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10b-Substituted hexahydropyrrolo-isoquinolines: studies on diastereoselective formation of a quaternary carbon stereocenter via *N*-acyliminium ion cyclization

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Abstract—The stereoselective synthesis of hexahydro-pyrroloisoquinolines with a quaternary carbon stereocenter is described. The presented methodology employs the addition of a Grignard reagent to the carbonyl group of imide **1**, derived from L-tartaric acid, followed by acetylation and $BF_3 \cdot Et_2O$ induced cyclization. The acetylation–cyclization sequence can be run either as a one-pot process, or stepwise in a selected solvents. The crucial step, an acid-catalyzed carbon–carbon bond-forming reaction via an *N*-acyliminium ion offers high stereoselectivity, which has been shown to be strongly dependent on the size of the R^1 substituents and the reaction conditions, that is, choice of solvent, amount of a Lewis acid, temperature, and concentration of the substrate. Based on the results observed, participation of solvent in the cyclization, via an *N*-acyliminium cation is proposed.
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1. Introduction

The numerous syntheses of chiral, nitrogen-containing heterocycles that involve an iminium ion cyclization in the construction of a new stereogenic center are widely reported.[1,2] The isoquinoline[3] and pyrrolo[2,1-*a*]isoquinoline[4] alkaloids with significant bioactivity often have the stereocenters located at the tertiary or quaternary carbon atom, in the α-nitrogen position. Consequently, iminium ion chemistry is widely utilized in preparation of such compounds.[5] The asymmetric construction of a quaternary carbon stereocenter, frequently present in a variety of naturally occurring products, is a challenging task by itself. During the last decade, special attention has been paid to the development of both catalytic[6] and non-catalytic[7] methods for the asymmetric synthesis of compounds containing carbon atoms with four different non-hydrogen substituents.

We have recently described the stereocontrolled synthesis of hexahydro-pyrrolo[2,1-*a*]isoquinolines that contain a quaternary carbon stereocenter.[8] Our methodology employs the addition of a Grignard reagent to imide **1**, derived from L-tartaric acid, followed by the one-pot acetylation–cyclization sequence (Scheme 1). Herein we detail the utility of this methodology and disclose further findings that the reaction conditions, that is, choice of solvent, amount of a Lewis acid, temperature, and even concentration of the substrate, have a great impact on the stereoselectivity of an *N*-acyliminium ion cyclization, the key step of the synthesis of 10b-substituted hexahydropyrrolo-isoquinolines.

2. Results and discussion

A preliminary study on the preparation of pyrroloisoquinolines **4a–f** from imide **1**, derived from L-tartaric acid, was carried out employing procedure analogous to that reported by Lete and co-workers[5f–g] (Scheme 1). The nucleophilic addition of a Grignard reagent to the carbonyl group of **1** led to hydroxylactam **2a–f**, which, in case of **2a**, was isolated and analysed. However, we found that the use of crude reaction product directly in the next step was more practical. Hydroxylactam **2a**, subjected to the cyclization in the presence of trifluoroacetic acid in dichloromethane at reflux,[9] led to the expected **5a** in a trace amounts only. Changing of the reaction conditions, that is, solvent, temperature, time, protic and/or Lewis acid did not improve the yield of **5a**.

We assumed that acetylation of the hydroxyl group of **2a** would increase the rate of the slowest step of the reaction,

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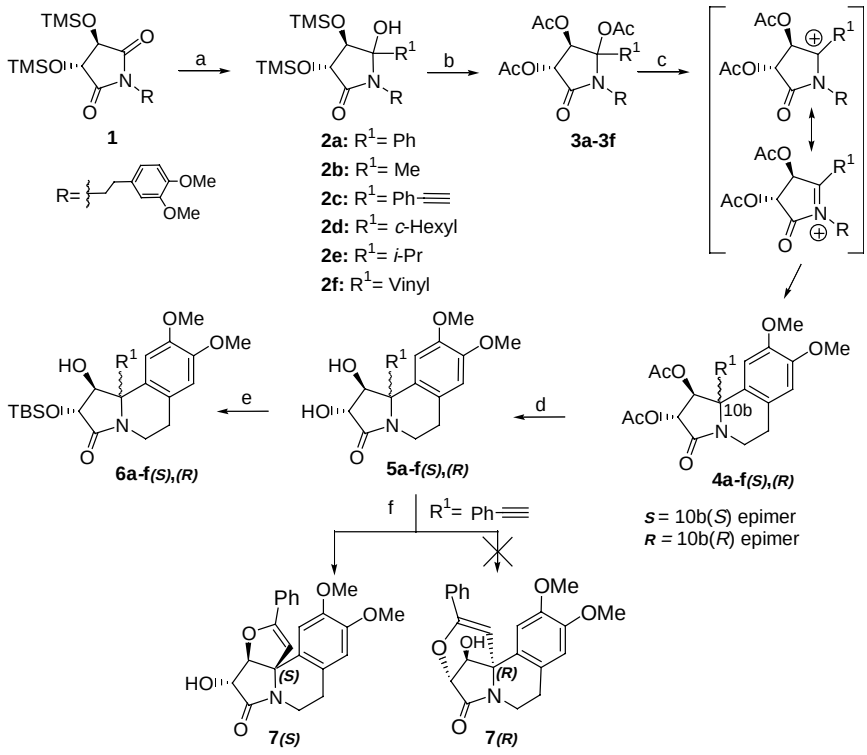

Scheme 1. Reagents and conditions: (a) R^1MgBr (1.5 equiv), THF, 0 °C gradually to rt, 1–2 h; (b) Ac_2O (4 equiv), DMAP (1.1 equiv), MeCN or Me_2CO rt, 3–4 h; (c) $BF_3 \cdot Et_2O$ (4 equiv), rt, 10 min then semi-satd aq $NaHCO_3$; (d) MeONa, MeOH; (e) TBS-Cl, imidazole, DMF, rt, 24 h; (f) $Pd(OAc)_2$ (0.2 equiv), TEA, THF, rt, 2 h.

namely the *N*-acyliminium ion formation,[10] thus facilitating the subsequent cyclization. Treatment of **2a** with acetic anhydride and DMAP in acetonitrile gave unstable triacetate **3a**, which was isolated by the chromatography on silica gel in only a 15% yield. Consequently, the crude triacetate **3a** in acetonitrile was treated with $BF_3 \cdot Et_2O$ to give hexahydro-pyrroloisoquinolines **4a**(*S*) and **4a**(*R*) in a 3:1 ratio, respectively. Several other 10b-substituted pyrroloisoquinolines **4b–f**(*S*),(*R*) were obtained as a mixture of diastereoisomers, utilizing the modified procedure consisting of addition of Grignard reagent to the imide **1** followed by the one-pot acetylation–cyclization of crude **2a–f**. The results are summarized in Table 1. The overall yields of **4a–f**(*S*),(*R*), based on the starting imide **1**, were high, except for entry 6. Although the 10b-epimers **4a–f**(*S*),(*R*) or their respective dihydroxy derivatives **5a–f**(*S*),(*R*) can be separated by tedious chromatography on silica gel, we have found that the respective 2-*t*-butyldimethylsilyloxy-pyrroloisoquinolines **6a–f**(*S*),(*R*) are much easier to purify due to the improved differentiation of the polarity of the **10b** epimers. The alkaline hydrolysis of the acetates **4a–f**(*S*),(*R*) followed by the silylation of the crude diols and separation of the resulting 2-silylethers gave optically pure pyrroloisoquinolines **6a–f**(*S*) and **6a–f**(*R*) in a high yield (Scheme 1, Table 1). The assignment of the configuration at the bridgehead carbon atom C-10b in pyrroloisoquinolines **4a–f**(*S*),(*R*) can be accomplished by NOESY experiment carried out with the mixture of diastereomers. However, due to the overlapping of the signals of epimers, only selected data of the major component can be collected and analysed, which may lead to some degree of uncertainty over data interpretation. The isolation of pure **6a–f**(*S*) and **6a–f**(*R*) allowed for an easy and unequivocal assignment of the configuration at C-10b of the obtained pyrroloisoquinolines.

The NOESY experiments, carried out with **6a–b**,**d–f**(*S*) showed an interaction between protons of the R^1 substituent (both α and β) at the C-10b-position with protons at C-2 and the OH group, as exemplified for **6f**(*S*) (Fig. 1). For the

Table 1. Stereocontrolled synthesis of hexahydro-pyrroloisoquinolines **4a–f**(*S*),(*R*) and separation of diastereomers as an optically pure 2-silyloxy-derivatives **6a–f**(*S*),(*R*)[a]

Entry	R^1	**4**(*S*),(*R*) Yield (%)[b]	*S*:*R*[c]	**6**(*S*) Yield (%)[d]	**6**(*R*) Yield (%)[d]
1	Ph	82	3:1	71	23
2	Me	85	5.6:1	61	11
3	PhC≡C	81	9.5:1	68	7.4
4	*c*-Hexyl	50	1:10	6.5	74
5	*i*-Pr	80	1:6.3	10	67
6	Vinyl	38	4.6:1	60	13

[a] General procedure A, for details see Section 4.
[b] Isolated yields of the mixture of diastereomers calculated for three-steps starting from **1**.
[c] Diastereomeric ratio was determined by ^{1}H NMR analysis.
[d] Isolated yields of pure diastereomers calculated for two-steps starting from **4**.

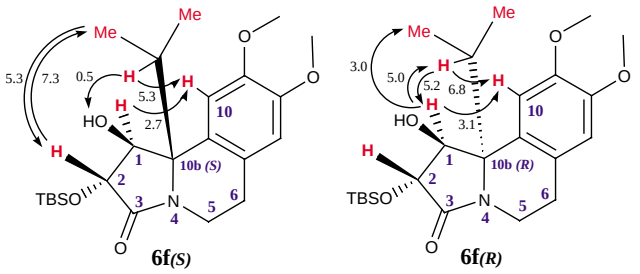

Figure 1.

C-10b*R* epimers, the respective protons of the R^1 substituent interact only with proton at C-1.

The 10b-phenylethynyl-substituted pyrroloisoquinolines **6c**(*S*),(*R*) do not possess diagnostic protons that are able to interact with protons at C-1 or C-2, thus it is impossible to carry out the direct assignment of configuration at C-10b solely on the basis of NOE experiments. However, the β-ethynyl-substituted alcohols easily undergo cyclization to give the respective dihydrofurans.[11] The epimeric mixture of **5c**(*S*),(*R*) was subjected to the palladium-catalyzed cyclization to give the dihydrofuranyl derivative **7**(*S*) in 82% yield. The epimeric **7**(*R*) compound was not detected in the crude reaction mixture. The exclusive formation of **7**(*S*)-isomer indicates that the major diastereomer of **4c**(*S*),(*R*) possesses the *S*-configuration at the C-10b.

Careful analysis of spectroscopic data of both the pyrroloisoquinolines **4a–f**(*S*),(*R*) and respective 2-silyloxy derivatives **6a–f**(*S*),(*R*) revealed an interesting regularity in their $J_{1,2}$ values (Tables 2 and 3). The $J_{1,2}$ values of **4a–f**(*S*) were in the range of 6.8 Hz (R^1=Ph) to 8.0 Hz (R^1=*i*-Pr), while the respective coupling constants of 10b(*R*)-series compounds were substantially smaller: 2.7 and 2.3 Hz (R^1=Ph, *c*-hexyl, respectively) and 0.0 Hz for the remaining compounds. The same regularity, even more pronounced, was observed for the 2-silyloxy derivatives **6a–f**(*S*),(*R*) (Table 3). The $J_{1,2}$ values of all 10b(*S*)-epimers were 8.3 Hz, while compounds of 10b(*R*)-series showed $J_{1,2}$ values in the range of 3.1–0.0 Hz. The large vicinal coupling constants (~8 Hz) of pyrroloisoquinolines of 10b(*S*) series indicate pseudo-equatorial arrangement of the substituents at C1 and C2, constrained by the steric interaction of the C-10b and C1 groups. Similar steric interactions lead to the pseudo-axial arrangement of the substituents at C1 and C2 of 10b(*R*) epimers, which is indicated by a small $J_{1,2}$ values (0–3.1 Hz).

Our observation that the values of $J_{1,2}$ coupling constants of all 10b(*S*) epimers **4a–f** and **6a–f** are large (6.8–8.3 Hz) and the respective values of compounds 10b(*R*) series are small (3.1–0.0 Hz) confirmed the above assignment. In addition, this regularity can be used as a rule for easy determination of the configuration at C-10b of pyrroloisoquinolines of this structure.

The unequivocal assignment of the configuration at C-10b for all pyrroloisoquinolines **4a–f** allowed for the rationalization of the observed stereoselectivity of cyclization reaction (Table 1). The plausible transition state of the cyclization is depicted on Figure 2. The internal nucleophile (dimethoxyphenyl moiety) may approach the *N*-acyliminium ion **A** either *anti*- or *syn*- with respect to the acetoxy group involved in the bridging of adjacent cationic center.[12] The diastereomer C-**10b**(*S*) and C-**10b**(*R*) is a product of *anti*- and *syn*-addition of the nucleophile, respectively.

The stereochemical outcome of the cyclization reactions described in this paper, can be rationalized by assuming the importance of differences in the steric interactions of the approaching nucleophile with the R^1 substituent versus the acetoxy group. The prevalent *anti*-addition of the nucleophile was observed for relatively small R^1 groups (phenyl, methyl, vinyl, phenylethynyl, entries 1–3, 6 Table 1). In contrast, when bulky R^1 groups (*c*-hexyl, *i*-propyl, entries 4 and 5) are present, *syn*-addition takes place primarily.

Our methodology of a simple, three-step synthesis of the C-10b-substituted-1,2-diacetoxy-hexahydro-pyrrolo-isoquinolines **4a–f**(*S*),(*R*) offers good overall chemical yield, but only moderate stereoselectivity. To improve the stereoselectivity of the key step, namely the acid-catalysed cyclization via *N*-acyliminium ion, we decided to re-investigate the reaction conditions.

The main question always associated with the nucleophilic addition to the *N*-acyliminium ion derived from 3-substituted-,[12,13] 3,4-disubstituted-pyrrolidine[14] or 3-substituted-piperdines,[15] is whether to expect *syn*- or *anti*-stereoselection in relation to the substituent adjacent to the cationic center. In general, the stereoselection primarily

Table 2. The $J_{1,2}$ coupling constants of hexahydro-pyrroloisoquinolines **4a–f**(*S*),(*R*)

C-10b	R^1						
	Ph	Me	Ph≡	*c*-Hexyl	*i*-Pr	Vinyl	
(*S*)	6.8	7.9	7.8	7.9	8.0	7.9	$J_{1,2}$ (Hz)
(*R*)	2.7	0	0	2.3	0	0	

Table 3. The $J_{1,2}$ coupling constants of hexahydro-pyrroloisoquinolines **6a–f**(*S*),(*R*)

C-10b	R^1						
	Ph	Me	Ph≡	*c*-Hexyl	*i*-Pr	Vinyl	
(*S*)	8.3	8.3	8.3	8.3	8.3	8.3	$J_{1,2}$ (Hz)
(*R*)	3.1	0	0	2.0	2.2	0	

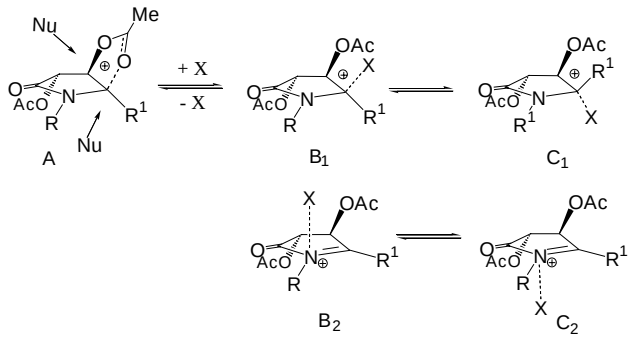

Figure 2.

depends on the C-3 substituent. Thus, the acetoxy-substituent should induce the high *anti* selectivity via neighboring group participation, while the 3-benzyloxy- or silyloxy- derivatives should prefer the moderate *syn*-addition of the nucleophile. However, the C-3 silyloxy-[14b] or benzyloxy-[15] substituent can induce the same level of trans-selectivity as the acetoxy group. Recently, Kobayashi and co-workers proposed a rationalization of this phenomenon by assuming a strong dependence of the stereochemistry on the nucleophile steric demand.[15] Additional factors, such as choice of acid catalyst, temperature, or solvent will usually influence the stereoselectivity to a limited degree only. In spite of the impressive number of reported fine syntheses based on chiral *N*-acyliminium ions where *syn*- versus *anti*- stereoselection was concerned, the reports presenting in-depth study of this important issue are rare as far as we know.[12,13e,14b,15]

The most frequently utilized solvent for reactions involving the *N*-acyliminium ion is dichloromethane, while other solvents, such as acetonitrile, toluene, diethyl ether or formic acid are less common.[12–15] For the initial evaluation of the influence of solvent choice on the stereoselectivity of the discussed cyclization, we selected compound **3a** as the *N*-acyliminium cation precursor. Due to its thermal and chemical instability, we used crude **3a**, which can be stored for weeks in a deep-freeze (−18 to −22 °C). The results of the $BF_3\cdot Et_2O$ induced cyclization of **3a** in a variety of solvents are summarized in Table 4.

Table 4. $BF_3\cdot Et_2O$ promoted cyclization of **3a**. The effect of solvent on the diastereoselectivity[a]

Entry	Solvent	*S*:*R*[b]
1	CH_2Cl_2	16.1:1
2	1,2-Dichloroethane	10.5:1
3	Toluene	7.7:1
4	Methyl pivaloate	6.8:1
5	$MeNO_2$	5.8:1
6	MeCN	3.3:1
7	Acetic acid	2.9:1
8	Tetrahydrofuran	2.5:1
9	Methyl acetate	2.6:1
10	Ethyl acetate	2.2:1
11	3-Pentanone	2.0:1
12	Acetone	1.9:1
13	Pinacolone	1.7:1
14	DMF	No reaction

[a] All reactions were carried out using standard procedure: crude acetate **3a** (0.1 M/solvent) obtained via procedure A or B was treated at rt with $BF_3\cdot Et_2O$ (4 equiv), stirred for 10 min then quenched by the addition of satd aq $NaHCO_3$. Isolated yields were always ≥80%.
[b] Diastereomeric ratio was determined by HPLC analysis.

The cyclization of **3a** conducted in CH_2Cl_2 gave a mixture of the product *anti*- [10b(*S*)] and *syn*-addition [10b(*R*)] in the ratio of 16.1:1, respectively (entry 1). When 1,2-dichloroethane was used the amount of *anti*-product decreased substantially (10.5:1, entry 2). The change to a more polar solvent such as acetonitrile, nitromethane, acetic acid, tetrahydrofuran or ethyl acetate, resulted in further decrease of *anti* selectivity (entries 3–10). The lowest *anti* selectivity was observed in unusual solvents such as 3-pentanone, acetone and pinacolone (entries 11–13). Although in the presence of a Lewis acid these ketones can undergo self-condensation, it apparently did not affect the very fast *N*-acyliminium cyclization.

We believe that solvents utilized in runs 3–10 may have stabilized the cationic center in direct competition to the acetoxy group, via proposed structures B_1, B_2, or C_1, C_2 (Fig. 2). Consequently, the acetoxy bridge in **A** may become broken, resulting in a decreased *anti*-stereoselection. Such participation of a solvent in the reaction involving the *N*-acyliminium cation was never before postulated, as far as we know. However, cases of a similar solvent participation are well documented in glycosylation reactions proceeding via an oxonium ion.[16]

In the course of the work presented in the above investigation, we have found that reliable and well-reproducible results can be realized only when $BF_3\cdot Et_2O$ is quickly injected via syringe directly into a vigorously stirred solution of **3a**. This observation can be rationalized by assumption that the stereoselectivity of a fast reaction (< 10 min) depends on a concentration of the Lewis acid catalyst. The cyclization of **3a** in the presence of 1 equiv of $BF_3\cdot Et_2O$ yielded a mixture of C-10b epimers in a ratio *S*:*R*=12.5:1 (Table 5, entry 1). An increase in the amount of Lewis acid led to the improvement of *anti* selection, which reached the maximum when 4 equiv of Lewis acid were used (entry 3). Further increase of the catalyst up to 10 equiv did not change the proportion of diastereomers significantly. Applying a sub-molar amount of $BF_3\cdot Et_2O$ (0.3 equiv) resulted in a sluggish reaction. In addition the substrate was not consumed completely, even when allowing the cyclization to run for up to 18 h. The triacetate **3a**, when treated with 4 equiv of $BF_3\cdot 2AcOH$ gave mixture of C-10b epimers *S* and *R* in a 8.6:1 ratio, respectively (Table 5, entry 4). In comparison with the result of run 3, the reaction catalyzed with $BF_3\cdot 2AcOH$ was slower and less selective.

Table 5. Cyclization of **3a**. The effect of varying amounts of $BF_3\cdot Et_2O$ on diastereoselectivity[a]

Entry	Catalyst, (equiv)	*S*:*R*[b]
1	$BF_3\cdot Et_2O$, 1	12.5:1
2	$BF_3\cdot Et_2O$, 2	13.6:1
3	$BF_3\cdot Et_2O$, 4	16.1:1
4[c]	$BF_3\cdot 2AcOH$, 4	8.6:1
5	$BF_3\cdot Et_2O$, 10	15.9:1

[a] Standard procedure of Table 4 was utilized, concd **3a** 0.1 M/CH_2Cl_2, rt. Isolated yields were always ≥80%.
[b] Diastereomeric ratio was determined by HPLC analysis.
[c] The cyclization required at least 30 min for completion.

The results presented in Table 4 (entry 7) and Table 5 indicated that the acetic acid evolved during carbon–carbon bond formation caused the decrease *anti* selectivity of cyclization either via formation of a less selective catalyst $BF_3 \cdot 2AcOH$, or by the complexation of *N*-acyliminium ion in competition to the adjacent acetoxy group.

In the course of our efforts to enhance the diastereoselectivity of the cyclization, we unexpectedly noticed that small changes in the concentration of **3a** in dichloromethane led to the substantial modification of the stereoselectivity of the reaction. Consequently, we carried out a series of cyclization experiments varying the concentration of **3a**. The results, presented in Table 6, can be rationalized as follows: the rate of intramolecular reaction, like the discussed cyclization, should not depend on the concentration of the iminium ion precursor. Acetic acid, evolved during carbon–carbon bond formation, could affect the stabilization of the cationic center competitively to the acetoxy group as depicted in Figure 2. A reversible cation

Table 6. Cyclization of **3a**. The effect of a concentration of the substrate on diastereoselectivity[a]

Entry	Concd **3a** [M]/CH_2Cl_2	*S*:*R*[b]
1	0.5	7.6:1
2	0.25	8.9:1
3	0.1	12.6:1
4	0.05	14.8:1
5	0.05[c]	11.0:1
6	0.005	28.6:1

[a] Standard procedure of Table 4 was followed, using 1.1 equiv of $BF_3 \cdot Et_2O$, rt. Isolated yields were always $\geq 80\%$.
[b] Diastereomeric ratio was determined by HPLC analysis.
[c] Reaction was run in the presence of acetic acid (4 equiv).

complexation, responsible for the decreased *anti*-stereoselection, is a second-order reaction, and as such should depend on the reactant concentration.

The above rationalization may explain why the reaction carried out under high-dilution conditions (0.005 M, entry 6) led to a considerable improvement in *anti* selectivity over the one conducted under a higher concentration (0.5 M, entry 1). The outcome of entries 4 and 5 showed that the presence of a small amount of cation-complexing solvent (4 equiv of acetic acid) can decrease the *anti* selectivity of the cyclization. The reported effect of concentration on the

Table 7. Cyclization of **3a**. The effect of the reaction temperature on diastereoselectivity[a]

Entry	Temperature (°C)	Reaction time (min)	*S*:*R*[b]
1	23	10	16.1:1
2	0	15	23.0:1
3	−10	20	17.3:1
4	−20	30	17.8:1
5	−40	60	17.6:1

[a] Standard procedure of Table 4 was utilized, concd **3a** 0.1 M/CH_2Cl_2, 4 equiv of $BF_3 \cdot Et_2O$. Isolated yields were always $\geq 80\%$.
[b] Diastereomeric ratio was determined by HPLC analysis.

stereoselectivity was not observed in other polar solvents such as acetic acid, ethyl acetate or acetone, supporting our rationale.

Table 7 presents the effect of temperature on the stereoselectivity. A decrease in the reaction temperature from 23 to 0 °C enhanced the *anti* selectivity (entries 1 and 2). However, further cooling to −10 °C resulted in a diminished selectivity, which remained unchanged for the other reactions carried out at −20 and −40 °C. Our results appear to be in agreement with a recent report by Wistrand, who observed that the *syn*/*anti*-stereoselections of the diastereoselective allylation of *N*-acyliminium ion at rt and at −78 °C were nearly the same.[13a]

The outcome of our optimization experiments, presented in Tables 4–7 allows the precise definition of the reaction conditions, which facilitate either *syn* or *anti* selectivity of the cyclization. Thus, to emphasize the *syn*-addition of the nucleophile, a solution of *N*-acyliminium ion precursor **3** in a polar solvent such as ethyl acetate, acetone or pinacolone (concentration is not important), should be treated at rt with $BF_3 \cdot Et_2O$ (1–2 equiv). In contrast, if the *anti*-addition product is required, the $BF_3 \cdot Et_2O$ (4 equiv) has to be added at 0 °C into a dilute solution of **3** in such a solvent as dichloromethane or 1,2-dichloroethane.

In order to assess the scope of the optimized reaction conditions, several other 10b-substituted pyrroloisoquinolines were prepared applying procedures B and C (Table 8). Procedure B, favoring the *syn*-addition, consists of the use of crude hydroxy-lactams **2a–e** in a 0.2 M acetone solution for the one-pot acetylation–cyclization reaction sequence. The acetone was used as a solvent of choice, since it is inexpensive, non-toxic and offers fast and clean conversion of trimethylsilylated hydroxy-lactams **2a–e** into respective triacetates **3a–e**. Furthermore, as evident from Table 4, entry 13, cyclization performed in acetone yields a relatively higher than expected proportion of *syn*-addition product. Procedure C, that favors the *anti*-addition of the nucleophile, is based on the use of crude triacetates **3a–e**, obtained applying procedure A or B. The cyclization step is conducted at 0 °C by treating the 0.05 M solution of **3a–e** in dichloromethane with 4 equiv of $BF_3 \cdot Et_2O$. Experiments using procedure B led to the epimeric mixtures **4a–e** (Table 8). The product of the *anti*-addition of the nucleophile was obtained preferentially when small C-10b substituents (R^1 = Ph, Me, PhC≡C, entries 1–3) were present. However, the values of de for the obtained products were very low. The reverse stereoselection was observed when the bulky R^1 groups (*c*-Hexyl, *i*-Pr, entries 4 and 5) were present. The **4d**(*R*) and **4e**(*R*) epimers were formed predominantly in a high de. The cyclization of triacetates **3a–e**, utilizing procedure C resulted in a remarkable increase in *anti* selectivity for the small R^1 (entries 1–3) and, as expected, the decrease of *syn* selectivity for bulky C-10b substituents (entries 4 and 5).

Analyzing the results of the cyclization experiments (Tables 4–8) it is possible to conclude that the *syn*- versus *anti*-stereoselection of this process is controlled to a major extent by the steric requirements of susbtituent R^1, and the acetoxy group forming the bridge with neighboring cationic center. However, the choice of solvent as well as other experimental parameters can have an effect of a lesser magnitude.

Table 8. The optimized synthesis of optical pure hexahydro-pyrroloisoquinolines **4a**(*S*), **4b**(*S*), **6c**(*S*), **7c**(*S*), **5d**(*R*), and **6e**(*R*)

Entry	R^1	Cyclization product	Procedure[a]	*R*:*S*[b]	Isolated product	Yield (%)[c]
1	Ph	**4a**(*S*),(*R*)	B	1:1.9		
			C	1:24	**4a**(*S*)	69
2	Me	**4b**(*S*),(*R*)	B	1:3.4		
			C	1:17.9	**4b**(*S*)	73
3	PhC≡C	**4c**(*S*),(*R*)	B	1:9.2		
			C	1:22	**6c**(*S*), [**7c**(*S*)]	69, (52)
4	*c*-Hexyl	**4d**(*S*),(*R*)	B	19:1	**5d**(*R*)	50
			C	4.5:1		
5	*i*-Pr	**4e**(*S*),(*R*)	B	11:1	**6e**(*R*)	42
			C	2.5:1		

[a] Procedure B: crude hydroxylactams **2a–e** were acetylated (0.2 M/acetone, DMAP 1.1 equiv, Ac_2O, 4.0 equiv, rt, 3 h) and treated at rt with $BF_3 \cdot Et_2O$ (3 equiv), stirred for 15 min then quenched with satd aq $NaHCO_3$. Procedure C: crude acetylated lactams **3a–e** obtained following Method A or B were isolated, then dissolved in CH_2Cl_2 (0.05 M), cooled to 0 °C, treated with $BF_3 \cdot Et_2O$ (4 equiv) in one portion, stirred for 15 min and then quenched with satd aq $NaHCO_3$.
[b] Diastereomeric ratio of pyrroloisoquinolines **4a–f** was determined by HPLC analysis.
[c] Isolated yield of optically pure product, based on the imide **1**.

We were pleased to see that the main products **4a**(*S*) and **4b**(*S*) can be isolated in a high overall yield as optically pure compounds after a single crystallization from ethanol (entries 1 and 2, procedure C). Also, the cyclohexyl derivative **4d**(*R*), after hydrolysis of the acetate groups can be isolated via crystallization from acetone as a dihydroxy derivative **5d**(*R*) (entry 4, procedure B). The remaining pyrroloisoquinolines **4c** and **4e** can be isolated by chromatography as respective derivatives **6c**(*S*), **7c**(*S*) and **6e**(*R*) (entries 3 and 5, procedure B).

3. Concluding remarks

In summary, we have successfully developed a simple, three-step synthesis of hexahydro-pyrroloisoquinolines with a quaternary carbon stereocenter at the C-10b carbon atom. The presented methodology utilizes the addition of a Grignard reagent to the carbonyl group of imide **1**, derived from L-tartaric acid, followed by acetylation and $BF_3 \cdot Et_2O$ induced cyclization. The acetylation–cyclization sequence can be run either stepwise or as a one-pot process, in selected solvents. The crucial step, an acid-catalysed carbon–carbon bond-forming reaction via an *N*-acyliminium ion offers high stereoselectivity. The degree of stereoselectivity was shown to be strongly dependent on the size of the R^1 substituent and, to a lesser degree, on the reaction conditions, that is, choice of solvent, amount of Lewis acid, temperature, and even concentration of the substrate. Based on the observed results, participation of solvent in the cyclization via *N*-acyliminium cation is proposed.

Our observation that the values of $J_{1,2}$ coupling constants of all 10b(*S*) epimers **4a–f** and **6a–f** are large (6.8–8.3 Hz), and the respective values of compounds 10b(*R*) series are small (3.1–0.0 Hz), can be used as a rule for the easy determination of the configuration at C-10b of pyrroloisoquinolines of this structure. The obtained pyrroloisoquinolines **4a**(*S*), **4b**(*S*) and **5d**(*R*) can be isolated in a high overall yield as optically pure compounds after a single crystallization, while the remaining compounds can be isolated by chromatography as their respective 2-silyloxy-derivatives.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured at 23 °C with a JASCO Dip-360 digital polarimeter. IR spectra were obtained using an FT-IR-1600 Perkin-Elmer spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ (except where indicated otherwise) using a Bruker AM 500 spectrometer. Chemical shifts are quoted in δ ppm relative to TMS for ^1H and $CDCl_3$ for ^{13}C NMR. Coupling constants *J* are reported in Hertz. Mass spectra were recorded using an AMD 640 or a Mariner mass spectrometer. Kugelrohr distillation was performed using Buchi glass oven B585. HPLC analyses were preformed with a Shimadzu LC-8A chromatograph with Hibar® 250-4 LiChrosob® Si 60 (5 μm). Thin-layer chromatography was carried out on precoated silica gel (Merck Kieselgel 60 F_{254}, 0.2 mm layer thickness). Flash column chromatography was preformed using Merck Kieselgel (230–400 mesh). All reactions were carried out under an argon atmosphere using anhydrous solvents. Most reagents were obtained from commercial suppliers and were used without further purification, unless noted. THF was distilled from Na and benzophenone, dichloromethane and toluene were distilled from CaH_2.

4.1.1. Preparation of (2*R*,3*R*)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3,4-trimethylsilanyloxy-pyrrolidine-2,5-dione (1). To a stirred suspension of (2*R*,3*R*) 3,4-dihydroxy-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-pyrrolidine-2,5-dione[5k] (29.5 g, 0.1 mol) in pyridine (50 mL, ~0.6 mol) and CH_2Cl_2 (300 mL) at 0 °C, trimethylsilyl chloride (33 mL, 0.26 mol) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min followed by an additional 1 h at rt. The solution was poured into ice-water mixture (~500 mL). The organic phase was separated, washed with cold water (3× ~300 mL), saturated sodium bicarbonate (200 mL), dried ($MgSO_4$), filtered and evaporated.

The crude product was purified by Kugelrohr distillation (oven temperature 150–160 °C, 0.1 Torr).

Yield: 41.3 g, 94%. Viscous oil, solidified on storage at rt, mp 60–61 °C; $[\alpha]_D$ +126.8 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2): 3055, 2961, 1721 cm^{-1}; ^1H NMR: 0.22 (s, 18H), 2.83 (m, 2H), 3.66 (m, 1H), 3.72 (m, 1H), 3.64 and 3.86 (two s, 6H), 4.33 (s, 2H), 6.75 (m, 3H); ^{13}C NMR: −0.01, 33.03 (t), 39.89 (t), 55.83, 55.89, 76.37, 111.37, 112.07, 120.91, 129.96 (s), 147.88 (s), 148.95 (s), 173.21 (s); MS (EI, HR) *m/z*: (M^+) calcd for $C_{20}H_{33}NO_6Si_2$: 439.1846. Found: 439.1842.

4.2. General procedures for the preparation of hexahydropyrrolo-isoquinolines [4a–f(*S*),(*R*)]

4.2.1. Procedure A. To a solution of imide **1** (878 mg, 2 mmol) in dry THF (3 mL), an organomagnesium bromide (3 mmol) in THF (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, gradually warmed up to rt, and stirring was continued until TLC indicated the disappearance of **1** (approx. 0.5 h). The reaction mixture was poured into ice-cold semi-satd aq $NaHCO_3$ (30 mL) and extracted with *t*-butyl methyl ether (3×30 mL). The combined extracts were washed with ice-cold water, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude hydroxy-lactam **2a–f** was dissolved in dry MeCN (10 mL), and after cooling to 0 °C, dimethylaminopyridine (270 mg, 2.2 mmol) and Ac_2O (756 μL, 8 mmol) were added. The cooling bath was removed and stirring was continued at rt for 3 h, then $BF_3 \cdot Et_2O$ (1.14 mL, 8 mmol) was added in one portion. The mixture was stirred at rt for 10 min then cooled to 0 °C, quenched with satd aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with water (2×20 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The product was purified by flash column chromatography on silica gel to yield pyrroloisoquinolines as a mixture of epimers. The yields of **4a–f**(*S*),(*R*) are calculated based on a sequence of three-steps from **1**.

4.2.2. Procedure B. The crude hydroxylactam **2**, obtained according to procedure A was acetylated in acetone (0.2 M/acetone, DMAP 1.1 equiv, Ac_2O, 4.0 equiv, 0 °C→rt, 3 h) and treated at rt with $BF_3 \cdot Et_2O$ (3 equiv) added in one portion. Workup and purification of obtained pyrroloisoquinolines **4a–f**(*S*),(*R*) as in procedure A.

4.2.3. Procedure C. The acetylated lactam **3**, obtained according to procedure A or B was isolated as follows: the reaction mixture was poured into ice-cold water and extracted twice with CH_2Cl_2, collected extracts were washed with cold water, satd aq sodium bicarbonate, and again with water, dried ($MgSO_4$) and evaporated. Crude **3** was carefully dried at rt under high vacuum (0.1 Torr, 2 h), then dissolved in CH_2Cl_2 (0.05 M), cooled to 0 °C and with vigorous stirring, $BF_3 \cdot Et_2O$ (4 equiv) was added in one portion. Stirring at 0 °C was continued for 15 min and then the reaction mixture was quenched by the addition of satd aq $NaHCO_3$. Workup and purification of the obtained pyrroloisoquinolines **4a–f**(*S*),(*R*) was as in procedure A.

4.2.4. Preparation of (2*R*,3*R*)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-5-hydroxy-5-phenyl-3,4-bis-trimethylsilanyloxy-pyrrolidin-2-one (2a). The crude hydroxylactam **2a** was obtained following procedure A from imide **1** (439 mg, 1 mmol) and filtered through a silica gel pad using *t*-butylmethyl ether/hexane=1:1 as eluent to give **2a** as a 10:1 mixture of epimers.

Yield: 388 mg, 75%, white solid, crystallization from hexane gave analytical pure sample of main epimer. Colourless crystals, mp 90–92 °C; $[\alpha]_D$ +23.0 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3499, 2961, 1717 cm^{-1}; ^1H NMR: −0.11 and 0.26 (two s, 18H), 2.74 (m, 2H), 2.86 (m, 1H), 3.58 (m, 1H), 3.76 and 3.80 (two s, 6H), 4.01 (s, 1H, exchangeable with D_2O), 4.14 (d, 1H, J=6.7 Hz), 4.31 (d, 1H, J=6.7 Hz), 6.52 (m, 2H), 6.68 (d, 1H, J=8.0 Hz), 7.32–7.49 (m, 5H); ^{13}C NMR: −0.23, 0.41, 34.40, 42.79, 55.77, 55.87, 75.50, 82.43, 88.69, 111.18, 111.94, 120.58, 126.77, 128.49, 128.61, 131.75, 139.98, 145.42, 148.79, 172.24; MS (LSIMS, HR) *m/z*: ($M+Na^+$) calcd for $C_{26}H_{39}NO_6NaSi_2$: 540.2214. Found: 540.2221.

4.2.5. Preparation of (2*R*,3*R*)-3,4,5-triacetoxy-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-5-phenyl-pyrrolidin-2-one (3a). Crude **3a** was obtained from **1** (439 mg, 1 mmol) according to procedure C and purified by flash column chromatography on silica gel using ethyl acetate/hexane=1:1 as an eluent.

Yield: 75 mg, 15%; white semisolid; IR (CH_2Cl_2): 2977, 1755, 1731 cm^{-1}.

Selected data of the main product taken from the 8:1 mixture of epimers.

^1H NMR: 2.06, 2.17 and 2.21 (three s, 9H), 2.68 (m, 2H), 3.05 (m, 1H), 3.42 (m, 1H), 3.79 and 3.81 (two s, 6H), 5.66 (d, 1H, J=5.9 Hz), 5.56 (d, 1H, J=5.9 Hz), 6.51 (m, 2H), 6.70 (d, 1H, J=6.7 Hz), 7.43 (m, 3H), 7.53 (m, 2H); ^{13}C NMR: 20.41, 20.68, 21.77, 33.25, 43.48, 55.80, 55.90, 74.87, 78.15, 93.34, 111.26, 111.92, 120.49, 125.77, 128.90, 129.36, 131.03, 138.36, 147.67, 149.93, 168.98, 169.43, 169.50, 170.09.

4.2.6. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-8,9-dimethoxy-10b-phenyl-1,2,3,5,6,10b-hexahydro-pyrrolo [2,1-*a*]isoquinolin-3-one [4a(*S*) and 4a(*R*)]. Procedure A, yield: 82%, **4a**(*S*): **4a**(*R*)=3:1,

Procedure B, yield: 83%, **4a**(*S*): **4a**(*R*)=1.9:1.

Procedure C, The crude reaction mixture of **4a**(*S*): **4a**(*R*)=24:1 was crystallized from ethanol to give pure **4a**(*S*). Yield: 69% (three-steps), white solid. The spectroscopic and physical properties of **4a**(*S*) and **4a**(*R*) were previously reported.[8]

4.2.7. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-8,9-dimethoxy-10b-methyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4b(*S*) and 4b(*R*)]. Procedure A, yield: 85%, **4b**(*S*): **4b**(*R*)=5.6:1.

Procedure B, yield: 83%, **4b**(*S*): **4b**(*R*)=3.4:1.

Procedure C, the isolation procedure of hydroxyamide **2b** was modified: for the extraction of **2b** dichloromethane was used. The crude reaction mixture of **4b**(*S*): **4b**(*R*)=17.9:1 was crystallized from ethanol to give pure **4b**(*S*). Yield: 73% (three-steps).

Compound **4b**(*S*). Colourless crystals, mp 168–169 °C (ethanol); $[\alpha]_D$ +152 (*c* 1.2, CH_2Cl_2); IR (CH_2Cl_2): 2939, 1752, 1715 cm^{-1}; ^1H NMR: 1.65 (s, 3H), 2.14 and 2.24 (two s, 6H), 2.71 (m, 1H), 2.96 (m, 1H), 3.12 (m, 1H), 3.81 and 3.82 (two s, 6H), 4.41 (dd, 1H, *J*=13.1, 6.2 Hz), 5.46 (d, 1H, *J*=7.9 Hz), 5.67 (d, 1H, *J*=7.9 Hz), 6.26 and 6.58 (two s, 2H); ^{13}C NMR: 20.68, 20.86, 23.44, 27.85 (t), 34.57 (t), 55.86, 55.89, 59.52 (s), 72.34, 79.32, 107.41, 111.73, 124.41 (s), 131.24 (s), 148.26 (s), 148.52 (s), 164.32 (s), 169.70 (s), 170.47 (s); MS (ES, HR) *m/z*: ($M+H^+$) calcd for $C_{19}H_{24}NO_7$: 378.1547. Found: 378.1552. Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.51; H, 6.08; N, 3.70.

Compound **4b**(*R*). Selected data taken from the mixture of epimers **4b**(*S*): **4b**(*R*)=5.6:1

^1H NMR: 1.68 (s, 3H), 1.69 and 2.20 (two s, 6H), 5.17, 5.55, 6.47, and 6.59 (four s, 4H).

4.2.8. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-8,9-dimethoxy-10b-phenylethynyl-1,2,3,5,6,10b-hexahydro-pyrrolo [2,1-*a*]isoquinolin-3-one [4c(*S*) and 4c(*R*)]. Procedure A, yield: 81%, **4c**(*S*): **4c**(*R*)=9.5:1.

Procedure B, yield: 83%, **4c**(*S*): **4c**(*R*)=9.2:1.

Procedure C, yield: 78%, **4c**(*S*): **4c**(*R*)=23:1

Oil; IR (CH_2Cl_2): 3008, 2939, 2232, 1754, 1722 cm^{-1}; MS (EI, HR) *m/z*: (M^+) calcd for $C_{26}H_{25}NO_7$: 463.1631. Found: 463.1646.

Selected data for the mixture of epimers **4c**(*S*): **4c**(*R*)= 9.2:1.

Compound **4c**(*S*). ^1H NMR: 2.14 and 2.25 (two s, 6H), 2.75 (m, 1H), 2.98, (m, 1H), 3.32 (m, 1H), 3.83 and 3.87 (two s, 6H), 4.40 (ddd, 1H, *J*=13.1, 6.2, 1.6 Hz), 5.84 (d, 1H, *J*=7.8 Hz), 5.80 (dd, 1H, *J*=7.8, 1.1 Hz), 6.60 (s, 1H), 6.86 (s, 1H), 7.30–7.43 (m, 5H); ^{13}C NMR: 20.66, 20.92, 27.56 (t), 35.48 (t), 55.92 (overlapped signals of two carbons), 58.43 (s), 74.38, 78.82, 85.44 (s), 87.37 (s), 108.14, 111.67, 121.81 (s), 124.77 (s), 127.44 (s), 128.35, 128.97, 131.86, 148.46 (s), 149.10 (s), 167.62 (s), 169.76 (s), 170.20 (s).

Compound **4c**(*R*). ^1H NMR: 1.67 and 2.16 (two s, 6H), 3.85 and 3.88 (two s, 6H), 2.90 (m, 1H), 5.13 (s, 1H), 6.61 (s, 1H).

4.2.9. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-10b-cyclohexyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4d(*S*) and 4d(*R*)]. Procedure A, yield: 50%, **4d**(*S*): **4d**(*R*)=1:10.

Procedure B, yield: 80%, **4d**(*S*): **4d**(*R*)=1:19.

Procedure C, yield: 77%, **4d**(*S*): **4d**(*R*)=1:4.5.

Oil; IR (CH_2Cl_2): 2936, 2857, 1753, 1702 cm^{-1}; MS (ES, HR) *m/z*: ($M+Na^+$) calcd for $C_{24}H_{31}NO_7Na$: 468.1993. Found: 468.2013.

Selected data for the mixture of epimers **4d**(*S*): **4d**(*R*)= 1:4.5.

Compound **4d**(*S*). ^1H NMR: 2.08 and 2.22 (two s, 6H), 3.79 and 3.85 (two s, 6H), 4.50 (m, 1H), 5.48 (d, 1H, *J*=7.9 Hz), 5,76 (d, 1H, *J*=7.9 Hz), 6.48 and 6.55 (two s, 2H).

Compound **4d**(*R*). ^1H NMR: 1.83 and 2.18 (two s, 6H), 2.66 (dd, 1H, *J*=16.1, 3.9 Hz), 2.91 (m, 1H), 3.25 (m, 1H), 3.80 and 3.86 (two s, 6H), 4.44 (ddd, 1H, *J*=13.3, 7.0, 1.3 Hz), 5.15 (d, 1H, *J*=2.3 Hz), 5,65 (d, 1H, *J*=2.3 Hz), 6.54 and 6.58 (two s, 2H); ^{13}C NMR: 20.71, 20.69, 26.15 (s), 26.57 (t), 27.23 (t), 27.60 (t), 28.07 (t), 29.86 (t), 37.67 (t), 49.64, 55.74, 55.93, 69.35 (s), 75.10, 75.92, 109.85, 111.57, 126.11 (s), 126.65 (s), 146.97 (s), 147.94 (s), 167.44 (s), 167.44 (s), 169.67 (s), 169.85 (s).

4.2.10. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-10b-isopropyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4e(*S*) and 4e(*R*)]. Method A, yield: 80%, **4e**(*S*): **4e**(*R*)=1:6.3.

Method B, yield: 80%, **4e**(*S*): **4e**(*R*)=1:11.

Method C, yield: 77%, **4e**(*S*): **4e**(*R*)=1:2.5.

Oil; IR (CH_2Cl_2): 2966, 2939, 1753, 1704 cm^{-1}; MS (ES, HR) *m/z*: ($M+Na^+$) calcd for $C_{21}H_{27}NO_7Na$: 428.1680. Found: 428.1704.

Selected data for the mixture of epimers **4e**(*S*): **4e**(*R*)= 1:2.5.

Compound **4e**(*S*). ^1H NMR: 0.82 (d, 1H, *J*=7.3 Hz), 1.19 (d, 1H, *J*=7.3 Hz), 2.09 and 2.21 (two s, 6H), 3.78 and 3.85 (two s, 6H), 4.52 (m, 1H), 5.50 (d, 1H, *J*=8.0 Hz), 5.73 (d, 1H, *J*=8.0 Hz), 6.50 and 6.57 (two s, 2H).

Compound **4e**(*R*). ^1H NMR: 0.89 (d, 3H, *J*=7.0 Hz), 1.09 (d, 3H, *J*=7.0 Hz), 1.83 and 2.18 (two s, 6H), 2.68 (m, 1H), 2.92 (m, 1H), 3.25 (m, 1H), 3.80 and 3.87 (two s, 6H), 4.46 (dd, 1H, *J*=13.3, 6.3 Hz), 5.17 (d, 1H, *J*=2.0 Hz), 5.61 (s, 1H), 6.55 and 6.59 (two s, 2H); ^{13}C NMR: 17.38, 20.02, 20.64, 20.90, 28.12, 37.54, 39.11, 55.69, 55.78, 69.48, 74.92, 75.89, 109.57, 111.46, 126.30, 126.50, 146.92, 147.84, 167.42, 169.61, 169.82.

4.2.11. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-8,9-dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4f(*S*) and 4f(*R*)]. Procedure A, yield: 38%; **4f**(*S*): **4f**(*R*)=4.6:1.

Oil; IR (CH_2Cl_2): 2939, 2855, 1753, 1716 cm^{-1}; MS (ES, HR) *m/z*: ($M+Na^+$) calcd for $C_{20}H_{23}NO_7Na$: 412.1367. Found: 412.1380.

Selected data for the mixture of epimers **4f**(*S*): **4f**(*R*)=4.6:1.

Compound **4c**(*S*). ^1H NMR: 2.12 and 2.19 (two s, 6H), 2.69

(m, 1H), 2.95 (m, 1H), 3.08 (m, 1H), 3.80 and 3.86 (two s, 6H), 4.31 (ddd, 1H, J=12.9, 6.3, 2.5 Hz), 5.04 (d, 1H, J=17.1 Hz), 5.36 (d, 1H, J=10.4 Hz), 5.54 (d, 1H, J=7.9 Hz), 5.63 (dd, 1H, J=7.9, 1.1 Hz), 6.09 (dd, 1H, J=17.1, 10.4 Hz), 6.59 and 6.64 (two s, 2H); ^{13}C NMR: 20.67, 20.86, 24.51 (t), 35.15 (t), 55.79, 55.89, 63.53 (s), 74.08, 79.82, 108.02, 111.74, 117.23 (t), 125.58 (s), 127.88 (s), 136.19 (s), 148.12 (s), 148.71 (s), 168.12 (s), 169.72 (s), 170.38 (s).

Compound **4f**(*R*) *epimer*. ^{1}H NMR: 1.70 and 2.14 (two s, 6H), 3.79 and 3.87 (two s, 6H), 4.38 (ddd, 1H, J=12.8, 6.0, 1.0 Hz), 5.05 (d, 1H, J=17.0 Hz), 5.15 (s, 1H), 5.29 (d, 1H, J=10.4 Hz), 5.62 (s, 1H), 6.06 (dd, 1H, J=17.0, 10.4 Hz), 6.47 and 6.60 (two s, 2H).

4.2.12. Preparation of (1*S*,2*R*,10b*R*)-10b-cyclohexyl-1,2-dihydroxy-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [5d(*R*)]. The crude mixture of **4d**(*S*),(*R*) obtained from imide **1** (878 mg, 2 mmol) using procedure B, was dissolved at rt in dry MeOH (20 mL) containing MeONa (54 mg, 1 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (~0.5 h), then the reaction was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (~20 mL), the precipitate was filtered off, washed with CH_2Cl_2 and the filtrate was evaporated. The residue was crystallized from methanol–ethyl acetate mixture to give pure dihydroxy-pyrroloisoquinoline **5d**(*R*).

Yield: 368 mg, 51%; colourless crystals; mp 236–238 °C; $[\alpha]_D$ −115.3 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3565, 3357, 2935, 1685 cm^{-1}.

^{1}H NMR ($CDCl_3+D_2O$): 1.12 (m, 4H), 1.25 (m, 1H), 1.45 (m, 1H), 1.65 (m, 1H), 1.78 (m, 3H), 2.02 (m, 1H), 2.64 (dd, 1H, J=16.4, 5.0 Hz), 2.93 (m, 1H), 3.18 (m,1H), 3.83 and 3.87 (two s, 6H), 4.04 (d, 1H, J=5.8 Hz), 4.26 (m, 1H), 4.41 (d, 1H, J=5.8 Hz), 6.55 and 7.27 (two s, 2H); ^{13}C NMR: 26.32 (t), 26.84 (t), 27.00 (t), 27.21 (t), 27.54 (t), 28.64 (t), 36.05 (t), 47.51, 55.71, 56.15, 66.63 (s), 76.11, 76.65, 111.86, 111.98, 126.72 (s), 127.63 (s), 146.48 (s), 147.98 (s), 172.75 (s); MS (ES, HR) *m*/*z*: (M^+) calcd for $C_{20}H_{27}NO_5$: 361.1889. Found: 361.1903. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.35; H, 7.38; N, 3.84.

4.3. General procedure for the preparation of 2-(*tert*-butyl-dimethyl-silanyloxy)-hexahydropyrrolo-isoquinolines [6a–f(*S*),(*R*)]

The mixture of diacetoxy-pyrroloisoquinolines **4a**–**f**(*S*),(*R*) (0.5 mmol) was dissolved at rt in dry MeOH (10 mL) containing MeONa (16 mg, 0.3 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (~0.5 h), then the reaction was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (~5 mL), the precipitate was filtered off and the filtrate was evaporated to yield the crude mixture of dihydroxy-pyrroloisoquinolines **5a**–**f**(*S*),(*R*). The obtained mixture was dissolved in DMF (3 mL) and imidazole (102 mg, 1.5 mmol) was added followed by the *tert*-butyldimethylchlorosilane (120 mg, 0.8 mmol). The stirring was continued for 24 h at rt. The mixture was poured into water, extracted with ethyl acetate (2×10 mL), washed with water and brine then dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography to give optical pure derivatives **6a**–**f**(*S*) and **6a**–**f**(*R*)

4.3.1. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-10b-phenyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6a(*S*)] and [6a(*R*)]. The spectroscopic and physical properties of **6a**(*S*) and **6a**(*R*) were previously reported.[8]

4.3.2. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-8,9-dimethoxy-10b-methyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6b(*S*)] and [6b(*R*)]. *Compound* **6b**(*S*). Yield: 61%; oil; $[\alpha]_D$ +195.0 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2): 3685, 3610, 2932, 1704 cm^{-1}; ^{1}H NMR: 0.17 and 0.21 (two s, 6H), 0.92 (s, 9H), 1.52 (s, 3H), 2.57 (br s, 1H, exchangeable with D_2O), 2.64 (m, 1H), 2.88 (m, 1H), 2.99 (m, 1H), 3.84 and 3.85 (two s, 6H), 4.03 (d, 1H, J=8.3 Hz), 4.30 (ddd, 1H, J=11.4, 6.1, 1.4 Hz), 4.37 (d, 1H, J=8.3 Hz), 6.53 and 6.97 (two s, 2H); ^{13}C NMR: −5.01, −4.21, 18.34 (s), 21.82, 25.87, 28.03 (t), 33.87 (t), 55.84, 56.02, 59.33 (s), 76.93, 82.50, 108.07, 111.48, 124.17 (s), 133.00 (s), 148.02 (s), 168.22 (s); MS (EI, HR) *m*/*z*: (M^+) calcd for $C_{21}H_{33}NO_5Si$: 407.2128. Found: 407.2138.

Compound **6b**(*R*). Yield: 11%; white crystals; mp 158–160 °C (*t*-butylmethylether–hexane); $[\alpha]_D$ −126.8 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3685, 3560, 2934, 1697 cm^{-1}; ^{1}H NMR: 0.20 and 0.22 (two s, 6H), 0.93 (s, 9H), 1.67 (s, 3H), 2.65 (dd, 1H, J=15.8, 3.8 Hz), 2.83 (m, 1H), 3.05 (m, 1H), 3.85 and 3.89 (two s, 6H), 4.05 and 4.09 (two s, 2H), 4.32 (dd, 1H, J=13.2, 5.5 Hz), 6.57 and 6.63 (two s, 2H); ^{13}C NMR: −5.24, −4.67, 18.07 (s), 25.72, 26.71, 28.58 (t), 34.29 (t), 55.89, 56.22, 66.00 (s), 77.83, 78.01, 108.03, 112.46, 127.46 (s), 128.03 (s), 148.50 (s, overlapped signals of two carbons), 170.07 (s); MS (EI, HR) *m*/*z*: (M^+) calcd for $C_{21}H_{33}NO_5Si$: 407.2128. Found: 42.2133.

4.3.3. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-8,9-dimethoxy-10b-phenylethynyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6c(*S*) and 6b(*R*)]. *Compound* **6c**(*S*). Yield: 68%; oil; $[\alpha]_D$ +129.7 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 3603, 3544, 2958, 2858, 1713 cm^{-1}; ^{1}H NMR: 0.21 and 0.24 (two s, 6H), 0.958 (s, 9H), 2.63 (br d, 1H, J=10.0 Hz, exchangeable with D_2O), 2.74 (ddd, 1H, J=16.1, 4.4, 1.8 Hz), 2.93 (m, 1H), 3.24 (m, 1H), 3.87 and 3.90 (two s, 6H), 4.05 (m, 1H), 4.34 (ddd, 1H, J=13.0, 6.3, 1.9 Hz), 4.42 (dd, 1H, J=8.3, 1.2 Hz), 6.58 (s, 1H), 7.19 (s, 1H), 7.3–7.43 (m, 5H); ^{13}C NMR: −4.97, −4.36, 18.39 (s), 25.73, 27.59 (t), 35.04 (t), 55.90, 56.08, 59.06 (s), 77.38, 82.48, 85.64 (s) 88.33 (s), 108.35, 111.42, 121.45 (s), 124.54 (s), 128.31 (s), 128.42, 129.12, 131.91, 148.38 (s), 148.81 (s), 168.54 (s); MS (ES, HR) *m*/*z*: ($M+Na^+$) calcd for $C_{28}H_{35}NO_5NaSi$: 516.2177. Found: 516.2182.

Compound **6c**(*R*). Yield: 7.4%; oil; $[\alpha]_D$ −86.7 (*c* 1, CH_2Cl_2);

IR (CH_2Cl_2): 3558, 3054, 2932, 2857, 1705 cm^{-1}; ^1H NMR: 0.20 and 0.22 (two s), 0.91 (s, 9H), 2.69 (dd, 1H, $J=5.9$, 3.5 Hz), 2.87 (m, 1H), 3.26 (m, 1H), 3.26 (m, 1H), 3.88 and 3.92 (two s, 6H), 4.16 (s, 1H), 4.35 (dd, 1H, $J=13.1$, 5.4 Hz), 4.46 (br s, 1H), 6.66 (s, 1H), 6.87 (s, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR: −5.15, −4.60, 18.16 (s), 25.71, 28.16 (t), 35.14 (t), 55.94, 56.31, 63.00 (s), 77.38, 78.79, 85.66 (s), 89.20 (s), 108.46, 112.35, 122.41 (s), 124.51 (s), 128.05 (s), 128.13, 128.46, 131.67, 148.84 (s), 149.04 (s), 170.44 (s); MS (ES, HR) *m/z*: ($M+Na^+$) calcd for $C_{28}H_{35}NO_5NaSi$: 516.2177. Found: 516.2191.

4.3.4. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-10b-cyclohexyl-1-hydroxy-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6d(*S*) and 6d(*R*)].

Compound **6d**(*S*). Yield: 6.5%; oil; $[\alpha]_D$ +103 (*c* 1.4, CH_2Cl_2); IR (CH_2Cl_2): 3609, 2932, 2856, 1700 cm^{-1}; ^1H NMR: 0.20 and 0.23 (two s, 6H), 0.94 (s, 9H), 0.9–1.4 (m, 6H), 1.69 (m, 2H), 1.90 (m, 2H), 2.27 (m, 1H), 2.64 (dd, 1H, $J=16.2$, 4.0 Hz), 1.88 (m, 1H), 3.18 (m, 1H), 3.87 and 3.91 (two s, 6H), 4.13 (d, 1H, $J=8.3$ Hz), 4.47 (ddd, 1H, $J=13.2$, 5.9, 1.2 Hz), 4.62 (d, 1H, $J=8.3$ Hz), 6.55 and 6.96 (two s, 2H); ^{13}C NMR: −4.94, −4.14, 18.38 (s), 25.84, 26.36 (t), 26.58 (t), 27.66 (t, overlapped signals of two carbons), 29.11 (t), 30.627 (t), 36.21 (t), 44.76, 55.81, 56.17, 65.74 (s), 76.829, 84.86, 107.36, 111.36, 124.87 (s), 132.53 (s), 147.82 (s), 148.23 (s), 170.57 (s); MS (ES, HR) *m/z*: ($M+Na^+$) calcd for $C_{26}H_{41}NO_5NaSi$: 498.2644. Found: 498.2632.

Compound **6d**(*R*). Yield: 74%; oil; $[\alpha]_D$ −75.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3557, 2933, 2857, 1692 cm^{-1}; ^1H NMR: 0.19 and 0.20 (two s, 6H), 0.93 (s, 9H), 0.8–1.3 (m, 5H), 1.60 (m, 2H), 1.75 (m, 2H), 1.94 (m, 1H), 2.11 (m, 1H), 2.67 (ddd, 1H, $J=16.2$, 5.3, 2.0 Hz), 2.84 (m, 1H), 3.25 (m, 1H), 3.87 and 3.88 (two s, 6H), 4.01 (d, 1H, $J=2.0$ Hz), 4.26 (dd, 1H, $J=3.5$, 2.0 Hz), 4.32 (ddd, 1H, $J=13.3$, 7.2, 2.0 Hz), 6.63 and 6.79 (two s, 2H); ^{13}C NMR: −5.17, −4.52, 18.12 (s), 25.73, 26.29 (t), 26.74 (t), 27.78 (t), 28.30 (t), 30.22 (t), 36.95 (t), 49.26, 55.79, 56.24, 70.17 (s), 77.16, 78.24, 109.70, 112.37, 125.75 (s), 128.39 (s), 147.47 (s), 148.26 (s), 171.42; MS (ES, HR) *m/z*: ($M+H^+$) calcd for $C_{26}H_{42}NO_5Si$: 476.2827. Found: 476.2842.

4.3.5. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-10b-isopropyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6e(*S*) and 6e(*R*)].

Compound **6e**(*S*). Yield: 10%; oil; $[\alpha]_D$ +167.7 (*c* 0.7, CH_2Cl_2); IR (CH_2Cl_2): 3687, 3605, 2960, 2857, 1701 cm^{-1}; ^1H NMR: 0.17 and 0.2 (two s, 6H), 0.78 (d, 1H, $J=7.3$ Hz), 0.92 (s, 9H), 1.10 (d, 1H, $J=6.6$ Hz), 2.40 (d, 1H, $J=5.3$ Hz, exchangeable with D_2O), 2.65 (m, 2H), 2.87 (m, 1H), 3.11 (m, 1H), 3.85 and 3.87 (two s, 6H), 4.11 (dd, 1H, $J=8.3$, 5.3 Hz), 4.45 (dd, 1H, $J=13.0$, 6.1 Hz), 4.56 (d, 1H, $J=8.3$ Hz), 6.54 and 6.94 (two s, 2H).

^{13}C NMR: −4.98, −4.19, 18.39 (s), 18.73, 20.72, 25.83, 27.77 (t), 34.40, 36.20 (t), 55.81, 56.06, 65.46 (s), 76.73, 84.60, 107.29, 111.39, 124,70 (s), 132.94 (s), 145.93 (s), 148.25 (s), 170.59 (s); MS (ES, HR) *m/z*: ($M+Na^+$) calcd for $C_{23}H_{37}NO_5NaSi$: 458.2333. Found: 458.2339.

Compound **6e**(*R*). Yield: 67%; oil; $[\alpha]_D$ −77.9 (*c* 1.3, CH_2Cl_2); IR (CH_2Cl_2): 3558, 2960, 2857, 1693 cm^{-1}; ^1H NMR: 0.18 and 0.19 (two s, 6H), 0.91 (d, 3H, $J=7.0$ Hz), 0.93 (s, 9H), 1.05 (d, 3H, $J=6.8$ Hz), 1.62 (d, 1H, $J=$ 3.8 Hz, exchangeable with D_2O), 2.33 (m, 1H), 2.65 (dd, 1H, $J=16.0$, 5.2 Hz), 2.85 (m, 1H), 3.21 (m, 1H), 3.85 and 3.86 (two s, 6H), 4.02 (d, 1H, $J=2.2$ Hz), 4.23 (dd, 1H, $J=$ 3.8, 2.2 Hz), 6.62 and 6.81 (two s, 2H); ^{13}C NMR: −5.17, −4.54, 18.14, 18.16 (s), 20.34, 25.74 (t), 27.89 (t), 36.66 (t), 38.66, 55.78, 56.16, 69.96 (s), 77.16, 78.35, 108.70, 112.39, 125.91 (s), 128.35 (s), 147.49 (s), 148.28 (s), 171.35 (s); MS (ES, HR) *m/z*: ($M+H^+$) calcd for $C_{23}H_{38}NO_5Si$: 436.2514. Found: 436.2526.

4.3.6. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-8,9-dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6f>(*S*) and 6f(*R*)].

Compound **6f**(*S*). Yield: 60%; oil; $[\alpha]_D$ +107.5 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2): 3608, 2933, 2858, 1709 cm^{-1}; ^1H NMR (C_6D_6): 0.17 and 0.22 (two s, 6H), 0.93 (s, 9H), 2.31 (d, 1H, $J=6.8$ Hz, exchangeable with D_2O), 2.66 (m, 1H), 2.90 (m, 1H), 3.00 (m, 1H), 3.86 and 3.88 (two s, 6H), 4.12 (dd, 1H, $J=8.3$, 6.8 Hz), 4.25 (m, 1H), 4.32 (d, 1H, $J=8.3$, 1.1 Hz), 5.07 (d, 1H, $J=17.2$ Hz), 5.33 (d, 1H, $J=10.5$ Hz), 6.11 (dd, 1H, $J=17.2$, 10.5 Hz), 6.58 and 7.10 (two s, 2H); ^{13}C NMR: −5.01, −4.24, 18.35 (s), 25.27, 27.69 (t), 34.76 (t), 55.87, 56.09, 63.65 (s), 76.58, 83.33, 108.39, 111.56 (t), 125.17 (s), 129.73 (s), 136.70, 148.06 (s), 148.31 (s), 169.04 (s); MS (EI, HR) *m/z*: ($M+H^+$) calcd for $C_{22}H_{34}NO_5Si$: 420.2201. Found: 420.2216.

Compound **6f**(*R*). Yield: 13%; oil; $[\alpha]_D$ −111.0 (*c* 0.6, CH_2Cl_2); IR (CH_2Cl_2): 3558, 2932, 2858, 1699 cm^{-1}; H NMR: 0.29 and 0.37 (two s, 6H), 1.05 (s, 9H), 1.80 (br s, 1H, exchangeable with D_2O), 2.09 (dd, 1H, $J=15.8$, 3.8 Hz), 2.61 (m, 1H), 2.81 (dt, 1H, $J=12.7$, 4.3 Hz), 3.36 and 3.37 (two s, 6H), 4.28 (br s, 1H), 4.35 (dd, 1H, $J=12.7$, 5.5 Hz), 4.50 (s, 1H), 4.90 (dd, 1H, $J=17.2$, 1.0 Hz), 5.069 (dd, 1H, $J=10.4$, 1.0 Hz), 6.23 (s, 1H), 6.30 (dd, 1H, $J=17.2$, 10.4 Hz), 6.49 (s, 1H); ^{13}C NMR: −5.25, −4.67, 18.05 (s), 25.69, 28.28 (t), 34.11 (t), 55.86, 56.18, 70.30 (s), 76.91, 77.97, 109.19, 112.42, 117.44 (t), 123.43 (s), 129.12 (s), 139.37, 148.10 (s), 148.66 (s), 170.36 (s); MS (EI, HR) *m/z*: ($M+H^+$) calcd for $C_{22}H_{34}NO_5Si$: 420.2201. Found: 420.2210.

4.3.7. Preparation of (1*R*,8b*S*,11a*S*)-1-hydroxy-6,7-dimethoxy-10-phenyl-1,3,4,11a-tetrahydro-11-oxa-2a-aza-pentaleno[6a,1-*a*]naphthalen-2-one (7).

The epimeric mixture of **4c**(*S*),(*R*) (232 mg, 0.5 mmol), obtained applying procedure A, was dissolved at rt in dry MeOH (10 mL) containing MeONa (16 mg, 0.3 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (~0.5 h), then the reaction was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (~5 mL), the precipitate was filtered off and the filtrate was evaporated to yield the crude mixture of dihydroxy-pyrroloisoquinolines **5c**(*S*),(*R*). The obtained mixture was then dissolved in THF (3 mL) and $Pd(OAc)_2$ (23 mg, 0.1 mmol) was added followed by triethylamine (28 μl, 0.2 mmol) and stirring was continued for 2 h at rt. The mixture was poured into

water and extracted with CH_2Cl_2 (2×15 mL). Collected extracts were washed with water, semi-satd aq $NaHCO_3$ and water again then dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography to give **7**.

Yield: 155 mg, 82%; oil; $[\alpha]_D$ +247.0 (*c* 0.9, CH_2Cl_2); IR (CH_2Cl_2): 3556, 3330, 2985, 2939, 1732, 1699 cm^{-1}; ^1H NMR: 2.69 (dd, 1H, $J=16.5$, 3.6 Hz), 2.99 (m, 1H), 3.15 (m, 1H), 3.77 and 3.86 (two s, 6H), 3.94 (br s, 1H, exchangeable with D_2O), 4.38 (dd, 1H, $J=13.0$, 5.2 Hz), 4.64 (br s, 1H), 5.03 (d, 1H, $J=3.9$ Hz), 5.70 (s, 1H), 6.56 (s, 1H), 6.64 (s, 1H), 7.39 (m, 3H), 7.66 (m, 2H); ^{13}C NMR: 27.53 (t), 36.74 (t), 55.94, 56.14, 73.06 (s), 77.68, 92.06, 101.56, 108.59, 111.23, 124.80 (s), 125. 84, 128.48, 129.53 (s), 129.70 (overlapped signals of two carbons), 148.63 (s) 148.80 (s), 157.29 (s), 170.97 (s); MS (EI, HR) *m/z*: (M^+) calcd for $C_{22}H_{21}NO_5$: 379.1420. Found: 379.1429.

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