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Synthesis of 4-alkyl-1-benzhydryl-2-(methoxymethyl)azetidin-3-ols by regio- and stereoselective alkylation of 1-benzhydryl-3-(*N*-alkyl)imino-2-(methoxymethyl)azetidine

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This article is dedicated to Professor R. Sheldon on the occasion of his 60th birthday

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Abstract—The regio- and stereoselective alkylation at the position C-4 of 1-alkyl-2-substituted azetidin-3-ones was investigated. Imination of 1-benzhydryl-2-methoxymethylazetidin-3-one, followed by alkylation under kinetic conditions and final hydrolysis of the imino group, gave 4-alkyl-1-benzhydryl-2-methoxymethylazetidin-3-ones in which the susbstituents at C-2 and C-4 had the *cis* stereochemistry. The reduction of the carbonyl group afforded the corresponding 4-alkyl-1-benzhydryl-2-methoxymethylazetidin-3-ols. The structure and the stereochemistry of the azetidinols were confirmed by single crystal X-ray diffraction analysis.

1. Introduction

Azetidin-3-ols are found in nature as the sphingosine type alkaloids Penaresidines A and B and Penazetidin A (Fig. 1). Penaresidines A and B were firstly isolated from the Okinawan marine sponge *Penares* sp.[1] Syntheses of these alkaloids, all of them having the common structural pattern of 2,4-disubstituted azetidin-3-ols **1**, have been reported by some groups.[1,2] It must be said that the absolute configuration of C-16 of Penazetidin A is still unknown.[2f]

These compounds possess remarkable pharmacological

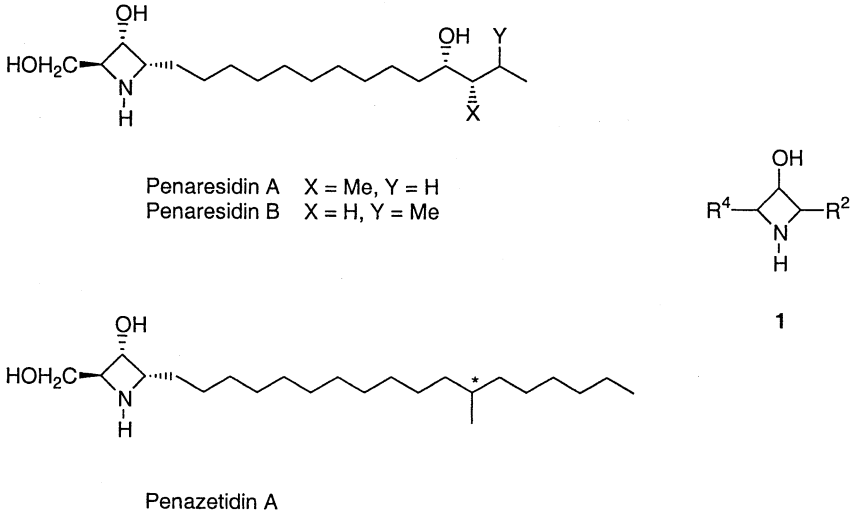

Figure 1.

Keywords: azetidine; azetidinone; alkylation.

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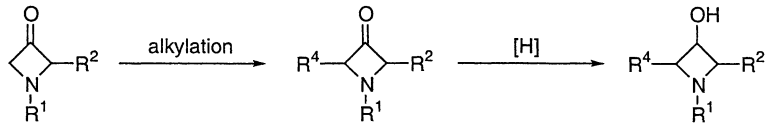

2 3 1

Scheme 1.

properties. Penaresidine A and B are known for their actomyosine-ATPase activating properties,[1] whereas Penazetidine A is a strong inhibitor of protein kinase C.[3] In other cases, azetidin-3-ols have been also incorporated as active moieties of some pharmaceutical drugs.[4,5] Due to their potential applicability, much effort has been recently dedicated to develop synthetic methods for this important class of compounds, either as racemates or in enantiopure form.[1,2]

Azetidin-3-ols were first prepared by Gaertner, who studied the ring transformation of primary amines with epichlorohydrin.[6] A reportedly improved version of this method consisted of the reaction of epichlorohydrin with bis(trimethylsilyl)methylamine (BSMA), followed by desilylation.[7] Other methods are based on the ring closure of conveniently functionalized 3-amino-1,2-propanediol precursors,[6b,8] the addition of amines to 2-*O*-benzyloxymethyl-1,3-bis(*O*-methanosulfonyl)glycerol,[4e] the regioselective halogenation of 2,3-epoxyamines,[9] or the reduction of azetidin-3-ones.[4e] In the case of the structurally more complex penaresidines and penazetidines, to the best of our knowledge, all the reported syntheses are based on the preparation of a suitable 3-amino-1,2-diol precursor, and the subsequent ring closure.[1,2] A synthetic strategy of this kind requires that the substituents at positions C-2 and C-4 of the azetidin ring have to be present in the acyclic precursor prior to the ring closure step. This implies that long and tedious synthetic protocols have to be devised for each single compound. In order to obtain several penaresidin-like derivatives, with which extensive and thus reliable structure–activity studies can be carried out, a more flexible method for these compounds and their stereoisomers would be desirable. We present here a protocol for the synthesis of 2,4-disubstituted azetidin-3-ols **1** via selective alkylation of an azetidin-3-one precursor **2**,[10] and subsequent reduction of the carbonyl group of **3**. (Scheme 1).

In this work, 1-benzhydryl-2-methoxymethylazetidin-3-one **4** was chosen as the substrate for the alkylation reactions because of the importance of 2-alkyl-3-hydroxy-4-(hydroxymethyl)azetidines **1** (Fig. 2).

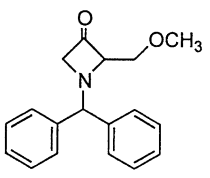

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Figure 2.

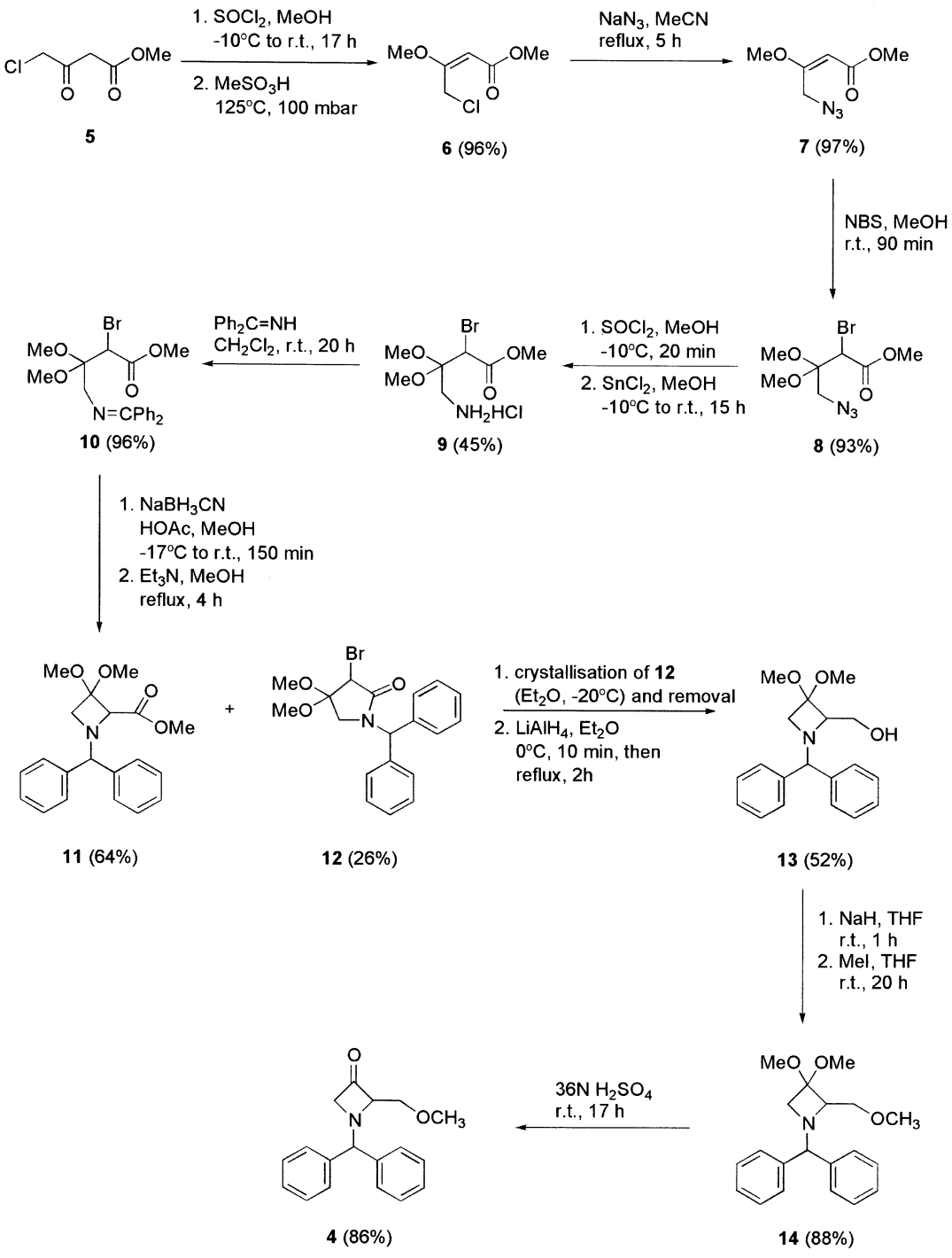
The results of the synthesis of azetidin-3-one **4** and those of our alkylation attempts are described below.

2. Results and discussion

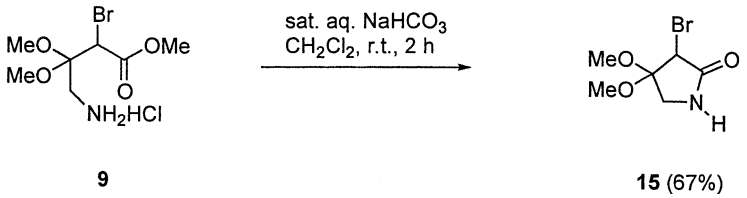
2.1. Preparation of 1-benzhydryl-2-(methoxymethyl)-azetidin-3-one 4

The synthetic route leading to azetidinone **4** is shown in Scheme 2. The synthesis started from the commercially available methyl 4-chloro-3-oxobutanoate **5**, which was converted into methyl 4-chloro-3-methoxy-2-butenoate **6** by acetalization and elimination of methanol, utilizing subsequently hydrogen chloride in methanol and methanesulfonic acid.[11] Methyl 4-chloro-3-methoxy-2-butenoate **6** was then reacted with sodium azide in acetonitrile under reflux,[12] to give methyl 4-azido-3-methoxy-2-butenoate **7**. Alkoxybromination of **7** with *N*-bromosuccinimide in methanol[13] afforded methyl 4-azido-2-bromo-3,3-dimethoxy butanoate **8**, the azido group of which was reduced with tin(II) chloride in dry methanol,[14] resulting in the amine hydrochloride derivative of methyl 4-amino-2-bromo-3,3-dimethoxybutanoate **12** in moderate yield. At this stage, the cyclization to the azetidine system could be attempted by intramolecular displacement of the bromine atom of compound **12** by the amino group. However, neutralization of **9** in a biphasic mixture of dichloromethane and aqueous sodium bicarbonate gave 3-bromo-4,4-dimethoxypyrrolidin-2-one **15** as the sole product after one hour (Scheme 3).[15] This finding was in agreement with the reported propensity of *N*-unsubstituted γ-aminobutanoates to cyclize to the five-membered ring.[16]

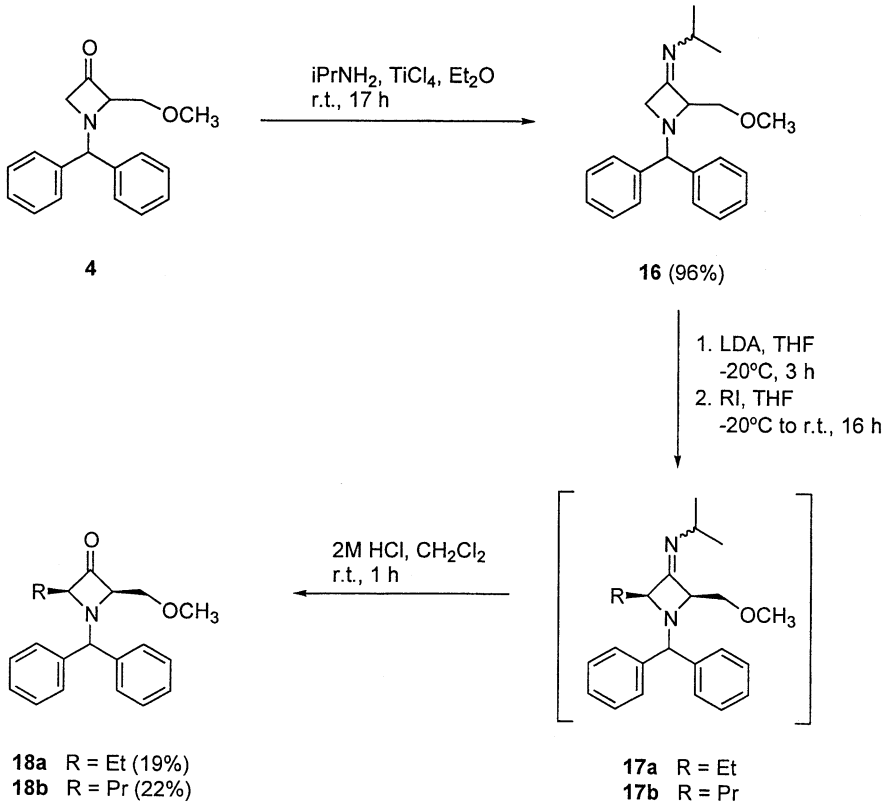
It was reasoned that a *N*-substituted γ-amino-2-bromobutanoate would be a better precursor for the cyclization to the four-membered azetidine system. Such precursor should be readily obtained from the reduction with hydride of the corresponding imine. Therefore, the amine hydrochloride **9** was reacted with benzophenone imine, i.e. *N*-diphenylmethylideneamine, which gave rise to methyl 2-bromo-3,3-dimethoxy-4-(diphenylmethyleneamino)butanoate **10**.[17] This precursor was thought to be amenable to afford an azetidine by reduction with hydride, according to the expertise gained in our group with *N*-(alkylidene)- or *N*-(arylidene)-3-haloalkylamines.[18] It must be taken into account that the comparable bulky diphenylmethylene group may conformationally assist the ring closure step to the azetidine, in the same way as in some reported syntheses of azetidin-3-ols.[8] Although it did not work out well in the case of the formation of an azetidine from γ-bromoamine **9**, the geminal dimethoxy effect[19] may favorably contribute in substrate **10** to produce the corresponding azetidine.



Scheme 2.



Scheme 3.



Scheme 4.

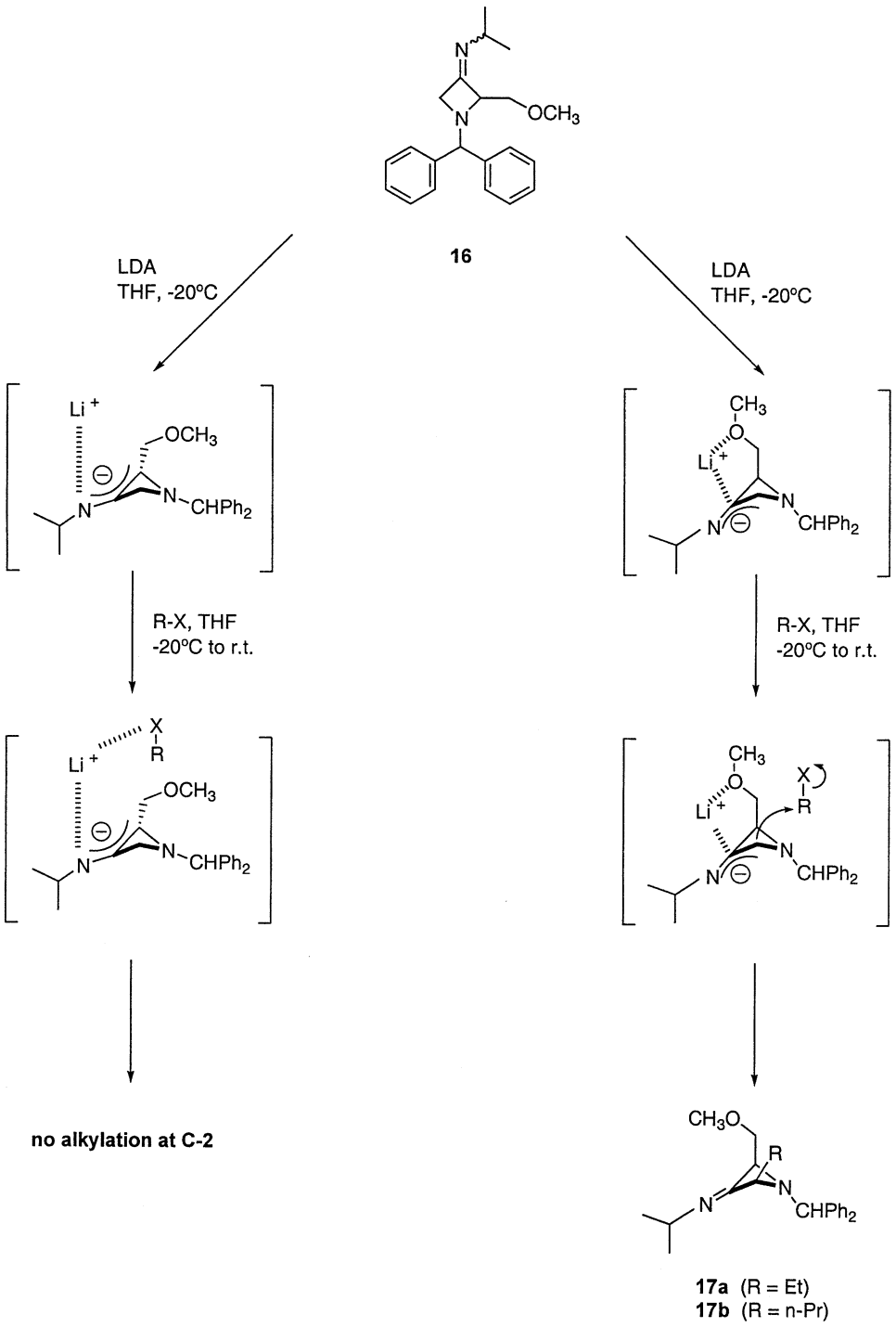
The reduction of the imine group of **10** was tried under several experimental conditions.[20] The best results were encountered when sodium cyanoborohydride was used as the reducing agent. The reaction of the *N*-(diphenylmethylidene)-3-bromoamine **10** with sodium borohydride in methanol gave complex reaction mixtures and resulted in lower yields of azetidine **11**. The reaction of the functionalized imine **10** with sodium cyanoborohydride in methanol in the presence of acetic acid, and followed by addition of an equivalent amount of triethylamine and heating under reflux, afforded methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylic acid **11**, mixed with the γ-lactam 1-benzhydryl-3-bromo-4,4-dimethoxypyrrolidin-2-one **12** in a ratio of ca. 2.5 to 1. As discussed above, the latter is a consequence of the ring closure on the ester group of **10**. This reaction was carried out under various experimental conditions, and in every case lactamization occurred to some extent. The highest azetidine ratio was obtained when the reaction was performed at high temperature. More γ-lactam resulted if the temperature was lowered (0°C). These findings can be rationalized on the basis that cyclization to a four-membered ring is a priori a kinetically and thermodynamically unfavored process when compared to the formation of a five-membered cycle,[21] even though the presence of a bulky substituent at the nitrogen atom of (**10**) would probably destabilize to some extent the transition state to the pyrrolidin-2-one system, thus favoring the formation of the azetidin-3-one derivative.

The mixture of azetidin **11** and γ-lactam **12** could not be separated by flash chromatography, as it happened that both components had the same R_f values under all the chromatographic conditions tried (TLC, silica gel). Nevertheless, the azetidine **11** and the pyrrolidone **12** were successfully separated by fractional crystallization from diethyl ether at −20°C, as the pyrrolidin-2-one **12** crystallized in the first place and could be then removed completely this way by filtration.

The reduction of methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate **11** with lithium aluminium hydride in diethyl ether gave 1-benzhydryl-3,3-dimethoxy-2-(hydroxymethyl)azetidine **13**. Its hydroxy group was protected by methylation with methyl iodide and sodium hydride in tetrahydrofuran,[22] resulting in 1-benzhydryl-3,3-dimethoxy-2-(methoxymethyl)azetidine **14**. Final hydrolysis of the acetal function with concentrated sulfuric acid[23] furnished 1-benzhydryl-2-(methoxymethyl)azetidin-3-one **4**.

2.2. Alkylation of 1-benzhydryl-2-methoxymethylazetidin-3-one 4

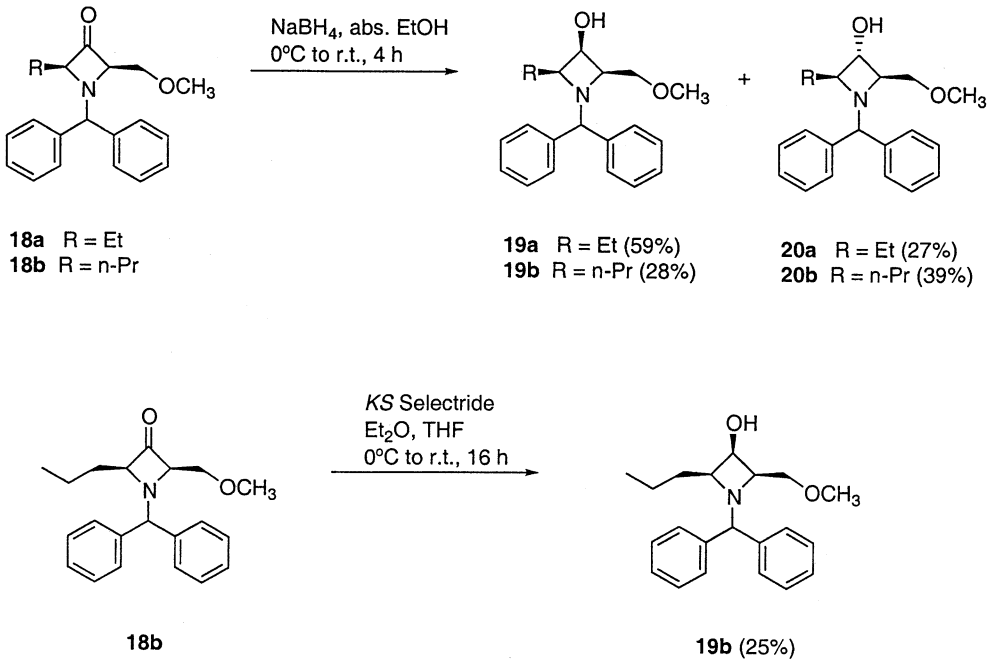
It is known that the use of imines in the α-alkylation of ketones is often advantageous as compared to the direct alkylation of carbonyl compounds because of some striking chemical properties of 1-azaenolates.[24] The addition at low temperature of a relatively sterically bulky base, such as lithium diisopropylamide, allows to deprotonate regioselectively the least sterically hindered α-position of the imine, whereas an increase of the temperature would favor an equilibrium shifted to the most stable 1-azaenolate. It was therefore attempted to alkylate the *N*-isopropylimine derived from azetidin-3-one **4**, using lithium diisopropylamide and an alkyl halide in tetrahydrofuran at −20°C,



Scheme 5.

with the aim to selectively achieve the conversion to the less hindered 1-azaenolate (Scheme 4).

The first step was the almost quantitative conversion of the 1-benzhydryl-2-(methoxymethyl)azetidin-3-one **4** to the corresponding *N*-isopropylimino derivative **16**. This reaction was performed by reacting azetidine **4** with isopropylamine and titanium(IV) chloride in diethyl ether, affording *N*-(1-benzhydryl-2-(methoxymethyl)-3-azetidinylidene)isopropylamine **16** in 96% yield.[25] The alkylation itself was done by sequential addition of the imine **16** to freshly prepared lithium diisopropylamide in THF, followed by the alkylating agent, i.e. iodoethane or iodopropane. These conditions exclusively furnished the C-4 alkylated imines **17a** and **17b**. Conventional hydrolysis of the imino groups of compounds **17a** and **17b** with aqueous hydrochloric acid in a two phase system with dichloromethane, respectively gave 1-benzhydryl-4-ethyl-2-(methoxymethyl)-azetidin-3-one **18a** and 1-benzhydryl-2-(methoxymethyl)-4-propyl-azetidin-3-one **18b** in 19 and 22% yield after the chromatographic purification. These yields, albeit modest, were in fact the combined yield of three sequential steps



Scheme 6.

(azaenolization, alkylation and acidic imine hydrolysis). Therefore, an overall yield of ca. 20% can be seen as the result of three 60% yield steps, moderate but acceptable.

All the collected ^{1}H, ^{13}C and DEPT NMR data of **18a** and **18b** supported the proposed structures. The ^{13}C NMR spectrum ($CDCl_3$) of **18a** showed two signals at 83.77 and 86.04 ppm, which were unambiguously assigned to the methine carbon atoms C-2 and C-4, respectively. The fact that, according to the DEPT experiment, the C-2 and C-4 carbon atoms of **18a** were methines completely demonstrated that the alkylation of **16** had exclusively occurred at the C-4 position. The same result was observed with **18b**, as the two signals (^{13}C NMR, $CDCl_3$) at 84.37 and 84.96 ppm were also attributed to the two methine carbons C-2 and C-4, thus proving the regioselectivity of the method.

Analytical GC and the fact that the signals in the ^{1}H and ^{13}C NMR spectra were not doubled indicated that uniquely one compound had been obtained. This implied that, under the given reaction conditions, not only alkylations did proceed regioselectively, but also stereoselectively, and only one stereoisomer of each azetidinone **18a** and **18b** was obtained. In relation to the relative stereochemistry of the azetidinones **18a** and **18b**, it was concluded that the substituents at C-2 and C-4 were *cis* to each other. This fact is in agreement with the reported mechanism of asymmetric alkylation of ketones using β-(alkoxy)amines as chiral auxiliaries, in which imines are used as intermediates.[26] According to that mechanism, an alkoxy group coordinates with the metal counterion in the enolization step. This process leads to a favoring of the *cis* approximation of the alkylating agent, as the halogen atom would also coordinate with the metal counterion, resulting in a more compact, and thus more stable, transition state.[27] In the case of an hypothetical alkylation at the C-2 position of the 3-iminoazetidine **16**, the sp^2 hybridation of that carbon atom in the azaenolization step would condition that the methoxymethyl group clearly is pointed outwards, therefore laying too distant to effectively coordinate with the metal counterion, and giving rise to a less stable transition state. Consequently, a plausible mechanism for the alkylation of the 3-iminoazetidine **15** is shown in Scheme 5. It was presumed that the preferred conformation of the benzhydryl substituent at the 1-position was *trans* to the 2-methoxymethyl group due to steric considerations. It is clear also that the kinetic deprotonation of the 3-iminoazetidine **16** by LDA favors the alkylation of the least substituted position, i.e. the methylene group at the 4-position.

In order to prove the *cis* stereochemistry of **18a** and **18b**, some nOe experiments were carried out. Unfortunately, these experiments were unsuccessful because the ^{1}H signals assigned to H-2 and H-4 were too close together. No W-pattern coupling was observed between H-2 and H-4, positioned on the same side of the ring. It has been reported that a W-coupling constant of ca. 4.4 Hz could be expected in such a four-membered ring.[10c]

2.3. Reduction of 4-alkyl-1-benzhydryl-2-(methoxymethyl)azetidin-3-ones 18

The reduction of 1-benzhydryl-4-ethyl-2-(methoxymethyl)-azetidin-3-one **18a** and 1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-one **18b** with sodium borohydride gave, in each case, the corresponding azetidin-3-ols **19** and **20** as mixtures of two epimers. Each epimeric pair was successfully resolved by flash chromatography (silica gel, hexane–ethyl acetate 5:1). The *all cis* epimer **19b** was also selectively prepared in 25% yield by reduction of **18b** with a bulky reducing agent, such as potassium trisiamylborohydride (*KS* Selectride) in diethyl ether at 0°C.[28] Reagents of this kind are used in the stereoselective

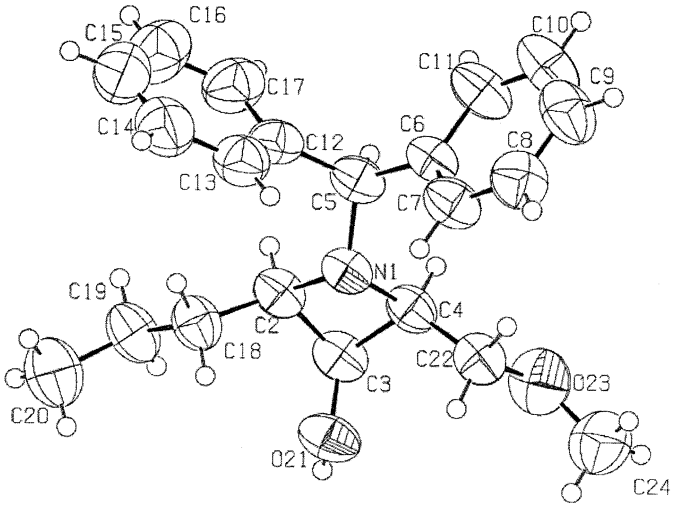


Figure 3. X-Ray crystallographic structure of 1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-ol **19b**.

reduction of ketones when steric factors are controlling.[29] It was therefore expected that *KS* Selectride would add hydride by attack from the less hindered diastereotopic face of the carbonyl group of the 3-azetidinone **18b**, uniquely affording the *all cis* 1-benzhydryl-2-methoxymethyl-4-propylazetidin-3-ol **19b** (Scheme 6).

The relative stereochemistry of the substituents at positions C-2 and C-4 of the azetidin-3-ols **19** and **20** could not be either proved with mono- and bidimensional nOe NMR experiments, due to the proximity of the H-2 and H-4 ^{1}H NMR signals. No W-coupling between H-2 and H-4 was observed. However, the *cis* relative configuration of the substituents at C-2, C-3 and C-4 of **19** and, therefore also that of the azetidinone precursors **18**, was unambiguously demonstrated from the X-ray diffraction analysis of 1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-ol **19b** (Fig. 3).[30] This result confirmed the assumption that the α-alkylation of azetidin-3-ones via the corresponding imine **16** proceeded in a regio- and stereoselective way. In addition, these results determined the stereochemistry of the isomeric azetidinols **20**.

Once fully determined the configuration of both epimeric azetidinols **19** and **20**, the accurate measuring of the chemical shifts and coupling constants in the ^{1}H NMR spectrum was performed as it should be useful in the structural determination of other 2,4-dialkylated azetidinols. To the best of our knowledge, the preparation of *all cis* 2,4-disubstituted azetidin-3-ol derivatives has been reported only once,[31] although no accurate NMR data on these compounds were provided. Detailed NMR data on disubstituted azetidinols are very scarce in the literature.[1,2i,3,10c,31–34] The chemical shifts and coupling constants of the 2,4-disubstituted azetidin-3-ols **19a–b** and **20a–b** are summarized in Table 1.

The *all cis* isomers **19a** and **19b** showed coupling constants between H-2 and H-3, and H-3 and H-4 of 6.3 Hz. Their epimers **20a** and **20b** gave a little smaller (5.6 Hz) *trans* vicinal coupling constants. These findings are consistent with the reported coupling constants of other azetidine derivatives, as it has been reported that *trans* vicinal coupling gave rise to smaller coupling constants.[32] For instance, the ^{1}H NMR spectrum (60 MHz) of the *cis* and *trans* isomers of 1-tertbutyl-2-methylazetidin-3-ol, gave vicinal coupling constant values of 6.2 and 6.0 Hz, respectively.[33] Also, *trans* 1-benzyl-2-phenylazetidin-3-ol gave a coupling constant value of 5.4 Hz,[34] while *cis* (2*S*,3*S*) 1-tert-butoxycarbonyl-2-methylazetidin-3-ol showed $J_{2,3}$= 6.5 Hz.[10c] These values are virtually identical to those measured for **20a** and **20b**.

3. Experimental

3.1. General

NMR spectra were recorded on Jeol JNM EX270 or Bruker AM500 spectrometers, with TMS as internal standard. IR spectra were recorded on a Perkin–Elmer PE 1310 FTIR spectrophotometer. Melting points were recorded on a Büchi 535 melting point apparatus. Boiling and melting points are uncorrected. Gas chromatographic analyses were carried out with a DELSI Instersmat IGC 120 ML gas chromatograph, fitted with a RSL 150 silica capillary column (20 m, 0.53 mm internal diameter), and using hydrogen as carrier gas. Flash chromatographic separations were performed on Merck Kieselgel 60 (230–400 mesh ASTM). Analytical TLC was performed on Merck Kieselgel 60 F_{254} precoated TLC plates (0.25 mm thickness). Dichloromethane was distilled over calcium hydride prior to use. Diethyl ether was distilled over lithium aluminium

Table 1. Selected ^{1}H NMR data of 2,4-disubstituted azetidin-3-ols **19** and **20** ($CDCl_3$, 270 or 500 MHz)

Compound	Configuration	R	δ H-2 (ppm)	δ H-3 (ppm)	δ OH (ppm)	δ H-4 (ppm)	$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)	$J_{3,OH}$ (Hz)
19a *all cis*	2*RS*,3*SR*,4*SR*	Et	3.09	4.46	3.55	3.01	6.6	6.3	7.9
19b *all cis*	2*RS*,3*SR*,4*SR*	*n*-Pr	3.12	4.44	3.53	3.08	6.3	6.3	7.9
20a *trans*,*trans*	2*RS*,3*RS*,4*SR*	Et	2.95	3.80	1.90	2.85	5.6	5.6	Not observed
20b *trans*,*trans*	2*RS*,3*RS*,4*SR*	*n*-Pr	2.93	3.80	1.90	2.85	5.7	5.7	Not observed

hydride before use. Tetrahydrofuran was distilled over sodium benzophenone ketyl before use. All other chemicals and solvents were used as supplied. Experiments with the azides **7** and **8** were carried out behind a safety shield.

3.1.1. Preparation of (*E*)-methyl 4-chloro-3-methoxy-2-butenoate 6.[11] In a 500 mL two-necked round-bottomed flask, provided with a magnetic stirrer, a side-arm dropping funnel and nitrogen inlet, thionyl chloride (169.9 g, 1.43 mol) was carefully added dropwise to anhydrous methanol (124.0 g, 3.90 mol). After cooling to −10°C, methyl 4-chloro-3-oxobutanoate (**5**, 196.0 g, 1.30 mol) was added at this temperature over a period of 20 min. It was stirred at room temperature for 17 h and then excess methanol and thionyl chloride were evaporated in vacuo. The residue was transferred to a 250 mL round-bottomed flask fitted with a fractional distillation set, methanesulphonic acid (1.26 g, 13.0 mmol) was added and the mixture was heated at ca. 150°C (oil bath temperature) at reduced pressure. First, methanol was distilled off (ca. 24°C/15 mmHg), while afterwards a main fraction of (*E*)-methyl 4-chloro-3-methoxy-2-butenoate (**6**, 205.6 g, 1.25 mol, 96.4%) was obtained as a colorless liquid. Bp: 124°C/15–16 mmHg (95–97°C/11–12 mmHg).[11] ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.15 (s, 1H, CH═); 4.66 (s, 2H, CH_2Cl); 3.73 and 3.71 (each s, each 3H, OCH_3 and $COOCH_3$).

3.1.2. Preparation of (*E*)-methyl 4-azido-3-methoxy-2-butenoate 7. In a 1 L two-necked round-bottomed flask, provided with a magnetic stirrer and reflux condenser, (*E*)-methyl 4-chloro-3-methoxy-2-butenoate (**6**, 49.2 g, 0.30 mol) and sodium azide (39.0 g, 0.60 mol) were dispersed in acetonitrile (600 mL). The mixture was refluxed for 5 h, cooled down to room temperature and residual sodium azide was filtered. The filtrate was evaporated and then diluted with *n*-pentane and stirred at 0°C for one hour. More sodium azide precipitated, which was filtered off. The filtrate was evaporated to afford (*E*)-methyl 4-azido-3-methoxy-2-butenoate (**7**, 49.8 g, 0.29 mol, 97.1%) as a reddish liquid, which was used without further purification (purity>96%). ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.18 (s, 1H, CH═); 4.42 (s, 2H, CH_2N_3); 3.72 and 3.71 (each s, each 3H, OCH_3 and $COOCH_3$).

3.1.3. Preparation of methyl 4-azido-2-bromo-3,3-dimethoxybutanoate 8. In a 1 L round-bottomed flask, provided with a magnetic stirrer, (*E*)-methyl 4-azido-3-methoxy-2-butenoate (**7**, 49.8 g, 0.29 mol) was dissolved in methanol (600 mL). To this solution, *N*-bromosuccinimide (53.4 g, 0.30 mol) was added portionwise and the mixture was stirred at room temperature and under subdued light for 90 min. The solvent was evaporated in vacuo and *n*-pentane (500 mL) was added. The resulting suspension was stirred at −15°C for one hour and was then filtered. The filtrate was evaporated to afford methyl 4-azido-2-bromo-3,3-dimethoxybutanoate (**8**, 77.5 g, 0.27 mol, 93.1%) as a pale yellow liquid, which was used directly in the next step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.52 (s, 1H, CHBr); 3.80 (s, 3H, $COOCH_3$ or $(OCH_3)_2$); 3.75 (s, 2H, CH_2N_3); 3.41 and 3.35 (each s, each 3H, $COOCH_3$ or $(OCH_3)_2$).

3.1.4. Preparation of methyl 4-amino-2-bromo-3,3-dimethoxybutanoate hydrochloride 9. In a 500 mL three-necked round-bottomed flask, provided with a magnetic stirrer, a side-arm dropping funnel and nitrogen inlet, thionyl chloride (71.4 g, 0.61 mol) was added dropwise and very cautiuosly to anhydrous methanol (300 mL) at −10°C over 20 min. The solution was stirred further at this temperature for another 20 min and methyl 4-azido-2-bromo-3,3-dimethoxybutanoate (**8**, 77.5 g, 0.27 mol) was added dropwise at −10°C over a period of 10 min. Then, tin(II) chloride (78.0 g, 0.41 mol) was added portionwise under a nitrogen stream at −10°C. The resulting suspension was stirred at room temperature for 15 h, filtered and evaporated. The residue was diluted with diethyl ether (450 mL) and stirred for one hour at 0°C. A white solid precipitated, which was filtered, washed with fresh diethyl ether (20 mL) and dried in vacuo over calcium chloride (25°C/10 mmHg). Methyl 4-amino-2-bromo-3,3-dimethoxybutanoate hydrochloride (**9**, 35.6 g, 0.12 mol, 45.2%) was obtained as an amorphous white solid. Mp: 135°C (decomp.). ^{1}H NMR (270 MHz, D_2O): δ 4.87 (s, 1H, CHBr); 3.76 (s, 3H, $COOCH_3$ or $(OCH_3)_2$); 3.58 and 3.64 (each d, J_{gem}= 14.5 Hz, AB system, 1H, CH_2N); 3.30 and 3.31 (each s, each 3H, $COOCH_3$ or $(OCH_3)_2$). ^{13}C NMR (67.5 MHz, D_2O): δ 168.59 (C═O); 97.25 ($C(OMe)_2$); 53.19 ($COOCH_3$); 48.39 and 49.54 ($O(CH_3)_2$); 43.92 (C–Br); 39.43 (CH_2N). IR (KBr, cm^{-1}): 3190 (N–H, broad); 1725 (C═O). No correct elemental analytical data could be obtained, probably due to the adventituous water present due to hygroscopicity.

3.1.5. Preparation of methyl 2-bromo-4-(diphenylmethylene)amino-3,3-dimethoxybutanoate 10. In a 500 mL round-bottomed flask, provided with a magnetic stirrer, methyl 4-amino-2-bromo-3,3-dimethoxybutanoate hydrochloride (**9**, 10.63 g, 36.4 mmol) and diphenylketimine (6.59 g, 36.4 mmol) were dissolved in dichloromethane (200 mL). The solution was stirred at room temperature for 20 h, filtered and 10% sodium bicarbonate (200 mL) was added to the filtrate. After stirring for 15 min, the resulting emulsion was filtered through a celite layer. The organic phase was decanted and the aqueous phase was extracted with dichloromethane (2×50 mL), the combined organic phases were washed with water (100 mL), dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. Methyl 2-bromo-4-(diphenylmethylene)amino-3,3-dimethoxybutanoate (**10**, 14.61 g, 34.78 mmol, 95.6%) was obtained as a caramel-like solid residue. R_f: 0.40 (silica gel, hexane–AcOEt 4:1). Mp: 86°C (white prisms from MeOH, −20°C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.10–7.70 (m, 10H, Ph_2); 5.01 (s, 1H, CHBr); 3.76 (d, J_{gem}=16.5 Hz, AB system, 1H, H-4); 3.71 (s, 3H, $COOCH_3$ or $(OCH_3)_2$); 3.61 (d, J_{gem}=16.5 Hz, AB system, 1H, H-4); 3.27 and 3.28 (each s, each 3H, $COOCH_3$ or $(OCH_3)_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 168.05 and 169.38 (C═O and C═N); 136.48 and 139.40 (Ar Cquat); 127.49, 127.98, 128.64 and 130.20 (Ar); 101.27 ($C(OMe)_2$); 54.64 (CH_2N); 53.05 ($COOCH_3$); 49.52 and 50.48 ($(OCH_3)_2$); 49.31 (CHBr). IR (NaCl, cm^{-1}): 1758 (C═O); 1630 (C═N). Elemental analysis ($C_{20}H_{22}BrNO_4$) calculated C 57.15%, H 5.28%, N 3.33%; found C 57.29%, H 5.14%, N 3.26%.

3.1.6. Preparation of methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate 11. In a 250 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen

inlet, methyl 2-bromo-4-(diphenylmethylene)amino-3,3-dimethoxybutanoate (**10**, 12.67 g, 30.17 mmol) was dispersed in dry methanol (180 mL). After cooling to −17°C with an ice–salt bath, sodium cyanoborohydride (3.79 g, 60.34 mmol, 2.0 equiv.) and acetic acid (1.81 g, 30.17 mmol, 1.0 equiv.) were carefully added in this order. The reaction mixture was left stirring to warm up to room temperature over two and a half hours. A reflux condenser was then fitted and triethylamine (9.14 g, 90.51 mmol) was added. The mixture was refluxed for 4 h, cooled down to room temperature, poured into water (250 mL) and extracted with dichloromethane (3×100 mL). The combined organic phases were washed with water (100 mL), dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was chromatographed (silica gel, column dimensions 45.0 cm×2.4 cm, hexane–AcOEt 4:1). Pooling of the appropriate fractions and evaporation in vacuo afforded a residue containing methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate **11** and 1-benzhydryl-3-bromo-4,4-dimethoxypyrrolidin-2-one **12**. After crystallization from diethyl ether at −20°C, 1-benzhydryl-3-bromo-4,4-dimethoxypyrrolidin-2-one (**12**, 2.99 g, 7.69 mmol, 26%) was obtained as white prisms, which were filtered off. Evaporation of the mother liquors afforded methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate (**11**, 6.55 g, 19.20 mmol, 64%) as a colorless oil. 1-Benzhydryl-3-bromo-4,4-dimethoxypyrrolidin-2-one **12**: R_f: 0.20 (silica gel, hexane–AcOEt 4:1). Mp: 147–148°C (white prisms from Et_2O, −20°C). ^1H NMR (270 MHz, $CDCl_3$): δ 7.34–7.37 and 7.20–7.26 (each m, 4H and 6H, respectively, Ph_2); 6.64 (s, 1H, C*H*Ph_2); 4.27 (s, 1H, CHBr); 3.28 (s, 3H, OCH_3); 3.25 and 3.16 (each d, J=11 Hz, each 1H, AB system, H-4); 3.13 (s, 3H, OCH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 168.95 (C=O); 137.55 and 137.89 (Ar Cquat); 127.85, 127.90, 128.08, 128.39, 128.46, 128.66 and 128.71 (Ar); 102.28 (*C*$(OMe)_2$); 58.29 (*C*HPh_2); 50.10 and 50.47 ($(OCH_3)_2$); 47.33 (CHBr); 47.17 (CH_2N). IR (NaCl, cm^{-1}): 3010, 3004 (C–H Ar); 2842 (OMe); 1709 (C=O). MS (EI, 70 eV), (*m*/*z*, %): 389/391 (M^+, 1), 310 (21), 309 (100), 168 (5), 167 (33), 166 (6), 165 (15), 152 (8), 149 (6), 147 (4), 146 (6), 129 (7), 115 (20), 101 (4), 99 (4), 89 (27), 88 (84), 71 (5), 70 (5), 69 (4), 59 (4), 58 (17), 57 (9), 55 (4), 45 (5), 44 (8), 43 (16), 41 (4), 40 (60). Elemental analysis ($C_{19}H_{20}BrNO_3$): calculated C 58.47%, H 5.17%, N 3.59%; found C 58.30%, H 5.10%, N 3.44%. Methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate **11**: R_f: 0.20 (silica gel, hexane–AcOEt 4:1). ^1H NMR (270 MHz, $CDCl_3$, δ): 7.44–7.54 and 7.14–7.32 (each m, 4H and 6H, respectively, Ph_2); 4.55 (s, 1H, C*H*Ph_2); 3.87 (s, 1H, H-2); 3.74 (d, J=8.9 Hz, 1H, H-4); 3.49 (s, 3H, $COOCH_3$); 3.29 and 3.20 (each s, each 3H, $(OCH_3)_2$); 2.88 (d, J=8.9 Hz, 1H, H-4). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 168.97 (*C*O_2CH_3); 141.28 and 140.48 (Ar Cquat); 128.39, 128.36, 128.25, 127.96 and 127.33 (Ar); 98.09 (*C*$(OCH_3)_2$); 77.39 (*C*HPh_2); 73.39 (C-2); 60.34 (C-4); 51.48 ($COOCH_3$); 49.47 and 49.38 ($(OCH_3)_2$). IR (NaCl, cm^{-1}): 3081, 3058, 3023 (C–H Ar); 2853 (OMe); 1715 (C=O). Elemental analysis ($C_{20}H_{23}NO_4$): calculated C 70.36%, H 6.79%, N 4.10%; found C 70.18%, H 6.85%, N 4.02%.

3.1.7. Preparation of 1-benzhydryl-3,3-dimethoxy-2-(hydroxymethyl)azetidine 13. In a 100 mL round-bottomed flask, provided with a magnetic stirrer, lithium aluminium hydride (0.83 g, 22.0 mmol) was added to dry diethyl ether (25 mL) and cooled to 0°C. To this suspension, methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate (**11**, 3.74 g, 0.011 mol, dissolved in 25 mL of diethyl ether) was added dropwise over 10 min at 0°C. A reflux condenser was fitted and the mixture was refluxed for two hours, cooled down to room temperature and all residual hydride was destroyed by dropwise addition of ethyl acetate (30 mL). The mixture was poured into water (50 mL) and was extracted with ethyl acetate (3×40 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was crystallized from diethyl ether at −20°C. Successive crops gave 1-benzhydryl-3,3-dimethoxy-2-(hydroxymethyl)azetidine **13** as white needles (1.79 g, 5.73 mmol, 52.1%). R_f: 0.09 (silica gel, hexane–AcOEt 4:1). Mp: 90.4–90.8°C (white prisms from Et_2O, −20°C). ^1H NMR (270 MHz, $CDCl_3$): δ 7.41–7.51 and 7.19–7.32 (each m, 4H and 6H, respectively, Ph_2); 4.55 (s, 1H, C*H*Ph_2); 3.66 (d, J_{gem}=9.2 Hz, 1H, H-4); 3.23–3.35 (m, 3H, H-2 and CH_2OH); 3.24 and 3.21 (each s, each 3H, $(OCH_3)_2$); 2.82 (d, J_{gem}=9.2 Hz, 1H, H-4). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 142.62 and 142.24 (Ar Cquat); 128.57, 128.51, 128.12, 127.76, 127.33 and 127.15 (Ar); 99.31 (*C*$(OMe)_2$); 77.23 (*C*HPh_2); 72.77 (C-2); 61.85 (*C*H_2OH), 60.68 (C-4); 49.23 and 48.93 ($(OCH_3)_2$). IR (NaCl, cm^{-1}): 3515 (OH); 3078, 3019 (C–H Ar); 2877, 2833 (OMe). Elemental analysis ($C_{19}H_{23}NO_3$): calculated C 72.82%, H 7.40%, N 4.47%; found C 73.25%, H 7.48%, N 4.40%.

3.1.8. Preparation of 1-benzhydryl-3,3-dimethoxy-2-(methoxymethyl)azetidine 14. In a 100 mL two-necked round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, sodium hydride (0.33 g of a 60% suspension in mineral oil, 8.32 mmol) was dispersed in dry tetrahydrofuran (15 mL). To this slurry was added dropwise 1-benzhydryl-3,3-dimethoxy-2-(hydroxymethyl)azetidine (**13**, 1.53 g, 4.88 mmol, dissolved in 15 mL of dry tetrahydrofuran) at room temperature over a period of 10 min. The mixture was stirred for one hour at room temperature, after which iodomethane (2.23 g, 15.70 mmol, dissolved in 10 mL of dry tetrahydrofuran) was then added dropwise at room temperature over 10 min. After stirring at room temperature for 6 h, additional iodomethane (1.0 mL, excess) was added in one portion. The reaction mixture was stirred for another 14 h and was then poured into water (150 mL) and extracted with diethyl ether (4×50 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. Column chromatography (silica gel, column dimensions 21 cm×2.4 cm, hexane–AcOEt 4:1) afforded 1-benzhydryl-3,3-dimethoxy-2-(methoxymethyl)azetidine **14** as a pale yellow solid (1.40 g, 4.28 mmol, 88%). It was purified by crystallization from dichloromethane–methanol. R_f: 0.30 (silica gel, hexane–AcOEt 4:1). Mp: 88–89°C (white prisms from CH_2Cl_2–MeOH). ^1H NMR (270 MHz, $CDCl_3$): δ 7.37–7.45 and 7.19–7.31 (each m, 4H and 6H, respectively, Ph_2); 4.48 (s, 1H, C*H*Ph_2); 3.59 (dd, J_{gem}=9.0 Hz, J=0.6 Hz, 1H, CH_2OCH_3); 3.45 (d, J=9.5 Hz, 1H, H-4); 3.35 (m, 1H, H-2); 3.25 and 3.19 (each s, each 3H, $(OCH_3)_2$); 3.00 (s, 3H, CH_2OCH_3); 2.73 (d, J=9.5 Hz, 1H, H-4); 2.34 (dd, J_{gem}=9.0 Hz, J=3.0 Hz, 1H, CH_2OCH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 142.12 (Ar Cquat); 128.48,

128.41, 128.28, 127.42 and 127.03 (Ar); 98.67 ($C(OMe)_2$); 77.92 ($CHPh_2$); 72.36 (CH_2OCH_3), 70.30 (C-2); 60.58 (C-4); 58.55 (CH_2OCH_3); 49.45 and 49.33 ($(OCH_3)_2$). IR (NaCl, cm^{-1}): 3073, 3023 (C–H Ar); 2868 (OMe). Elemental analysis ($C_{20}H_{25}NO_3$): calculated C 73.37%, H 7.70%, N 4.28%; found C 73.53%, H 7.74%, N 4.27%.

3.1.9. Preparation of 1-benzhydryl-2-(methoxymethyl)-azetidin-3-one 4. In a 100 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, 1-benzhydryl-3,3-dimethoxy-2-(methoxymethyl)azetidine (**14**, 0.736 g, 2.25 mmol) was stirred with 36N sulfuric acid (1.25 mL, 22.5 mmol) for 17 h at room temperature The mixture was then carefully neutralized with 1 M sodium hydroxide under ice cooling and extracted with diethyl ether (4×30 mL). The combined organic phases were washed with water (20 mL), dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. The residue was column chromatographed (silica gel, column dimensions 12 cm×2.4 cm, hexane–AcOEt 4:1). Pooling and evaporation of the appropriate fractions gave 1-benzhydryl-2-(methoxymethyl)azetidin-3-one (**4**, 0.545 g, 1.94 mmol, 86.2%) as a solid yellow residue. R_f: 0.29 (silica gel, hexane–AcOEt 4:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.48–7.53 and 7.22–7.34 (each m, 4H and 6H, respectively, Ph_2); 4.67 (s, 1H, C*H*Ph_2); 4.23 (dd, J_{gem}=16.2 Hz, J_{2-4}=4.0 Hz, 1H, H-4); 4.11 (ddd, J=4.3 Hz, J_{2-4}=4.0 Hz, J=3.3 Hz, 1H, H-2); 3.73 (d, J=16.2 Hz, 1H, H-4); 3.25 (s, 3H, CH_2OCH_3); 3.22 (dd, J_{gem}=10.9 Hz, J=3.3 Hz, 1H, CH_2OCH$_3$); 3.05 (dd, J_{gem}=10.9 Hz, J=3.3 Hz, 1H, CH_2OCH$_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 201.96 (C=O); 142.14 (Ar Cquat); 128.34, 128.18, 127.82 and 126.99 (Ar); 84.58 ($CHPh_2$); 76.80 (C-2); 72.92 (CH_2OCH_3), 70.30 (C-4); 58.96 (CH_2OCH_3). IR (NaCl, cm^{-1}): 3061 (C–H Ar); 1810 (C=O).

3.1.10. Preparation of *N*-(1-benzhydryl-2-(methoxymethyl)-3-azetidinylidene)isopropylamine 16. In a 50 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, 1-benzhydryl-2-(methoxymethyl)azetidin-3-one (**4**, 325 mg, 1.159 mmol) and isopropylamine (0.6 mL, 6.94 mmol, 6.0 equiv.) were dissolved in dry diethyl ether (15 mL). To this solution was added dropwise titanium(IV) chloride (132 mg, 0.694 mmol, dissolved in 2.0 mL pentane) at room temperature over five minutes. After stirring for 17 h at room temperature, the reaction mixture was added to 1 M sodium hydroxide (15 mL). The aqueous phase was extracted with diethyl ether (3×20 mL) and the combined organic phases were dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. *N*-(1-Benzhydryl-2-(methoxymethyl)-3-azetidinylidene)isopropylamine (**16**, mostly *E* isomer, 359 mg, 1.114 mmol, 96.2%) was obtained as a yellow residue and was used without further purification because of its lability. R_f: 0.53 (silica gel, CH_2Cl_2–MeOH–conc. NH_3 80:1:0.05). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.43–7.50 and 7.17–7.31 (each m, 4H and 6H, respectively, Ph_2); 4.62 (s, 1H, C*H*Ph_2); 4.21 (dd, J_{gem}=14.2 Hz, J=3.6 Hz, 1H, H-4); 4.02–4.10 (m, 1H, H-2); 3.45–3.58 (m, 1H, H-4); 3.28 (m, 2H, CH_2OCH$_3$ and C*H*$(CH_3)_2$); 3.19 (s, 3H, CH_2OCH_3); 3.13 (m, 1H, CH_2OCH$_3$); 1.11 (d, J=6.7 Hz, 6H, CH$(CH_3)_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 161.62 (C=N); 142.69 (Ar Cquat); 128.59, 128.55, 128.50, 128.46, 128.37 and 128.25 (Ar); 98.71 ($CHPh_2$); 72.24 (CH_2OCH_3), 62.75 and 59.23 (C-2 and C-4); 52.97 (CH_2OCH_3); 49.29 (C=N*C*HMe$_2$); 23.67 and 23.60 (C=NCH(CH_3)$_2$). IR (NaCl, cm^{-1}): 3061 (C–H Ar), 1725 (C=N).

3.1.11. Preparation of *cis*-1-benzhydryl-4-ethyl-2-(methoxymethyl)azetidin-3-one 18a. In a 50 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, *N*-(1-benzhydryl-2-(methoxymethyl)-3-azetidinylidene)isopropylamine (**16**, 278 mg, 0.863 mmol, dissolved in 6 mL of dry tetrahydrofuran) was added dropwise at −20°C over 5 min to a solution of lithium diisopropylamide (0.95 mmol), freshly prepared from diisopropylamine (0.15 mL, 1.036 mmol) and *n*-butyllithium (0.34 mL of a 2.5 M solution in hexane, 0.95 mmol) in 3 mL of tetrahydrofuran. The reaction mixture was stirred at −20°C for 3 h, after which iodoethane (269 mg, 1.726 mmol, dissolved in 3 mL of tetrahydrofuran) was added at −20°C over five minutes. After this addition, the ice–salt bath was removed and the reaction mixture was left stirring to warm up to room temperature for 15 h. Then it was poured into 1 M sodium hydroxide (30 mL). The aqueous phase was extracted with diethyl ether (3×20 mL) and the combined organic phases were dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. A yellow oil (282 mg), mostly containing *N*-(1-benzhydryl-4-ethyl-2-(methoxymethyl)-3-azetidinylidene)isopropylamine **17a** (mixture of isomers) was obtained and used as such. It was dissolved in dichloromethane (10 mL) and was then vigorously stirred with 2 M hydrochloric acid (4.0 mL) for one hour at room temperature. The mixture was then carefully neutralized with 1 M sodium hydroxide (ca. 10 mL), transferred to a separating funnel and the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic phases were dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, column dimensions 16.0 cm×2.4 cm, hexane–AcOEt 5:1). *cis*-1-Benzhydryl-4-ethyl-2-(methoxymethyl)-azetidin-3-one (**18a**, 49.5 mg, 0.160 mmol, 19%) was obtained as a yellow oil after pooling and evaporation of the appropriate fractions. R_f: 0.46 (silica gel, hexane–AcOEt 4:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.53–7.59 and 7.22–7.34 (each m, 4H and 6H, respectively, Ph_2); 4.65 (s, 1H, C*H*Ph_2); 3.94 (dd, J=4.9, 3.96 Hz, 1H, H-2); 3.86 (dd, J=7.6, 4.6 Hz, 1H, H-4); 3.18–3.30 (m, 2H, CH_2OCH$_3$); 3.23 (s, 3H, CH_2OCH_3); 1.39 (m, 2H, CH_2CH$_3$); 0.84 (t, J=7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 207.02 (C=O); 142.42 and 142.30 (Ar Cquat); 128.42, 128.39, 128.17, 127.69 and 127.49 (Ar); 86.04 (C-4); 83.77 (C-2); 78.74 ($CHPh_2$); 70.78 (CH_2OCH_3), 59.28 (CH_2OCH_3); 23.92 (CH_2CH_3); 9.42 (CH_2CH_3). IR (NaCl, cm^{-1}): 3059, 3024 (C–H Ar); 2961, 2850 (C–H); 1801 (C=O). Elemental analysis ($C_{21}H_{25}NO_2$): calculated C 77.99%, H 7.79%, N 4.33%; found C 77.81%, H 7.91%, N 4.20%.

3.1.12. Preparation of *cis*-1-benzhydryl-2-methoxymethyl-4-propylazetidin-3-one 18b. In a 50 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, *N*-(1-benzhydryl-2-(methoxymethyl)-3-azetidinylidene)isopropylamine (**16**, 359 mg, 1.114 mmol, dissolved in 12 mL tetrahydrofuran) was added dropwise at −20°C

over a period of 10 min to a solution of lithium diisopropylamide (1.225 mmol), freshly prepared from diisopropylamine (0.19 mL, 1.34 mmol) and *n*-butyllithium (0.49 mL of a 2.5 M solution in hexane, 1.225 mmol) in 2 mL of dry tetrahydrofuran. The reaction mixture was stirred at −20°C for 3 h, after which iodopropane (380 mg, 2.23 mmol, dissolved in 5 mL of dry tetrahydrofuran) was added at −20°C over five minutes. After this addition, the ice–salt bath was removed and the reaction mixture was left stirring to warm up to room temperature for 18 h. It was then poured into 1 M sodium hydroxide (15 mL), the aqueous phase was extracted with diethyl ether (3×20 mL) and the combined organic phases were dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. A yellow oil (318 mg), mostly containing *N*-(1-benzhydryl-2-(methoxymethyl)-4-propyl-3-azetidinylidene)-isopropylamine **17b**, as a mixture of isomers, was obtained. It was dissolved in dichloromethane (10 mL) and it was vigorously stirred with 2 M hydrochloric acid (4.5 mL) for one hour at room temperature, after which it was carefully neutralized with 1 M sodium hydroxide (ca. 10 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic phases were dried (K_2CO_3), filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, column dimensions 15.0 cm×2.4 cm, hexane–AcOEt 5:1). *cis*-1-Benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-one (**18b**, 78 mg, 0.241 mmol, 22%) was obtained as a yellow oil. R_f: 0.46 (silica gel, hexane–AcOEt 4:1). ^{1}H NMR (270 MHz, C_6D_6): δ 7.40–7.50 and 6.95–7.16 (each m, 4H and 6H, respectively, Ph_2); 4.26 (s, 1H, C*H*Ph_2); 3.68–3.64 (m, 2H, H-2 and H-4); 3.19 (dd, J_{gem}=10.6 Hz, J=3.3 Hz, 1H, CH_2OCH_3); 3.09 (dd, J_{gem}=10.6 Hz, J=4.3 Hz, 1H, CH_2OCH_3); 3.02 (s, 3H, CH_2OCH_3); 1.54 (m, 2H, C$H_2$$CH_2CH_3$); 1.33 (m, 2H, $CH_2CH_2CH_3$); 0.70 (t, J=7.0 Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR (67.5 MHz, C_6D_6): δ 205.16 (C=O); 143.09 and 142.97 (Ar Cquat); 132.04, 130.17, 129.22, 128.93 and 128.86 (Ar); 84.96 and 84.37 (C-2 and C-4); 78.58 (*C*HPh_2); 71.04 (*C*H_2OCH_3), 58.87 (CH_2OCH_3); 33.39 (*C*$H_2CH_2CH_3$); 18.62 ($CH_2CH_2CH_3$); 14.17 ($CH_2CH_2CH_3$). IR (NaCl, cm^{-1}): 3061, 3027 (C–H Ar); 2958, 2872 (C–H); 1804 (C=O). MS (CI, NH_3, *m/z*): $C_{21}H_{25}NO_2$ requires 323.1885; found 323.1892 (M^+, 0.45%); 278 (100%).

3.1.13. Preparation of 1-benzhydryl-4-ethyl-2-(methoxymethyl)azetidin-3-ol 19a and 20a. In a 50 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, *cis* 1-benzhydryl-4-ethyl-2-(methoxymethyl)-azetidin-3-one (**18a**, 40 mg, 0.129 mmol) was dissolved in absolute ethanol (5 mL) and cooled to 0°C. Sodium borohydride (10 mg, 0.260 mmol) was then added portionwise. After addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 4 h. Water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. Purification by column chromatography (silica gel, column dimensions 9 cm×2.4 cm, hexane–AcOEt 4:1) of the residue gave two compounds, i.e. compounds **19a** and **20a**, each as a colorless oil. The first eluting compound was (*all cis*)-1-benzhydryl-4-ethyl-2-methoxymethylazetidin-3-ol (**19a**, 23.7 mg, 0.076 mmol, 59.1%). R_f: 0.20 (silica, hexane–AcOEt 4:1). Mp (CH_2Cl_2–hexane): 115–116.5°C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.49–7.44 and 7.15–7.29 (each m, 4H and 6H, respectively, Ph_2); 4.46 (ddd, J=7.9 Hz, $J_{2,3}$=6.6 Hz, $J_{3,4}$=6.3 Hz, 1H, H-3); 4.38 (s, 1H, C*H*Ph_2); 3.55 (d, J=7.9 Hz, 1H, OH); 3.26 (s, 3H, CH_2OCH_3); 3.16 (m, 1H, C$H_2$$OCH_3$); 3.09 (m, 2H, H-2 and C$H_2$$OCH_3$); 3.01 (m, 1H, H-4); 1.70 and 0.75 (each m, each 1H, C$H_2$$CH_3$); 0.59 (t, J=7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 143.04 (Ar Cquat); 128.41, 128.25, 128.14, 128.05, 127.33 and 127.26 (Ar); 78.44 (*C*HPh_2); 72.04 (*C*$H_2$$OCH_3$); 73.28 (C-3); 67.55 and 66.04 (C-2 and C-4); 59.16 (CH_2OCH_3); 22.21 (*C*$H_2$$CH_3$); 9.97 ($CH_2CH_3$). IR (NaCl, cm^{-1}): 3440 (broad, O–H); 1638 (C=C, Ar). MS (EI, *m/z*): $C_{20}H_{25}NO_2$ requires 311.1885; found 311.1896. The second eluting compound was (*trans*,*trans*)-1-benzhydryl-4-ethyl-2-methoxymethylazetidin-3-ol (**20a**, 11.0 mg, 0.035 mmol, 27.4%). R_f: 0.11 (silica, hexane–AcOEt 4:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.47–7.42 and 7.18–7.29 (each m, 4H and 6H, respectively, Ph_2); 4.45 (s, 1H, C*H*Ph_2); 3.80 (dd, J_{2-3}= $J_{3,4}$=5.6 Hz, 1H, H-3); 3.17 (s, 3H, CH_2OCH_3); 3.04 (dd, J_{gem}=9.0 Hz, J_{vic}= 7.4 Hz, 1H, C$H_2$$OCH_3$); 2.95 (m, 1H, H-2); 2.85 (m, 2H, H-4 and C$H_2$$OCH_3$); 1.30–1.05 (m, 2H, C$H_2$$CH_3$); 0.73 (t, J=7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 142.69, 142.37 (Ar Cquat); 128.37, 128.28, 128.16, 128.05, 127.37, 127.28 (Ar); 79.03 (*C*HPh_2); 74.63 and 74.23 (C-3 and *C*$H_2$$OCH_3$); 71.59 and 71.02 (C-2 and C-4); 59.03 (CH_2OCH_3); 26.97 (*C*$H_2$$CH_3$); 8.82 ($CH_2CH_3$). IR (NaCl, cm^{-1}): 3438 (broad, O–H); 1635 (C=C, Ar). MS (EI, *m/z*): $C_{20}H_{25}NO_2$ requires 311.1885; found 311.1868.

3.1.14. Preparation of 1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-ol 19b and 20b. In a 50 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, *cis*-1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-one (**18b**, 65 mg, 0.201 mmol) was dissolved in absolute ethanol (7 mL) and cooled to 0°C. To this solution, sodium borohydride (15 mg, 0.397 mmol) was added in small portions. After this addition, the ice bath was removed and the reaction mixture was left stirring at room temperature for one hour. Water (15 mL) was added and stirring was continued for one more hour. Then the reaction mixture was extracted with diethyl ether (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, column dimensions 20 cm×2.4 cm, hexane–AcOEt 5:1). Pooling and evaporation of the solvent in vacuo afforded two compounds, i.e. **19b** and **20b**, as colorless oils. The first eluting compound was (*all cis*)-1-benzhydryl-2-methoxymethyl-4-propylazetidin-3-ol (**19b**, 18.4 mg, 0.057 mmol, 28.2%). R_f: 0.22 (silica, hexane–AcOEt 3:1). Mp (CH_2Cl_2/hexane): 119–121°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.50 and 7.18–7.29 (m, 4H and 6H, respectively, Ph_2); 4.44 (ddd, J_{2-3}=J_{3-4}=6.3 Hz, J_{H-OH}=7.9 Hz, becomes a triplet upon shaking with D_2O, 1H, H-3); 4.39 (s, 1H, C*H*Ph_2); 3.53 (d, J_{H-OH}=7.9 Hz, disappears upon shaking with D_2O, 1H, OH); 3.27 (s, 3H, CH_2OCH_3); 3.16 (m, 1H, C$H_2$$OCH_3$); 3.12 (m, 1H, H-2); 3.09 (dd, J=10.6, 4.3 Hz, 1H, C$H_2$$OCH_3$); 3.08 (m, 1H, H-4); 1.65 (m, 2H, C$H_2$$CH_2CH_3$); 1.14 and 0.72 (each m, each 1H, $CH_2CH_2CH_3$); 0.67 (t, J=7.2 Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 143.01, 142.71 (Ar Cquat); 128.48, 128.25, 127.83, 127.31, 127.28 (Ar); 78.42 (*C*HPh_2); 72.08 (*C*$H_2$$OCH_3$); 69.38, 67.80,

66.25 (C-2, C-3 and C-4); 59.16 (CH_2OCH_3); 31.16 ($CH_2CH_2CH_3$); 18.83 ($CH_2CH_2CH_3$); 14.00 ($CH_2CH_2CH_3$). IR (NaCl, cm^{-1}): 3438 (broad, O–H); 1637 (C=C, Ar). MS (EI, *m/z*): $C_{21}H_{27}NO_2$ requires 325.2042; found 325.2036 (M^+, 3%). The second eluting compound was (*trans*, *trans*)-1-benzhydryl-2-methoxymethyl-4-propylazetidin-3-ol (**20b**, 25.4 mg, 0.078 mmol, 39%). R_f: 0.12 (silica gel, hexane–AcOEt 3:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46–7.43 and 7.17–7.29 (each m, 4H and 6H, respectively, Ph_2); 4.44 (s, 1H, $CHPh_2$); 3.80 (dd, $J_{2-3}=J_{3,4}=5.7$ Hz, 1H, H-3); 3.17 (s, 3H, CH_2OCH_3); 3.04 (dd, $J_{gem}=9.6$ Hz, $J_{vic}=7.4$ Hz, 1H, CH_2OCH_3); 2.93 (ddd, $J_{2-3}=5.7$ Hz, $J=7.4$, 3.8 Hz, 1H, H-2); 2.85 (ddd, $J_{3-4}=5.7$ Hz, $J=9.3$, 3.7 Hz, 1H, H-4); 2.83 (dd, $J_{gem}=9.6$ Hz, $J_{vic}=3.8$ Hz, 1H, CH_2OCH_3); 0.95–1.30 (m, 4H, $CH_2CH_2CH_3$); 0.73 (t, $J=7.3$ Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 142.28 (Ar Cquat); 128.43, 128.30, 128.16, 127.35, 127.30 (Ar); 79.03 ($CHPh_2$); 74.23, 73.28, 71.70, 71.48 (C-2, C-3, C-4 and CH_2OCH_3); 59.05 (CH_2OCH_3); 36.48 ($CH_2CH_2CH_3$); 17.93 ($CH_2CH_2CH_3$); 14.11 ($CH_2CH_2CH_3$). IR (NaCl, cm^{-1}): 3440 (broad, O–H); 1636 (C=C, Ar). MS (EI, *m/z*): $C_{21}H_{27}NO_2$ requires 325.2042; found 325.2039 (M^+, 2%).

3.1.15. Stereoselective preparation of (*all cis*)-1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-ol 19b. In a 50 mL round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, *cis*-1-benzhydryl-2-(methoxymethyl)-4-propylazetidin-3-one (**18b**, 40 mg, 0.124 mmol) was dissolved in dry diethyl ether (10 mL) and cooled to 0°C. To this solution was added dropwise with a syringe, potassium trisiamylborohydride (*KS* Selectride, 0.31 mL of a 1 M solution in THF, 0.310 mmol). The mixture was left stirring to warm up to room temperature for sixteen hours, water (5 mL) was added and the aqueous phase was extracted with diethyl ether (2×5 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica, column dimensions 14× 2.4 cm), eluting with hexane–AcOEt 5:1. (*All cis*)-1-benzhydryl-2-methoxymethyl-4-propylazetidin-3-ol (**19b**, 10 mg, 0.031 mmol, 25%) was obtained as a white solid after pooling and evaporation in vacuo of the solvent.

3.1.16. X-Ray crystallographic analysis of (*all cis*)-1-benzhydryl-2-(methoxymethyl)-4-propyl-azetidin-3-ol 19b. Compound **19b** was recrystallized from dichloromethane–hexane to afford single crystals for X-ray analysis. The crystallographic data are as follows: $C_{21}H_{27}NO_2$; $M_r=325.44$; monoclinic; space group $P2_1/n$ with $a=11.834(4)$, $b=7.785(3)$, $c=20.433(6)$ Å; $\beta=93.76(3)°$; $V=1878.4(11)$ $Å^3$; $Z=4$; $\rho_{calc}=1.151$ g cm^{-3}; $F(000)=704$. Crystal with dimensions 0.20×0.15×0.03 mm^3. A Huber four circle diffractometer fitted with a Rigaku rotating anode generator was employed, using graphite monochromatized Cu Kα radiation ($\lambda=1.54178$ Å). θ range for data collection: 4.2–67.5° by a $\theta/2\theta$ scan at room temperature. A total of 6496 reflections were integrated, of which 3387 were unique ($R_{int}=5.5\%$). Of the unique reflections, 1919 were observed with $I>2\sigma(I)$. Solution was achieved by direct methods using SHELXS-97.[35] Least squares refinement was applied by SHELXL-97[36] with anisotropic displacement parameters for the non hydrogen atoms. Conventional refinement indices are $R_1=0.0595$ for the 1919 observed reflections and $wR_2=0.1787$ for all data.

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