (dd, *J* = 12.9, *J* = 2.5 Hz, 1 H, 7-H_a), 2.63 (dd, *J* = 12.9, *J* = 6.5 Hz, 1 H, 7-H_b), 2.55 (ddd, *J* = 11.9, *J* = 2.3, *J* = 1.9 Hz, 1 H, 10-H), 2.37 (dd, *J* = 13.1, *J* = 3.8 Hz, 1 H, 12-H_b), 1.94 (dd, *J* = 1.4, *J* = 0.8 Hz, 3 H, 15-H), 1.89 (dd, *J* = 14.3, *J* = 2.0 Hz, 1 H, 9-H_a), 1.77 (ddd, *J* = 14.3, *J* = 6.6, *J* = 2.3 Hz, 1 H, 9-H_b) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 149.5 (C-13), 139.1 (C-12a), 137.7 (C-4a), 136.4 (C-2′), 128.5 (C-2), 127.9 (C-3′), 127.7 (C-4′, C-6′), 127.6 (C-7′), 127.4 (C-3), 127.3 (C-1), 126.0 (C-5′), 125.6 (C-4), 110.9 (C-14), 75.9 (C-8), 75.0 (C-11), 70.4 (C-1′), 62.1 (C-7), 62.0 (C-11a), 55.4 (C-5), 45.8 (C-10), 33.5 (C-12), 27.8 (C-9), 22.5 (C-15) ppm. IR (ATR): $\tilde{\nu}$ = 3421 (br., OH), 3064, 3027 (C−H aromat.), 2918, 2855 (C−H aliphat.), 1641, 1495 (s, C=C aromat.), 1088, 1061 (s, C−O), 738 (1,2-disubst. aromat.) cm^{-1}. TMS derivative: MS (EI): *m*/*z* (%) = 435 (2) [M^+], 420 (4) [$M^+ - CH_3$], 392 (3) [$M^+ - 43$], 344 (27) [$M^+ - 91$], 184 (87), 172 (80) [$C_{12}H_{14}N^+$], 146 (53) [$C_{10}H_{12}N^+$], 132 (100) [$C_9H_{10}N^+$], 91 (80) [$C_7H_7^+$].

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