Stereodivergent Synthesis of Hetero-Fused Isoquinolines by Acyliminium and Metallation Methods

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Diastereodivergent syntheses of 1,10b-*cis*- and 1,10b-*trans*-thiazolo[4,3-*a*]isoquinoline systems are reported. The key transformations are based on the intramolecular cyclization of aryllithiums and *N*-acyliminium ions. With 5-substituted *N*-phenethylthiazolidinediones as substrates, hydride reduction or the organolithium addition–*N*-acyliminium cyclization sequence stereoselectively afforded the 1,10b-*cis* derivatives. Alternatively, the tandem Parham cyclization–hydroxyl reduction using the corresponding iodinated thiazolidinediones occurred with complete control of stereoselectivity, producing the 1,10b-*trans* diastereomers. Although it was not possible to synthesise imidazo[4,3-*a*]isoquinolinones by *N*-acyliminium cyclizations, application of the Parham cyclization–reduction sequence to *N*-phenethylhydantoins constituted an efficient alternative for the synthesis of these hetero-fused isoquinolines with 1,10b-*trans* stereochemistry. Ready access to 1-phenethylisoquinolines is also described.

Introduction

N-Acyliminium ion cyclization[1] and Parham[2] methodology are efficient methods of carbon−carbon bond formation and have been used extensively in the assembly of complex polycyclic natural products. In this context, we have demonstrated that application of the tandem nucleophilic addition−*N*-acyliminium ion cyclization sequence to *N*-phenethylimides constitutes an effective route to several types of isoquinoline alkaloids (pyrrolo[2,1-*a*]isoquinolinones, benzo[*a*]quinolizidones and their 2-oxa analogues, isoindoloisoquinolones, dibenzo[*a*,*h*]quinolizidones, etc.), with the capability to introduce a variety of substituents at the C-1 position of the isoquinoline unit by changing the organolithium reagent used in the first step. Alternatively, although bromine−lithium exchange is not fast enough to compete effectively with organolithium addition to the imide carbonyl, iodinated *N*-phenethylimides tolerate fast iodine−lithium exchange, giving rise to the isoquinoline nucleus through a Parham-type cyclization.[3]

To develop this chemistry fully, we decided to investigate and compare the stereochemical features of both types of cyclizations. While the intramolecular reactions of *N*-acyliminium ions have been widely used in the stereocontrolled synthesis of a variety of nitrogen heterocycles, stereoselective Parham cyclization has received only sporadic attention. In fact, it has been shown that intramolecular reactions of cyclic *N*-acyliminium ions with π-nucleophiles usually produce *trans*-substituted compounds, with very high stereoselectivity due to steric control by the substituents already present in the ring.[4] Maryanoff has studied the effect of stereogenic centres along the chain connecting the aromatic π-nucleophiles and the nitrogen atom.[5] Thus, high diastereoselectivity was found in the cyclization of *N*-phenethyl-*N*-(1-alkoxyalkyl)lactams to tetrahydroisoquinolines with substituents at the C-3 or C-4 positions. Reversal of diastereoselection was observed on changing from phenyl to cyclohexyl or *tert*-butyl substituents; this was attributed to a balance of *syn*-axial and $A^{(1,3)}$ interactions. Considerable efforts have also been devoted to the stereocontrolled addition of aromatic π-nucleophiles to cyclic *N*-acyliminium ions possessing a substituent adjacent to the iminium carbon. This class of intramolecular amidoalkylations, involving bond formation at the least hindered side, opposite to the substituent, has been used in the synthesis of heterocyclic systems.[6] Similar facial diastereoselectivities have been observed by Padwa[7] and Allin[8] in their synthesis of *Erythrina*-type alkaloids and ring-fused chiral isoindolones, respectively, via bicyclic *N*-acyliminium ions.

However, there are only a few cases in the literature in which the stereoselectivity of the aromatic metallation-cyclization sequence has been studied. For instance, Snieckus reported a facile diastereoselective assembly of benzofurans by an *ortho*-metallation-induced epoxy cycloalkylation.[9] Similarly, intramolecular cyclization of aryllithiums derived from lithium−halogen exchange resulted in stereoselective formation of 3,4-disubstituted tetrahydroisoquinolin-4-ols.[10] A related strategy of metallation-cyclization involving an anion translocation has enabled the diastereoselective construction of functionalized benzo[*e*]isoindolinone derivatives from *N*-benzylnaphthamides.[11]

On the other hand, we have previously observed[3c−3d] that *N*-phenethylimides in which one carbonyl group is part of a thio(carbamate) or urea function usually displayed complete chemoselectivity in the addition of alkyllithiums to the other carbonyl group. Therefore, we imagined that the Parham methodology might allow for a stereocontrolled

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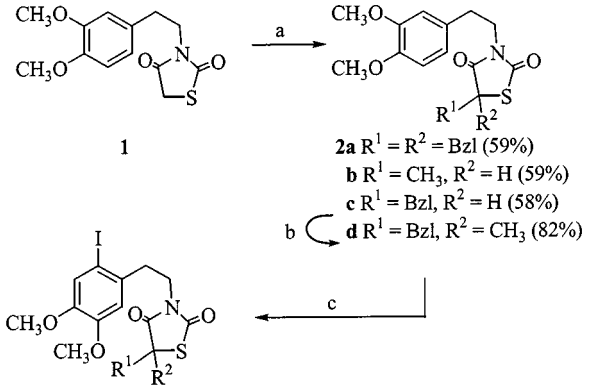
synthesis of thiazolo-, and imidazo[4,3-*a*]isoquinolinones. We anticipated that the Parham cyclization−hydroxyl reduction sequence on the iodinated 1-substituted *N*-phenethylimides might stereoselectively afford the 1,10b-*trans* heterocycles, whereas the corresponding *cis* diastereomers could be obtained by the tandem reduction−*N*-acyliminium cyclization on the non-iodinated imides. To assess the scope of the *N*-acyliminium ion cyclizations, we also decided to study the stereoselectivity of the organolithium nucleophilic addition−*N*-acyliminium cyclization sequence for the synthesis of these hetero fused isoquinolines. We now wish to report the complete details of our investigations,[12] which have culminated in diastereodivergent approaches to the target thiazolo- and imidazo[4,3-*a*]isoquinolinones.

Results and Discussion

To begin our study, a series of thiazolidine-2,4-diones **2a-d** and hydantoins **5a−d**, with substituents of different bulk at C-5, were prepared as depicted in Scheme 1 and Scheme 2. Thus, di- and monoalkylation of thiazolidinedione **1**[3d] and hydantoin **4**[3d] was achieved in satisfactory yields, using LDA or *sec*BuLi/TMEDA. Subsequent alkylation of **2c** and **5b** yielded disubstituted **2d** and **5d**, respectively, in high yield. Thiazolidinediones **2a−d** and hydantoins **5a−d** were iodinated with iodine monochloride to afford the corresponding **3a−d** and **6a−d**, respectively, in high yields and with complete regioselectivity.

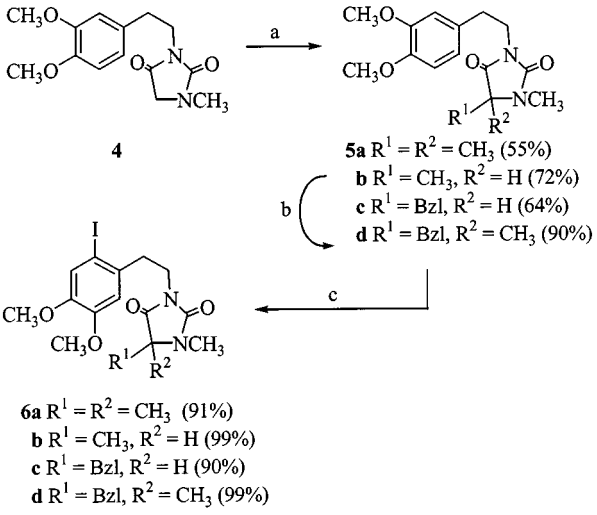


Reagents: (a) LDA or *s*-BuLi/TMEDA; R^1X; (b) *s*-BuLi/TMEDA; MeI; (c) ICl, AcOH

Scheme 1

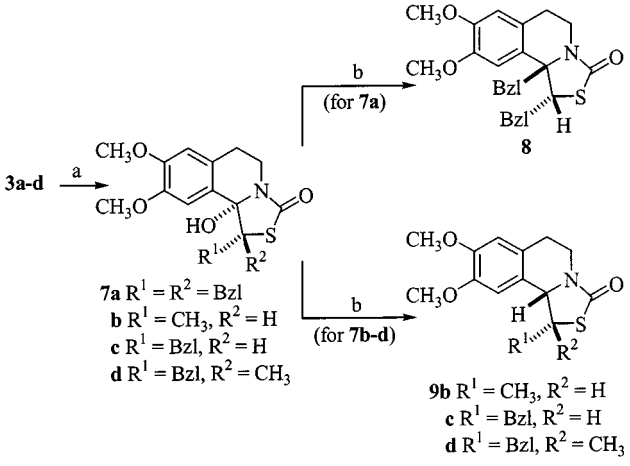
Synthesis of Thiazolo[4,3-*a*]isoquinolones

Firstly, we decided to study the Parham cyclization on thiazolidinediones **3a−d** (Scheme 3). To test the reaction conditions and the regioselectivity of the cyclization, the C-5 disubstituted thiazolidine-2,4-dione **3a** was chosen as substrate. Iodine−lithium exchange was carried out with *t*BuLi at −78 °C in THF and, after workup, 10b-hydroxy thiazoloisoquinoline **7a** was obtained in high yield. As expected, the addition of the organolithium intermediate proceeded regioselectively at the more electrophilic amide carbonyl, despite the substitution at C-5. In order to study the stereochemistry of the cyclization, thiazolidines **3b−d** were treated with *t*BuLi. It could be observed that on C-5 monosubstituted thiazolidines **3b** and **3c**, iodine−lithium exchange was faster than C-5 deprotonation, and cyclization took place efficiently. Thus, 10b-hydroxy thiazoloisoquinolines **7b−d** were obtained in good yields, as shown by the ^{1}H NMR spectra of the crude reaction mixtures. However, these products were highly unstable, and partially decomposed upon purification. Thus, only low isolated yields were obtained (Table 1, entries 2−4). In all cases, attack of the organolithium intermediate occurred from the less



Reagents: (a) LDA or *s*-BuLi/TMEDA; R^1X; (b) LDA; BzlBr (c) ICl, AcOH

Scheme 2



Reagents: (a) *t*-BuLi, –78 °C; b) $NaBH_4$, TFA, 0 °C to room temp.

Scheme 3

hindered face of the amide carbonyl group, affording the 1,10b-*cis* thiazoloisoquinolines with complete regio- and stereoselectivity.

Table 1. Parham cyclization−reduction sequence

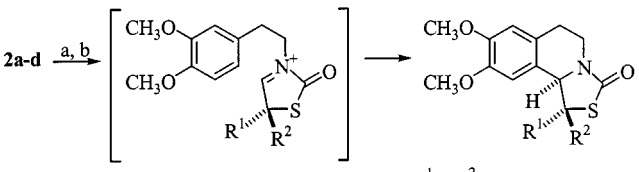
Entry	Substrate	Product	Yield [%]	*dr*
1	**3a**	**7a**	80[a]	–
2	**3b**	**7b**	46[a]	>95:<5
3	**3c**	**7c**	49[a]	>95:<5
4	**3d**	**7d**	14[a]	>95:<5
5	**3a**	**8**	98[b]	>95:<5
6	**3b**	**9b**	66[b]	>95:<5
7	**3c**	**9c**	71[b]	>95:<5
8	**3d**	**9d**	64[b]	88:12

[a] Yield of pure isolated products. – [b] Overall yield of the two steps.

To make the corresponding 1,10b-*trans* thiazoloisoquinolines accessible, we carried out the reduction of the 10b-hydroxyl group with $NaBH_4$-TFA, a reagent that has proven to be synthetically valuable for this purpose.[13] Thus, treatment of **7b−d** with $NaBH_4$-TFA afforded the corresponding thiazoloisoquinolines **9b−d** in almost quantitative yield, with inversion of configuration at C-10b. Only in the case of the 1,1-disubstituted substrate **3d** was a minor quantity of the 1,10b-*cis* diastereomer detected (Table 1, entry 8). However, in the reduction of **7a** with $NaBH_4$−TFA, the 1,10b-dibenzyl thiazoloisoquinoline **8** was the only product isolated. Because of the instability of the hetero-fused isoquinolines **7a−d**, Parham cyclizations and subsequent reduction reactions were carried out without purification of the intermediate 10b-hydroxythiazoloisoquinolines. High overall yields of 1,10b-*trans* thiazoloisoquinolines **8** and **9b−d** were therefore obtained (Table 1, entries 6−8).

It has been suggested that, in most cases, this type of reduction proceeds through the formation of an intermediate cation resulting from loss of a hydroxy group.[13] In our case, the intermediate would be a very stable bicyclic *N*-acyliminium ion, favouring the course of the reaction. The high stereoselectivity may be explained as a result of 1,2-induction, where hydride attacks in an *anti* relationship with respect to the bulkiest group in C-1. The intermediacy of an *N*-acyliminium ion would explain the rearrangement observed in the reduction of **7a**. The formation of the product **8** could be explained by a 1,2-benzyl migration in the intermediate *N*-acyliminium ion prior to hydride attack, which would be not fast enough due to the steric hindrance of the benzyl groups. Similar migrations have been reported in related reductions and in other reactions via *N*-acyliminium ion intermediates.[14]

Our next concern was the stereoselectivity of the cyclization of thiazolidinediones **2a−d** via *N*-acyliminium ions. Since it is known that intramolecular reactions of cyclic *N*-acyliminium ions with π-nucleophiles proceed with high stereoselectivity,[4] we expected a reversal of the diastereoselectivity on application of the reduction−*N*-acyliminium ion cyclization sequence to 1-substituted thiazolidinediones **2**. Thus, selective reduction of the amide carbonyl was carried out with $NaBH_4$ to afford the 4-hydroxythiazolidinones, which were not isolated. Subsequent treatment with $BF_3{\cdot}Et_2O$ yielded 1,10b-*cis* thiazoloisoquinolines **10a−d** in excellent yields (Scheme 4). As expected, attack of the aromatic ring occurred from the less hindered side of the intermediate *N*-acyliminium ion, affording the 1,10b-*cis* diastereomers with complete diastereoselectivity. No benzyl migration was observed in the reaction of 5,5-dibenzyl thiazolidinedione **2a**, which afforded **10a** in almost quantitative yield.



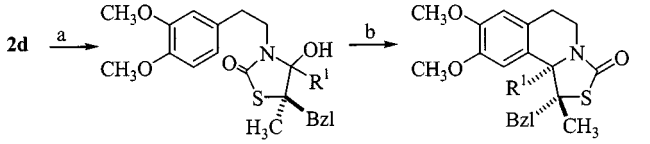
10a $R^1 = R^2$ = Bzl (98%)
b $R^1 = CH_3$, R^2 = H (89%)
c R^1 = Bzl, R^2 = H (71%)
d R^1 = Bzl, $R^2 = CH_3$ (92%)

Reagents: (a) $NaBH_4$, CH_2Cl_2/MeOH, –40 °C to –20 °C; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to room temp.

Scheme 4

As an extension of this methodology, we decided to study the stereochemistry of the organolithium addition−*N*-acyliminium ion cyclization sequence on thiazolidinediones. With this approach, we might have been able to access 10b-substituted thiazoloisoquinolines with a relative 1,10b-*cis* stereochemistry, with the possibility of varying the substituent at C-10b just by changing the organolithium used in the addition step. In this case, however, only 5,5-disubstituted thiazolidine-2,4-diones proved to be suitable substrates. When monosubstituted thiazolidinediones **2b** and **2c** were treated with organolithiums, H-5 deprotonation was faster than addition to carbonyl. Thus, thiazolidinedione **2d** was treated with *n*BuLi or MeLi to afford the corresponding hydroxy lactams **11a** and **11b** in high yields, as a single diastereomer in both cases (Scheme 5). These hydroxy lactams were highly unstable and were immediately submitted to cyclization. Thus, upon treatment with TFA, an intermediate tertiary *N*-acyliminium ion was formed, which was attacked from the direction opposite to the benzyl group to afford the 1,10b-*cis* thiazoloisoquinolines **12a** and **12b**. Cyclization was completely stereoselective for **12a**, but stereoselectivity was lost in the case of the 10b-methyl-substituted thiazoloisoquinoline **12b**.

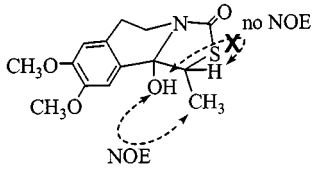
The relative stereochemistry of 1,10b-*cis* and *trans* thiazoloisoquinolines was confirmed by nuclear Overhauser effect difference spectroscopy and ^1H-^1H decoupling experiments. Selected examples are represented in Figure 1. For instance, 10b-hydroxythiazoloisquinoline **7b** demonstrated signal enhancement of the C-1 methyl hydrogens upon irradiation of the C-10b hydroxyl hydrogen and vice versa. This fact, together with the absence of NOEs between OH and H-1, confirms the *cis* disposition for these substituents. In the case of the diastereomers **9c** and **10c**, a NOE enhance-



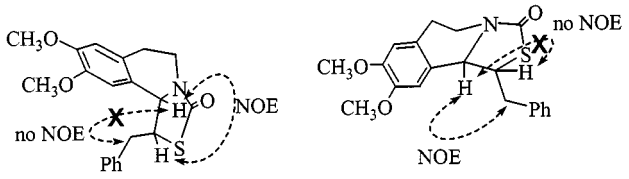
Reagents: (a) R^1Li, –78 °C, 6 h; (b) TFA, CH_2Cl_2, reflux

Scheme 5

ment of the H-1 signal was observed in **9c** upon irradiation of H-10b (and vice versa), whereas in **10c**, a NOE enhancement of the signal corresponding to the benzylic protons on C-1 was observed instead. The rest of the NOE experiments carried out on all the thiazoloisoquinolines prepared were fully consistent with the proposed stereochemistry in each case.



7b (*1RS, 10bSR*)

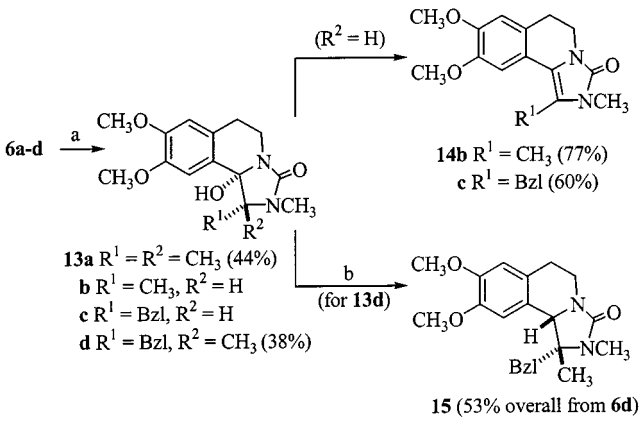


9c (*1RS, 10bSR*) **10c** (*1RS, 10bRS*)

Figure 1. Selected NOE enhancements

Synthesis of Imidazo[4,3-*a*]isoquinolones

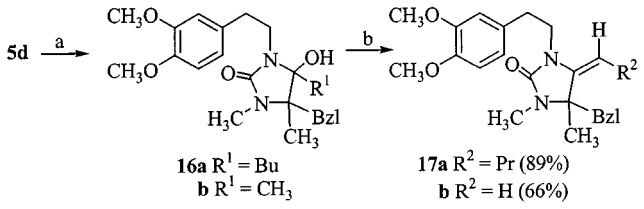
To extend the synthetic utility of the Parham and *N*-acyliminium ion cyclizations further, we turned our attention to the synthesis of another type of hetero-fused isoquinolines, the imidazo[4,3-*a*]isoquinolones. We first investigated the Parham cyclization of hydantoins **6a–d** (Scheme 6). As previously, the regioselectivity of the cyclization was checked with 5,5-dimethylhydantoin **6a**, treatment of which under metallation-cyclization conditions (*t*BuLi, −78 °C, THF) regioselectively afforded 10b-hydroxy imidazoisoquinoline **13a** in moderate yield. Under similar conditions, hydantoins **6b–c** underwent lithiation-cyclization, but the resulting 10b-hydroxy derivatives readily dehydrated during workup, and only imidazoisoquinolines **14b** and **14c** were isolated in good yields. However, hydantoin **6d** produced the desired 1,10b-*cis* 10b-hydroxy imidazoisoquinoline **13d** with complete regio- and stereoselectivity, confirming that the attack of the intermediate aryllithium onto the carbonyl group also occurred from the less hindered side in this case. Reduction of the 10b-hydroxyl group with $NaBH_4$–TFA afforded the corresponding 1,10b-*trans* imidazoisoquinoline **15** in almost quantitative yield. As with thiazolidines, reduction proceeded with inversion of configuration at C-10b. The isolated yield of **13d** was rather low (38%), due to partial decomposition upon purification. However, if the Parham cyclization–reduction sequence was carried out without purification of **13d**, **15** was obtained in an overall yield of 53%. The relative stereochemistry was assigned by NOE difference spectroscopy, in a manner similar to that described above for thiazoloisoquinolines.



Reagents: (a) *t*-BuLi, –78 °C; b) $NaBH_4$, TFA, 0 °C to room temp.

Scheme 6

We next turned our attention to the cyclization of hydantoins **5a–d** via *N*-acyliminium ions. Firstly, we studied the organolithium addition–*N*-acyliminium cyclization sequence on disubstituted **5d**. Thus, treatment of **5d** with MeLi or BuLi afforded the corresponding hydroxylactams **16a** and **16b** (Scheme 7). However, these lactams dehydrated upon purification on silica gel, and were characterised as the enamides **17a** and **17b**. Attempts to perform the cyclization of hydroxylactams **16** without purification were unsuccessful. Under various cyclization conditions, **16a** and **16b** only dehydrated to enamides **17**. This problem probably arose because the *N*-acyliminium ions were not trapped fast enough by the π-nucleophile and, since this side reaction is not reversible in acidic media, it precludes cyclization. In view of these results we did not undertake the sequential reduction–cyclization with hydantoins **5b** and **5c**. Nevertheless, we attempted the reduction–cyclization sequence using **5d**, as there is no possibility of a competitive dehydration reaction in this case. However, when **5d** was treated with $LiAlH_4$[17] followed by $BF_3{\cdot}Et_2O$, only a complex mixture of products was obtained. Thus, it was not possible to produce imidazoisoquinolines through *N*-acyliminium cyclization. It had in fact been previously reported that the synthesis of imidazoisoquinolines by means of *N*-acyliminium ion cyclizations requires that the nitrogen atom at C-2 should be unsubstituted.[15] Thus, the Parham cyclization–reduction sequence circumvents this problem and permits the synthesis of these hetero-fused isoquinoline systems.

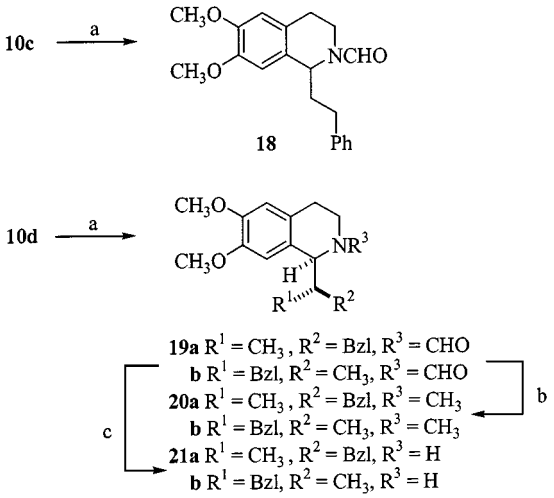


Reagents: (a) RLi, –78 °C, 6 h; (b) SiO_2 or TFA

Scheme 7

Desulfurization of Thiazolo[4,3-*a*]isoquinolinones − Access to 1-Phenethylisoquinolines

Cyclic thio *N*-acyliminium ions can be regarded as masked iminium variants, since the sulfur atom can be removed, allowing several heterocyclic systems to be produced.[16] As a consequence, the stereoselective synthesis of 1-benzyl-substituted thiazolo[4,3-*a*]isoquinolinones has the potential to provide valuable intermediates for the synthesis of biologically active compounds such as the 1-phenethylisoquinoline alkaloids, which are precursors of other alkaloids, such as homoaporphines, homoprotoberberines, homoerythrines, and colchicine.[17] To test this approach, and expand the synthetic utility of this methodology, we decided to attempt the desulfurization of selected thiazolo[4,3-*a*]isoquinolinones.[16] Reductive desulfurization of thiazoloisoquinolines **10c** and **10d** was observed upon treatment with Raney nickel (Scheme 8). Thus, **10c** provided 2-formyl-1-phenethyltetrahydroisoquinoline **18**, which was obtained as a mixture of *cis* and *trans* rotamers in a 1:1 ratio (determined by NMR) in good yield. When the method was applied to **10d**, although desulfurization proceeded well, the formation of two chromatographically inseparable diastereomeric phenethylisoquinolines **19a** and **19b** (in a 1.2:1 ratio) was observed. Since NMR spectra of



Reagents: (a) Raney Ni, EtOH, reflux; (b) $LiAlH_4$, THF, reflux; (c) NaOH, EtOH, reflux

Scheme 8

the phenethylisoquinoline mixture **19a−b** were very complex, due to the presence of the rotamers of both isomers, it was transformed into the corresponding amines **20a−b** or **21a−b**, by LAH reduction or hydrolysis, respectively. Although most of the signals for both diastereomers overlapped in the ^1H NMR spectra of the amines, the doublets of the methyl groups of the phenethyl substituent at C-1 permitted characterisation of the diastereomers and determination of their ratio (see Experimental Section).

Conclusion

In summary, we have achieved a stereodivergent synthesis of 1,10b-*cis*- and -*trans*-thiazolo[4,3-*a*]isoquinolinones, starting from *N*-3,4-dimethoxyphenethylthiazolidinedione and using *N*-acyliminium ion or Parham cyclizations. Particularly noteworthy is the Parham cyclization directly followed by the hydroxyl reduction, to produce the desired 1,10b-*trans* diastereomer. On the other hand, hydride reduction or organolithium addition followed by *N*-acyliminium cyclization stereoselectively affords the 1,10b-*cis* thiazoloisoquinolines. Although it was not possible to provide access to imidazo[4,3-*a*]isoquinolinones by means of *N*-acyliminium cyclizations, due to competitive enamide formation, the Parham cyclization−reduction sequence constitutes an efficient alternative that allows the 1,10b-*trans* derivatives to be synthesised with complete control over the stereochemistry. Furthermore, the utility of thiazolo[4,3-*a*]isoquinolinones as precursors of 1-phenethylisoquinolines has also been demonstrated.

Experimental Section

General Remarks:[18] Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or neat (oils). − NMR spectra were recorded at 20−25 °C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solutions. Assignment of individual ^{13}C resonances is supported by DEPT experiments. − Mass spectra were recorded under electron impact conditions at 70 eV. − TLC was carried out with 0.2 mm thick silica gel plates (Merck Kieselgel GF_{254}). Viewing was accomplished by means of UV light or by spraying with 10% phosphomolybdic acid in EtOH.[19] − Flash column chromatography[20] on silica gel was performed with Merck Kieselgel 60 (230−400 mesh). HPLC was performed using a LiChrosorb Si60 (7μm) column with a refraction index detector. − All solvents used in reactions were anhydrous and purified according to standard procedures.[21] Organolithium reagents were titrated periodically with diphenylacetic acid prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

Parham Cyclizations. − General Procedure: *t*BuLi was added at −78 °C to a solution of the iodinated imide **3** or **6** (1 mmol) in dry THF (20 mL), and the resulting solution was stirred at this temperature for 4−24 h. The reaction was quenched by the addition of saturated NH_4Cl (5 mL), and allowed to warm to 20 °C. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concen-

trated in vacuo to afford thiazoloisoquinolines **7** or imidazoisoquinolines **13/14**.

1,1-Dibenzyl-10b-hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (7a): Following the general procedure for Parham cyclizations, thiazolidinone **3a** (140 mg, 0.2 mmol) was treated with *t*BuLi (0.33 mL of a 1.2 M solution, 0.4 mmol) at −78 °C over 4 h. After workup, the residue was purified by column chromatography (silica gel, 60% hexane/AcOEt) to afford **7a** as a colourless oil (75 mg, 80%). − IR (neat): $\tilde{\nu}$ = 3490, 1676 cm^{-1}. − ^1H NMR ($CDCl_3$): 1.00 (s, 1 H), 2.39−2.55 (m, 2 H), 2.78 (d, *J* = 13.5 Hz, 1 H), 2.97−3.08 (m, 1 H), 3.28 (s, 2 H), 3.51 (d, *J* = 13.5 Hz, 1 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 4.13−4.20 (m, 1 H), 6.37 (s, 1 H), 6.70 (s, 1 H), 7.01−7.40 (m, 10 H). − ^{13}C NMR ($CDCl_3$): 27.7, 36.7, 44.5, 46.0, 55.7, 56.0, 65.3, 90.7, 108.3, 110.2, 123.8, 126.9, 127.7, 128.3, 129.3, 130.7, 131.3, 135.7, 136.7, 147.9, 148.9, 171.6. − MS (EI): *m*/*z* (%) = 461 [M^+] (4), 444 (13), 428 (19), 370 (13), 338 (69), 336 (58), 221 (23), 208 (62), 192 (28), 178 (31), 165 (16), 150 (17), 131 (68), 105 (16), 91 (100), 77 (22).

(1*RS*,10b*SR*)-10b-Hydroxy-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (7b): Following the general procedure for Parham cyclizations, thiazolidinone **3b** (140 mg, 0.3 mmol) was treated with *t*BuLi (0.37 mL of a 1.2 M solution, 0.4 mmol) at −78 °C over 5 h. After workup, the residue was purified by column chromatography (silica gel, 50% hexane/AcOEt) to afford **7b** as a colourless oil (45 mg, 46%). − IR (neat): $\tilde{\nu}$ = 3384, 1651 cm^{-1}. − ^1H NMR ($CDCl_3$): 1.73 (d, *J* = 6.7 Hz, 3 H), 2.65−2.71 (m, 1 H), 2.86−2.93 (m, 1 H), 3.15 (td, *J* = 12.3, 3.2 Hz, 1 H), 3.39 (s, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.86−3.94 (m, 1 H), 4.30 (dd, *J* = 12.3, 4.7 Hz, 1 H), 6.65 (s, 1 H), 7.02 (s, 1 H). − ^{13}C NMR ($CDCl_3$): 13.5, 29.6, 37.5, 50.5, 55.8, 55.9, 87.6, 109.0, 111.2, 127.3, 128.1, 147.7, 149.1, 169.4. − MS (EI): *m*/*z* (%) = 295 [M^+] (1), 278 (19), 277 (100), 262 (9), 218 (12), 174 (17), 77 (6), 59 (8).

(1*RS*,10b*SR*)-1-Benzyl-10b-hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (7c): Following the general procedure for Parham cyclizations, thiazolidinone **3c** (160 mg, 0.3 mmol) was treated with *t*BuLi (0.33 mL of a 1.2 M solution, 0.4 mmol) at −78 °C over 6 h. After workup, the residue was purified by column chromatography (silica gel, 40% hexane/AcOEt) to afford **7c** as a colourless oil (58 mg, 49%). − IR (neat): $\tilde{\nu}$ = 3490, 1676 cm^{-1}. − ^1H NMR ($CDCl_3$): 2.67−2.73 (m, 1 H), 2.82−2.95 (m, 1 H), 3.16 (td, *J* = 12.3, 3.6 Hz, 1 H), 3.30 (s, 1 H), 3.24−3.34 (m, 1 H), 3.79 (dd, *J* = 13.9, 3.6 Hz, 1 H), 3.90 (s, 6 H), 4.12−4.17 (dd, *J* = 11.9, 3.6 Hz, 1 H), 4.29−4.36 (m, 1 H), 6.70 (s, 1 H), 6.82 (s, 1 H), 7.14−7.31 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 29.8, 35.2, 37.6, 56.1, 58.7, 87.7, 109.1, 111.4, 127.3, 127.6, 128.6, 128.8, 137.6, 148.0, 149.4, 168.7. − MS (EI): *m*/*z* (%) = 371 [M^+] (6), 353 (100), 292 (20), 276 (22), 207 (56), 178 (17), 105 (11), 91 (39).

(1*RS*,10b*SR*)-1-Benzyl-10b-hydroxy-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (7d): Following the general procedure for Parham cyclizations, thiazolidinone **3d** (130 mg, 0.2 mmol) was treated with *t*BuLi (0.25 mL of a 1.2 M solution, 0.3 mmol) at −78 °C over 6 h. After workup, the residue was purified by column chromatography (silica gel, 50% hexane/AcOEt) to afford **7d** as a colourless oil (13 mg, 14%). − ^1H NMR ($CDCl_3$): 1.70 (s, 3 H), 2.57 (dd, *J* = 16.2, 3.2 Hz, 1 H), 2.77 (d, *J* = 13.5 Hz, 1 H), 2.74−2.89 (m, 1 H), 3.08 (td, *J* = 12.7, 3.4 Hz, 1 H), 3.50 (d, *J* = 13.5 Hz, 1 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.91 (s, 1 H), 4.22 (dd, *J* = 12.7, 4.8 Hz, 1 H), 6.47 (s, 1 H), 6.72 (s, 1 H), 7.29−7.44 (m, 5 H). This product was highly unstable, and was only characterised by ^1H NMR before it was submitted to reduction.

10b-Hydroxy-8,9-dimethoxy-1,1,2-trimethyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-imidazo[4,3-*a*]isoquinolin-3-one (13a): Following the general procedure for Parham cyclizations, hydantoin **6a** (170 mg, 0.4 mmol) was treated with *t*BuLi (0.66 mL of a 1.2 M solution, 0.8 mmol) at −78 °C over 4 h. After workup, the residue was purified by column chromatography (silica gel, AcOEt) to afford **13a** as a colourless oil (54 mg, 44%). − IR (neat): $\tilde{\nu}$ = 3300, 1685 cm^{-1}. − ^1H NMR ($CDCl_3$): 0.70 (s, 3 H), 1.58 (s, 3 H), 2.63−2.69 (m, 1 H), 2.74 (s, 3 H), 2.74−2.81 (m, 1 H), 3.17 (td, *J* = 12.5, 3.7 Hz, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.92−4.12 (m, 1 H), 6.61 (s, 1 H), 6.95 (s, 1 H). − ^{13}C NMR ($CDCl_3$): 19.9, 21.1, 24.4, 29.6, 34.4, 55.7, 55.9, 65.3, 86.4, 108.9, 111.4, 126.3, 127.9, 148.9, 150.8, 157.2. − MS (EI): *m*/*z* (%) = 306 [M^+ + 1] (1), 289 (2), 256 (100), 257 (19), 91 (67).

8,9-Dimethoxy-1,2-dimethyl-5,6-dihydro-3*H*-[1,3]-imidazo[4,3-*a*]-isoquinolin-3-one (14b): Following the general procedure for Parham cyclizations, hydantoin **6b** (220 mg, 0.5 mmol) was treated with *t*BuLi (0.62 mL of a 1.3 M solution, 0.8 mmol) at −78 °C over 24 h. After workup, the residue was purified by column chromatography (silica gel, 95% AcOEt/MeOH) to afford **14b** as a colourless oil (109 mg, 77%). − IR (neat): $\tilde{\nu}$ = 1682 cm^{-1}. − ^1H NMR ($CDCl_3$): 2.34 (s, 3 H), 2.85 (t, *J* = 6.1 Hz, 2 H), 3.25 (s, 3 H), 3.77 (t, *J* = 6.1 Hz, 2 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 6.70 (s, 1 H), 6.92 (s, 1 H). − ^{13}C NMR ($CDCl_3$): 10.1, 27.1, 29.2, 37.3, 55.9, 56.0, 106.9, 111.7, 113.2, 114.6, 119.9, 125.1, 147.3, 147.8, 151.6. − MS (EI): *m*/*z* (%) = 275 [M^+ + 1] (17), 274 [M^+] (100), 259 (40), 230 (39), 231 (16), 216 (28), 137 (16). − $C_{15}H_{18}N_2O_3$ (274.3): calcd. C 65.68, H 6.61, N 10.21; found C 65.24, H 6.80, N 9.83.

1-Benzyl-8,9-dimethoxy-2-methyl-5,6-dihydro-3*H*-[1,3]-imidazo[4,3-*a*]-isoquinolin-3-one (14c): Following the general procedure for Parham cyclizations, hydantoin **6c** (130 mg, 0.2 mmol) was treated with *t*BuLi (0.23 mL of a 1.3 M solution, 0.3 mmol) at −78 °C over 6 h. After workup, the residue was purified by column chromatography (silica gel, 95% AcOEt/MeOH) to afford **14c** as a white solid (53 mg, 60%): m.p. 108−109 °C (Et_2O). − IR (KBr): $\tilde{\nu}$ = 1684 cm^{-1}. − ^1H NMR ($CDCl_3$): 2.93 (t, *J* = 6.2 Hz, 2 H), 3.18 (s, 3 H), 3.56 (s, 3 H), 3.87 (t, *J* = 6.2 Hz, 2 H), 3.87 (s, 3 H), 4.13 (s, 2 H), 6.73 (s, 2 H), 7.21−7.36 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 27.2, 29.2, 30.0, 37.5, 55.7, 56.0, 106.6, 111.7, 115.2, 116.5, 119.4, 125.1, 126.9, 127.5, 129.0, 137.3, 147.6, 147.9, 151.7. − MS (EI): *m*/*z* (%) = 351 [M^+ + 1] (24), 350 [M^+] (100), 275 (71), 190 (22), 91 (37). − $C_{21}H_{22}N_2O_3$ (350.4): calcd. C 71.98, H 6.33, N 7.99; found C 71.56, H 6.29, N 7.75.

(1*RS*,10b*SR*)-1-Benzyl-10b-hydroxy-8,9-dimethoxy-1,2-dimethyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-imidazo[4,3-*a*]isoquinolin-3-one (13d): Following the general procedure for Parham cyclizations, hydantoin **6d** (140 mg, 0.3 mmol) was treated with *t*BuLi (0.50 mL of a 1.2 M solution, 0.6 mmol) at −78 °C over 6 h, allowed to warm up to −50 °C, and further stirred for 18 h. After workup, the residue was purified by column chromatography (silica gel, AcOEt) to afford **13d** as a colourless oil (40 mg, 38%). − IR (neat): $\tilde{\nu}$ = 3220, 1695 cm^{-1}. − ^1H NMR ($CDCl_3$): 1.69 (s, 3 H), 1.84−1.98 (m, 1 H), 2.32−2.38 (m, 2 H), 2.49 (d, *J* = 14.3 Hz, 1 H), 2.65 (s, 3 H), 3.02−3.12 (m, 1 H), 3.74−3.84 (m, 1 H), 3.88 (s, 3 H), 3.92 (s, 3 H), 4.13 (s, 1 H), 6.49 (s, 1 H), 6.56 (d, *J* = 7.1 Hz, 2 H), 6.98 (s, 1 H), 7.02−7.11 (m, 3 H). − ^{13}C NMR ($CDCl_3$): 19.3, 25.9, 28.8, 34.5, 42.2, 55.9, 56.0, 86.4, 109.2, 111.1, 126.3, 126.4, 127.6, 129.1, 130.2, 136.0, 147.8, 149.0, 156.7. − MS (EI): *m*/*z* (%) = 383 [M^+ + 1] (1), 365 (7), 291 (49), 275 (89), 274 (40), 273 (69), 272 (88), 189 (48), 91 (76), 56 (100).

Hydroxyl Reduction Reactions. − General Procedure: A solution of **7** or **13** (obtained from **3** or **6**, without purification) (1 mmol) in dry CH_2Cl_2 (25 mL) was added to the reducing mixture, prepared by portionwise addition of $NaBH_4$ (175 mg, 4.5 mmol) to TFA (1.03 mL, 13.5 mmol) at 0 °C. The reaction mixture was allowed to reach 20 °C and stirred for 3 h. The reaction was quenched by addition of aqueous 1 M NaOH (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford thiazoloisoquinolines **8**, **9**, or imidazoisoquinoline **15**.

(1*RS*,10b*SR*)-1,10b-Dibenzyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (8): Following the general procedure for reduction reactions, **7a** (obtained from **3a**, without purification; 433 mg, 0.9 mmol) was treated with a reducing mixture prepared from $NaBH_4$ (110 mg, 3.65 mmol) and TFA (1.00 mL, 11.0 mmol) at 0 °C. After workup, purification by flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **8** as a white solid (410 mg, 98%): m.p. 106−108 °C (AcOEt). − IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}. − ^1H NMR ($CDCl_3$): 2.46−2.54 (m, 1 H), 2.60−2.79 (m, 2 H), 2.88 (d, *J* = 13.1 Hz, 1 H), 3.23−3.40 (m, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.26−4.39 (m, 2 H), 6.34 (s, 1 H), 6.74 (s, 1 H), 7.19−7.32 (m, 10 H). − ^{13}C NMR ($CDCl_3$): 27.3, 39.2, 45.0, 45.5, 55.6, 55.8, 56.5, 63.9, 107.6, 111.0, 124.5, 126.5, 126.7, 126.9, 127.5, 127.7, 130.3, 130.4, 136.0, 147.8, 147.9, 172.3. − MS (EI): *m*/*z* (%) = 445 [M^+] (3), 412 (4), 355 (26), 354 (100), 353 (57), 276 (17), 192 (44), 176 (10), 135 (20), 91 (39). − $C_{27}H_{27}NO_3S$ (445.6): calcd. C 72.78, H 6.11, N 3.14; found C 72.37, H 5.96, N 2.88.

(1*RS*,10b*SR*)-8,9-Dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (9b): Following the general procedure for reduction reactions, **7b** (obtained from **3b**, without purification; 51 mg, 0.2 mmol) was treated with a reducing mixture prepared from $NaBH_4$ (66 mg, 1.7 mmol) and TFA (0.20 mL, 5.2 mmol) at 0 °C. After workup, purification by flash column chromatography (silica gel, 80% hexane/AcOEt) afforded **9b** as a white solid (32 mg, 66%): m.p. 120−122 °C (pentane/Et_2O). − IR (KBr): $\tilde{\nu}$ = 1674 cm^{-1}. − ^1H NMR ($CDCl_3$): 0.99 (d, *J* = 6.7 Hz, 3 H), 2.67−2.73 (m, 1 H), 2.80−3.03 (m, 2 H), 3.79−3.90 (m, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.32−4.39 (m, 1 H), 5.04 (d, *J* = 5.5 Hz, 1 H), 6.53 (s, 1 H), 6.65 (s, 1 H). − ^{13}C NMR ($CDCl_3$): 17.4, 29.0, 39.7, 43.2, 55.8, 56.1, 62.0, 108.4, 111.5, 123.9, 127.4, 148.1, 148.3, 170.3. − MS (EI): *m*/*z* (%) = 279 [M^+] (38), 192 (15), 191 (100), 176 (37), 91 (9). − $C_{14}H_{17}NO_3S$ (279.4): calcd. C 60.19, H 6.13, N 5.01; found C 59.77, H 6.04, N 4.83.

(1*RS*,10b*SR*)-1-Benzyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (9c): Following the general procedure for reduction reactions, **7c** (obtained from **3c**, without purification; 65 mg, 0.2 mmol) was treated at 0 °C with a reducing mixture prepared from $NaBH_4$ (35 mg, 0.9 mmol) and TFA (0.20 mL, 2.7 mmol). After workup, purification by flash column chromatography (silica gel, 50% hexane/AcOEt) afforded **9c** as a white solid (44 mg, 71%): m.p. 192−193 °C (pentane). − IR (KBr): 1670 cm^{-1}. − ^1H NMR ($CDCl_3$): 2.39 (dd, *J* = 13.9, 11.1 Hz, 1 H), 2.69 (dd, *J* = 13.9, 3.6 Hz, 1 H), 2.81−3.06 (m, 3 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 3.91−4.00 (m, 1 H), 4.32−4.46 (m, 1 H), 5.15 (d, *J* = 5.5 Hz, 1 H), 6.61 (s, 1 H), 6.69 (s, 1 H), 7.00−7.05 (m, 2 H), 7.14−7.33 (m, 3 H). − ^{13}C NMR ($CDCl_3$): 29.2, 36.6, 39.8, 51.4, 55.9, 56.1, 62.0 108.2, 111.6, 123.8, 126.6, 127.5, 128.3, 129.2, 138.2, 148.3, 148.4, 170.4. − MS (EI): *m*/*z* (%) = 355 [M^+] (20), 263 (100), 191 (97), 91 (44). − $C_{20}H_{21}NO_3S$ (355.5): calcd. C 67.58, H 5.95, N 3.94; found C 67.32, H 5.65, N 3.72.

(1*RS*,10b*SR*)-1-Benzyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (9d): Following the general procedure for reduction reactions, **7d** (obtained from **3d**, without purification; 212 mg, 0.55 mmol) was treated at 0 °C with a reducing mixture prepared from $NaBH_4$ (75 mg, 2.5 mmol) and TFA (0.70 mL, 7.5 mmol). After workup, purification by flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **9d** as a 88.5:11.5 mixture of diastereomers. Data for the major diastereomer are given (130 mg, 64%). − IR ($CHCl_3$): $\tilde{\nu}$ = 1684 cm^{-1}. − ^1H NMR ($CDCl_3$): 1.62 (s, 3 H), 2.35−2.63 (m, 1 H), 2.64−2.86 (m, 2 H), 3.05 (d, *J* = 12.3 Hz, 1 H), 3.07 (d, *J* = 12.3 Hz, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 4.35−4.48 (m, 1 H), 5.78 (s, 1 H), 6.47 (s, 1 H), 6.53 (s, 1 H), 7.09−7.32 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 26.5, 27.6, 40.0, 45.5, 55.8, 56.2, 58.1, 58.4, 108.0, 111.2, 125.1, 126.7, 127.7, 130.3, 136.2, 147.9, 148.2, 174.1. − MS (EI): *m*/*z* (%) = 369 [M^+] (2), 278 (100), 192 (52), 176 (22), 91 (54), 59 (50). − $C_{21}H_{23}NO_3S$ (369.5): calcd. C 68.27, H 6.27, H 3.79; found C 67.89, H 6.01, N 3.46.

(1*RS*,10b*SR*)-1-Benzyl-8,9-dimethoxy-1,2-dimethyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-imidazo[4,3-*a*]isoquinolin-3-one (15): Following the general procedure for reduction reactions, **13d** (obtained from **6d**, without purification; 332 mg, 0.9 mmol) was treated with a reducing mixture prepared from $NaBH_4$ (157 mg, 4.1 mmol) and TFA (0.90 mL, 11.7 mmol) at 0 °C. After workup, purification by flash column chromatography (silica gel, 90% hexane/AcOEt) afforded **15** (157 mg, 53%) as a white solid: m.p. 122−124 °C (Et_2O/pentane). − IR (KBr): $\tilde{\nu}$ = 1685 cm^{-1}. − ^1H NMR ($CDCl_3$): 1.67 (s, 3 H), 1.84−2.03 (m, 1 H), 2.28−2.34 (m, 1 H), 2.44 (d, *J* = 14.3 Hz, 1 H), 2.57 (d, *J* = 14.3 Hz, 1 H), 2.73 (s, 3 H), 2.72−2.80 (m, 1 H), 3.87 (s, 6 H), 3.87−3.96 (m, 1 H), 4.56 (s, 1 H), 6.49 (s, 1 H), 6.54 (d, *J* = 7.5 Hz, 2 H), 6.70 (s, 1 H), 7.03−7.26 (m, 3 H). − ^{13}C NMR ($CDCl_3$): 25.6, 26.2, 28.8, 36.8, 39.3, 55.8, 56.0, 63.3, 63.5, 108.8, 111.8, 123.5, 126.1, 127.5, 129.2, 130.1, 136.0, 147.4, 148.1, 157.7. − MS (EI): *m*/*z* (%) = 276 (22), 275 (100), 260 (20), 245 (6), 244 (4), 216 (3), 191 (4), 176 (3), 130 (4), 91 (8). − $C_{22}H_{26}N_2O_3$ (366.5): calcd. C 72.11, H 7.15, N 7.64; found C 71.75, H 7.23, N 7.39.

Reduction−*N*-Acyliminium Cyclization Reactions. − General Procedure: $NaBH_4$ (74 mg, 2 mmol) was added at −40 °C to a solution of imide **2** (1 mmol) in a mixture of MeOH (5 mL) and CH_2Cl_2 (10 mL). The reaction mixture was warmed to −20 °C, and stirred at this temperature for 5 h. The reaction was quenched by addition of H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford the corresponding hydroxy derivative, which, without further purification, was dissolved in dry CH_2Cl_2 (30 mL). $BF_3{\cdot}Et_2O$ (1.46 mL, 11.5 mmol) was added at 0 °C; the reaction mixture was allowed to warm to room temp., and stirred for 3 days. After addition of aqueous saturated $NaHCO_3$ (10 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford thiazoloisoquinolines **10**.

1,1-Dibenzyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (10a): Following the general procedure described for the reduction−*N*-acyliminium cyclization reactions, imide **2a** (70 mg, 0.15 mmol) was treated with $NaBH_4$ (11 mg, 0.3 mmol). After workup, the corresponding hydroxy derivative was treated with $BF_3{\cdot}Et_2O$ (0.22 mL, 1.7 mmol). Standard workup, followed by flash column chromatography (silica gel, 60% hexane/AcOEt), afforded **10a** as a white solid (66 mg, 98%): m.p. 149−151 °C (pentane). − IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}. − ^1H NMR ($CDCl_3$): 2.57−2.66 (m, 3 H), 2.72−2.80 (m, 1 H), 2.86 (d, *J* =

13.9 Hz, 1 H), 3.20 (d, J = 15.5 Hz, 1 H), 3.35 (d, J = 15.5 Hz, 1 H), 3.92 (s, 3 H), 4.03 (s, 3 H), 4.27−4.32 (m, 1 H), 5.10 (s, 1 H), 6.66 (s, 1 H), 7.11−7.42 (m, 11 H). − ^{13}C NMR ($CDCl_3$): 29.5, 39.8, 42.4, 42.8, 55.9, 56.3, 62.9, 63.2, 109.4, 112.1, 123.8, 126.8, 127.3, 127.6, 128.4, 129.3, 131.2, 131.4, 135.6, 135.9, 147.7, 148.2, 168.6. − MS (EI): m/z (%) = 445 [M^+] (2), 353 (83), 276 (10), 263 (7), 191 (100), 176 (24), 135 (8), 91 (63). − $C_{27}H_{27}NO_3S$ (445.6): calcd. C 72.78, H 6.11, N 3.14; found C 72.38, H 6.04, N 3.08.

(*1RS*,10b*RS*)-8,9-Dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (10b): Following the general procedure described for the reduction−*N*-acyliminium cyclization reactions, imide **2b** (180 mg, 0.6 mmol) was treated with $NaBH_4$ (47 mg, 1.2 mmol). After workup, the corresponding hydroxy derivative was treated with $BF_3{\cdot}Et_2O$ (0.91 mL, 7.2 mmol). Standard workup, followed by flash column chromatography (silica gel, 90% hexane/AcOEt), afforded **10b** as a white solid (154 mg, 89%): m.p. 108−110 °C (pentane-Et_2O). − IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 1.74 (d, J = 6.7 Hz, 3 H), 2.61−2.69 (m, 1 H), 2.88−3.10 (m, 2 H), 3.70−3.79 (m, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.23−4.35 (m, 1 H), 4.56 (d, J = 8.3 Hz, 1 H), 6.63 (s, 1 H), 6.70 (s, 1 H). − ^{13}C NMR ($CDCl_3$): 20.3, 28.6, 40.1, 45.2, 55.7, 55.9, 65.2, 107.8, 111.8, 126.2, 127.1, 147.6, 148.1, 169.8. − MS (EI): m/z (%) = 279 [M^+] (44), 278 (7), 264 (2), 191 (100), 176 (37), 164 (5), 133 (5), 117 (5), 91 (9). − $C_{14}H_{17}NO_3S$ (279.4): calcd. C 60.19, H 6.13, N 5.01; found C 59.90, H 6.01, N 4.95.

(*1RS*,10b*RS*)-1-Benzyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (10c): Following the general procedure described for the reduction−*N*-acyliminium cyclization reactions, imide **2c** (120 mg, 0.3 mmol) was treated with $NaBH_4$ (24 mg, 0.6 mmol). After workup, the corresponding hydroxy derivative was treated with $BF_3{\cdot}Et_2O$ (0.47 mL, 3.7 mmol). Standard workup, followed by flash column chromatography (silica gel, 60% hexane/AcOEt), afforded **10c** as a white solid (80 mg, 71%): m.p. 142−143 °C (pentane). − IR (KBr): $\tilde{\nu}$ = 1671 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 2.52−2.62 (m, 1 H), 2.95−3.16 (m, 2 H), 3.22 (dd, J = 13.6, 7.5 Hz, 1 H), 3.38 (dd, J = 13.6, 7.9 Hz, 1 H), 3.70 (s, 3 H), 3.83 (s, 3 H), 3.93−4.01 (m, 1 H), 4.24−4.40 (m, 1 H), 4.81 (d, J = 5.5 Hz, 1 H), 6.28 (s, 1 H), 6.57 (s, 1 H), 7.00−7.05 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 27.6, 40.6, 43.2, 50.6, 55.8, 55.9, 62.8, 107.2, 111.7, 126.8, 127.0, 127.2, 128.5, 128.9, 129.0, 137.7, 147.1, 147.2, 170.4. − MS (EI): m/z (%) = 355 [M^+] (4), 263 (100), 191 (46), 176 (23), 91 (39). − $C_{20}H_{21}NO_3S$ (355.5): calcd. C 67.58, H 5.95, H 3.94; found C 67.06, H 5.83, N 3.70.

(*1RS*,10b*RS*)-1-Benzyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (10d): Following the general procedure described for the reduction−*N*-acyliminium cyclization reactions, imide **2d** (214 mg, 0.5 mmol) was treated with $NaBH_4$ (104 mg, 2.8 mmol). After workup, the corresponding hydroxy derivative was treated with $BF_3{\cdot}Et_2O$ (0.86 mL, 6.7 mmol). Standard workup, followed by flash column chromatography (silica gel, 60% hexane/AcOEt), afforded **10d** as a colourless oil (187 mg, 92%). − IR ($CHCl_3$): $\tilde{\nu}$ = 1675 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 1.04 (s, 3 H), 2.63−2.70 (m, 1 H), 2.72−2.93 (m, 2 H), 3.30 (d, J = 12.7 Hz, 1 H), 3.38 (d, J = 12.7 Hz, 1 H), 3.87 (s, 6 H), 4.39−4.42 (m, 1 H), 4.98 (s, 1 H), 6.69 (s, 1 H), 6.79 (s, 1 H), 7.02−7.33 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 22.3, 29.8, 39.8, 45.7, 55.7, 55.9, 61.3, 67.9, 109.4, 111.9, 123.3, 127.2, 128.7, 130.0, 136.4, 147.5, 148.1, 169.2. − MS (EI): m/z (%) = 369 [M^+] (2), 277 (67), 191 (100), 176 (26), 133 (5), 117 (5), 91 (22). − $C_{21}H_{23}NO_3S$ (369.5): calcd. C 68.27, H 6.27, H 3.79; found C 67.92, H 5.91, N 3.56.

Addition of RLi to Imides. − General Procedure: RLi (2 mmol) was added at −78 °C to a solution of the imide **2d** or **5d** (1 mmol) in dry THF (20 mL). The resulting mixture was stirred at this temperature for 6 h, quenched by the addition of H_2O (5 mL), and allowed to warm to 20 °C. Et_2O (5 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford hydroxy lactams **11a** and **11b**, or **16a** and **16b** (isolated as the corresponding enamides **17a** and **17b**).

5-Benzyl-4-butyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-5-methylthiazolidin-2-one (11a): According to the general procedure for RLi addition, thiazolidine-2,4-dione **2d** (105 mg, 0.27 mmol) was treated with *n*BuLi (0.42 mL of a 1.3 M solution, 0.5 mmol) to afford hydroxy lactam **11a** as a single diastereomer, which was purified by flash column chromatography (silica gel, 60% hexane/AcOEt) (107 mg, 89%). − IR (neat): $\tilde{\nu}$ = 3363, 1639 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 0.94 (t, J = 7.5 Hz, 3 H), 1.14 (s, 1 H), 1.28−1.38 (m, 4 H), 1.45- 2.02 (m, 5 H), 2.81−3.10 (m, 3 H), 3.12−3.25 (m, 1 H), 3.41−3.51 (m, 1 H), 3.58−3.76 (m, 1 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 6.76−6.82 (m, 3 H), 7.18−7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 13.9, 23.4, 26.3, 34.4, 35.1, 41.4, 41.9, 44.0, 55.8, 61.1, 61.9, 95.1, 111.2, 112.0, 120.8, 127.0, 128.0, 130.5, 131.4, 136.5, 147.6, 148.8, 170.2. − MS (EI): m/z (%) = 443 [M^+] (1), 425 [M^+ − 18] (3), 334 (29), 165 (42), 164 (100), 151 (33), 91 (23).

5-Benzyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-4,5-dimethylthiazolidin-2-one (11b): According to the general procedure for RLi addition, thiazolidine-2,4-dione **2d** (135 mg, 0.3 mmol) was treated with MeLi (0.44 mL of a 1.6 M solution, 0.7 mmol) to afford hydroxy lactam **11b** as a single diastereomer, which was purified by flash column chromatography (silica gel, 60% hexane/AcOEt) (136 mg, 98%). − IR (neat): $\tilde{\nu}$ = 3378, 1646 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 1.33 (s, 3 H), 1.38 (s, 3 H), 2.78 (s, 1 H), 2.84−3.03 (m, 3 H), 3.22 (d, J = 13.9 Hz, 1 H), 3.52−3.59 (m, 2 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 6.76−6.82 (m, 3 H), 7.20−7.34 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 19.7, 25.5, 35.0, 40.8, 43.7, 55.9, 61.8, 94.3, 111.2, 112.1, 120.9, 127.1, 128.3, 130.3, 131.3, 136.6, 147.7, 148.9, 170.4. − MS (EI): m/z (%) = 383 [M^+ − 18] (3), 292 (5), 264 (3), 231 (3), 164 (100), 151 (27), 107 (6), 105 (5), 91 (16).

4-Benzyl-5-butylidene-1-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dimethyl-4,5-dihydroimidazol-2[*3H*]-one (17a): According to the general procedure for RLi addition, hydantoin **5d** (64 mg, 0.2 mmol) was treated with *n*BuLi (0.25 mL of a 1.6 M solution, 0.4 mmol) to afford hydroxy lactam **16a**, which upon purification by flash column chromatography (silica gel, 80% hexane/AcOEt) dehydrated to afford **17a** (64 mg, 89%). − IR (neat): $\tilde{\nu}$ = 1666 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 1.02 (t, J = 7.3 Hz, 3 H), 1.45−1.51 (m, 2 H), 1.53 (s, 3 H), 2.00−2.06 (m, 1 H), 2.17−2.39 (m, 3 H), 2.97 (s, 3 H), 2.98 (d, J = 2.4 Hz, 2 H), 3.02−3.18 (m, 1 H), 3.37−3.50 (m, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 4.37 (t, J = 7.5 Hz, 1 H), 6.59−6.62 (m, 2 H), 6.74 (d, J = 8.7 Hz, 1 H), 7.02−7.24 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 13.9, 23.5, 24.3, 29.0, 31.6, 55.7, 55.8, 63.1, 97.4, 111.0, 111.7, 120.5, 126.7, 127.9, 129.6, 131.7, 136.0, 139.6, 147.3, 156.3. − MS (EI): m/z (%) = 422 [M^+] (1), 332 (24), 331 (100), 180 (3), 167 (13), 165 (42), 151 (13), 150 (9). − $C_{26}H_{34}N_2O_3$ (422.6): calcd. C 73.90, H 8.11, H 6.63; found C 73.45, H 7.89, N 6.35.

4-Benzyl-1-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dimethyl-5-methylidene-4,5-dihydroimidazol-2(*3H*)-one (17b): According to the general procedure for RLi addition, hydantoin **5d** (64 mg, 0.2 mmol) was treated with MeLi (0.25 mL of a 1.6 M solution, 0.4 mmol) to afford hydroxy lactam **16b**, which upon purification by flash column chromatography (silica gel, 90% hexane/AcOEt) dehydrated to afford **17b** (50 mg, 66%). − IR (neat): $\tilde{\nu}$ = 1718 cm^{-1}. − ^{1}H

NMR ($CDCl_3$): 1.46 (s, 3 H), 2.13 (ddd, J = 13.5, 11.1, 5.5 Hz, 1 H), 2.32 (td, J = 13.5, 5.1 Hz, 1 H), 2.68 (d, J = 13.9 Hz, 1 H), 2.92 (s, 3 H), 3.02 (d, J = 13.9 Hz, 1 H), 3.15 (ddd, J = 13.5, 11.1, 5.1 Hz, 1 H), 3.47 (ddd, J = 13.5, 11.1, 5.5 Hz, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 4.00 (d, J = 2.4 Hz, 1 H), 4.01 (d, J = 2.4 Hz, 1 H), 6.64−6.77 (m, 3 H), 7.05−7.24 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 24.9, 25.4, 31.7, 41.3, 44.2, 55.8, 62.9, 78.3, 111.0, 111.7, 120.4, 126.7, 127.8, 129.8, 131.3, 135.4, 147.3, 148.7, 149.3, 156.3. − MS (EI): *m*/*z* (%) = 380 [M^+] (4), 289 (100), 165 (51), 151 (17), 125 (45), 91 (35). − $C_{23}H_{28}N_2O_3$ (380.5): calcd. C 72.60, H 7.42, H 7.36; found C 72.44, H 7.12, N 7.06.

(1*RS*,10b*RS*)-1-Benzyl-10b-butyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (12a): TFA (1 mL, 13.5 mmol) was added to a solution of hydroxy lactam **11a** (78 mg, 0.2 mmol) in CH_2Cl_2 (12 mL), and the resulting solution was heated at reflux for 3 days. The reaction mixture was treated with saturated aqueous Na_2CO_3, the organic layer was decanted and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded **12a** as a white solid (76 mg, 89%): m.p. 166−168 °C (Et_2O). − IR (KBr): $\tilde{\nu}$ = 1667 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 0.84−0.89 (m, 6 H), 1.03−1.08 (m, 1 H), 1.25−1.46 (m, 4 H), 2.08−2.19 (m, 1 H), 2.66−2.72 (m, 1 H), 2.76−2.94 (m, 1 H), 3.05 (d, J = 12.3 Hz, 1 H), 3.05−3.15 (m, 1 H), 3.57 (d, J = 12.3 Hz, 1 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.52 (dd, J = 12.9, 3.1 Hz, 1 H), 6.67 (s, 1 H), 6.81 (s, 1 H), 6.93−7.33 (m, 5 H). − ^{13}C NMR ($CDCl_3$): 14.0, 23.4, 24.8, 27.4, 30.0, 36.3, 40.5, 41.1, 55.7, 56.2, 64.3, 71.3, 108.3, 111.9, 126.7, 127.1, 128.3, 129.0, 130.1, 136.6, 147.8, 148.0, 169.3. − MS (EI): *m*/*z* (%) = 426 [M^+ + 1] (1), 368 (84), 277 (55), 247 (12), 206 (17), 205 (100). − $C_{25}H_{31}NO_3S$ (425): calcd. C 70.56, H 7.34, N 3.29; found C 70.16, H 7.54, N 3.21.

(1*RS*,10b*RS*)-1-Benzyl-8,9-dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydro-3*H*-[1,3]-thiazolo[4,3-*a*]isoquinolin-3-one (12b): TFA (1 mL, 13.5 mmol) was added to a solution of hydroxy lactam **11b** (80 mg, 0.2 mmol) in CH_2Cl_2 (12 mL), and the resulting solution was heated at reflux for 3 days. The reaction mixture was treated with saturated aqueous Na_2CO_3, the organic layer was decanted and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 60% hexane/AcOEt) afforded an inseparable diastereomeric mixture of (1*RS*,10b*RS*)-**12b** and (1*RS*,10b*SR*)-**12b** in a 60:40 ratio. Data for the mixture are given (75 mg, 98%): m.p. 82−84 °C (Et_2O). − IR (KBr): $\tilde{\nu}$ = 1667 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 0.99 (s, 3 H, major diast), 1.55 (s, 3 H, minor diast), 1.77 (s, 3 H, minor diast), 1.85 (s, 3 H, major diast), 2.18 (d, J = 13.1 Hz, 1 H, minor diast), 2.66−2.78 (m, 1 H, minor diast; 2 H, both diast), 2.86−3.06 (m, 4 H, both diast), 3.18 (d, 12.5 H, 1 H, major diast), 3.57 (d, J = 12.5 Hz, 1 H, major diast), 3.88 (s, 3 H, minor diast), 3.90 (s, 3 H, major diast), 3.91 (s, 3 H, major diast), 3.93 (s, 3 H, minor diast), 4.35−4.49 (m, 2 H, both diast), 6.66 (s, 2 H, both diast), 6.77 (s, 1 H, minor diast), 6.82 (s, 1 H, major diast), 7.10−7.55 (m, 10 H, both diast). − ^{13}C NMR ($CDCl_3$): 19.7 (1 diast), 22.1 (1 diast), 22.7 (1 diast), 24.7 (1 diast), 29.9 (1 diast), 30.0 (1 diast), 37.2 (1 diast), 37.4 (1 diast), 41.7 (1 diast), 43.3 (1 diast), 55.7 (both diast), 56.2 (both diast), 62.6 (1 diast), 62.9 (1 diast), 68.9 (1 diast), 69.1 (1 diast), 108.7 (1 diast), 108.9 (1 diast), 111.7 (1 diast), 111.8 (1 diast), 126.6 (1 diast), 127.2 (1 diast), 127.4 (1 diast), 127.8 (1 diast), 128.3 (1 diast), 128.9 (1 diast), 129.1 (1 diast), 130.1 (1 diast), 131.6 (1 diast), 136.4 (1 diast), 136.5 (1 diast), 147.5 (1 diast), 147.7 (1 diast), 148.0 (1 diast), 148.1 (1 diast), 168.0 (both diast). − MS (EI): *m*/*z* (%) = 383 [M^+] (2), 368 (7), 277 (7), 233 (5), 206 (13), 205 (100), 204 (15), 190 (14), 174 (6), 91 (25), 77 (6), 65 (6), 59 (10). − $C_{22}H_{25}NO_3S$ (383.5): calcd. C 68.90, H 6.57, N 3.65; found C 68.57, H 6.76, N 3.61.

6,7-Dimethoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline-2-carbaldehyde (18): Raney nickel slurry (2.6 g) was added to a solution of thiazoloisoquinolone **10c** [obtained from **2c** (87 mg, 0.2 mmol) without purification] in EtOH (30 mL), and the solution was heated under reflux for 6 h. The reaction mixture was cooled, filtered over Celite, and the filtrate concentrated in vacuo. Flash column chromatography (silica gel, 40% hexane/AcOEt) afforded the isoquinoline **18** as an oil (38 mg, overall yield from **2c**, 50%). − IR (neat): $\tilde{\nu}$ = 1670 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 1.93−2.19 (m, 4 H, both rotamers), 2.56−2.78 (m, 6 H, both rotamers), 2.78−2.98 (m, 1 H, rotamer A), 3.10 (td, J = 12.3, 4.5 Hz, 1 H, rotamer B), 3.57 (td, J = 12.3, 4.7 Hz, 1 H, rotamer A), 3.67−3.74 (m, 1 H, rotamer B), 3.82 (s, 6 H, both rotamers), 3.84 (s, 6 H, both rotamers), 3.78−3.91 (m, 1 H, rotamer A), 4.41 (dd, J = 9.1, 4.7 Hz, 1 H, rotamer A), 4.52 (dd, J = 12.3, 5.5 Hz, 1 H, rotamer B), 5.41−5.46 (m, 1 H, rotamer B), 6.50 (s, 1 H, rotamer A), 6.55 (s, 2 H, both rotamers), 6.58 (s, 1 H, rotamer B), 7.14−7.34 (m, 10 H, both rotamers), 8.17 (s, 1 H, rotamer A), 8.24 (s, 1 H, rotamer B). − ^{13}C NMR ($CDCl_3$): 27.3 (1 rotamer), 29.2 (1 rotamer), 32.4 (1 rotamer), 32.5 (1 rotamer), 34.0 (1 rotamer), 37.6 (1 rotamer), 38.2 (1 rotamer), 39.9 (1 rotamer), 50.5 (both rotamers), 55.7 (1 rotamer), 55.8 (1 rotamer), 55.9 (1 rotamer), 56.2 (1 rotamer), 109.2 (1 rotamer), 109.6 (1 rotamer), 111.1 (1 rotamer), 111.4 (1 rotamer), 124.5 (1 rotamer), 125.5 (1 rotamer), 125.8 (1 rotamer), 126.2 (1 rotamer), 128.2 (1 rotamer), 128.3 (1 rotamer), 128.6 (1 rotamer), 140.3 (1 rotamer), 141.4 (1 rotamer), 147.4 (1 rotamer), 147.6 (1 rotamer), 147.7 (1 rotamer), 147.9 (1 rotamer), 161.4 (1 rotamer), 161.6 (1 rotamer). − MS (EI): *m*/*z* (%) = 325 [M^+] (5), 221 (17), 220 (100), 192 (20), 176 (12), 160 (2), 91 (9). − $C_{20}H_{23}NO_3$ (325.4): calcd. C 73.82, H 7.12, N 4.30; found C 73.40, H 7.11, N 4.24.

(1*RS*,1′*RS*)- and (1*RS*,1′*SR*)-6,7-Dimethoxy-2-methyl-1-(1-methylphenethyl)-1,2,3,4-tetrahydroisoquinoline (20a) and (20b): Raney nickel slurry (7.82 g) was added to a solution of thiazoloisoquinolone **10d** [obtained from **2d** (393 mg, 1.0 mmol) without purification] in EtOH (30 mL), and the solution was heated under reflux for 8 h. The reaction mixture was cooled, filtered over Celite, and the filtrate concentrated in vacuo. Flash column chromatography (silica gel, 50% hexane/AcOEt) afforded a mixture of diastereomeric 6,7-dimethoxy-1-(1-methylphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbaldehydes **19a** and **19b** in a 1.2:1 ratio (193 mg, overall yield from **2d**, 56%). − IR (neat): $\tilde{\nu}$ = 1670 cm^{-1}. − MS (EI): *m*/*z* (%) = 339 [M^+] (1), 220 (100), 192 (14), 176 (8), 91 (9). − $C_{21}H_{25}NO_3$ (339.4): calcd. C 74.31, H 7.42, N 4.12; found C 73.96, H 7.25, N 3.98

$LiAlH_4$ (11.5 mg, 0.30 mmol) was added at 0 °C to a solution of the mixture of **19a−b** (34 mg, 0.1 mmol) in THF (10 mL). The reaction mixture was heated under reflux for 12 h. It was allowed to cool to room temperature, then to 0 °C, and quenched by addition of MeOH (10 mL). The suspension thus obtained was filtered over Celite and water was added (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, AcOEt) afforded the mixture of diastereomeric phenethylisoquinolines **20a** and **20b** in a 1.2:1 ratio (24 mg, 72%). − IR (neat): $\tilde{\nu}$ = 1615, 1520 cm^{-1}. − ^{1}H NMR [$CDCl_3$): 0.80 (d, J = 6.7 Hz, 3 H, major diast), 0.86 (d, J = 6.3 Hz, 3 H, minor diast), 2.10−2.26 (m, 4 H, both diast), 2.46 (s, 3 H,

major diast), 2.50 (s, 3 H, minor diast), 2.52−2.82 (m, 6 H, both diast), 2.91−3.12 (m, 2 H, both diast), 3.18−3.45 (m, 4 H, both diast), 3.85 (s, 3 H, major diast), 3.87 (s, 9 H, both diast), 6.57 (s, 2 H, both diast), 6.60 (s, 2 H, both diast), 7.14−7.31 (m, 10 H, both diast). − ^{13}C NMR ($CDCl_3$): 16.4 (minor diast), 16.7 (major diast), 25.4 (minor diast), 25.7 (major diast), 39.9 (major diast), 40.2 (minor diast), 41.5 (major diast), 42.5 (minor diast), 43.9 (major diast), 44.5 (minor diast), 48.1 (major diast), 49.3 (minor diast), 55.6 (both diast), 55.8 (minor diast), 55.9 (major diast), 67.5 (both diast), 110.9 (minor diast), 111.0 (major diast), 111.1 (minor diast), 111.5 (major diast), 125.5 (both diast), 127.5 (major diast), 127.9 (minor diast), 128.0 (both diast), 128.3 (minor diast), 128.6 (major diast), 129.0 (minor diast), 129.2 (both diast), 141.6 (minor diast), 142.0 (major diast), 146.4 (major diast), 146.9 (minor diast), 147.0 (both diast). − MS (EI): *m*/*z* (%) = 325 [M^+] (1), 206 (100), 190 (12), 176 (10), 162 (5), 91 (10). − $C_{21}H_{27}NO_2$ (325.4): calcd. C 77.50, H 8.36, N 4.30; found C 77.16, H 8.12, N 4.20.

(1*RS*,1′*RS*)- and (1*RS*,1′*SR*)-6,7-Dimethoxy-1-(1-methylphenethyl)-1,2,3,4-tetrahydroisoquinoline (21a) and (21b): Aqueous NaOH (40%, 10 mL) was added to a solution of the mixture of **19a−b** (48 mg, 0.14 mmol), obtained as described above, in EtOH (10 mL). The reaction mixture was heated under reflux for 12 h and was then cooled to room temperature and water was added (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 7:2.4:0.6 hexane/AcOEt/triethylamine) afforded a mixture of diastereomeric phenethylisoquinolines **21a** and **21b** in a 1.2:1 ratio (41 mg, 93%). IR ($CHCl_3$): $\tilde{\nu}$ = 33340, 1660, 1615, 1520 cm^{-1}. − ^{1}H NMR ($CDCl_3$): 0.70 (d, *J* = 6.7 Hz, 3 H, minor diast), 1.05 (d, *J* = 6.3 Hz, 3 H, major diast), 1.70 (broad s, 2 H), 2.20−2.37 (m, 4 H, both diast), 2.51−2.70 (m, 4 H, both diast), 2.72−3.01 (m, 4 H, both diast), 3.28−3.32 (m, 2 H, both diast), 3.83 (s, 3 H, major diast), 3.85 (s, 9 H, both diast), 4.00−4.06 (m, 2 H, both diast), 6.56 (s, 1 H, minor diast), 6.59 (s, 1 H, minor diast), 6.61 (s, 1 H, major diast), 6.77 (s, 1 H, minor diast), 7.02- 7.32 (m, 10 H, both diast). − ^{13}C NMR ($CDCl_3$): 12.9 (minor diast), 16.8 (major diast), 29.9 (both diast), 36.5 (minor diast), 40.1 (minor diast), 40.6 (major diast), 41.0 (major diast), 48.9 (both diast), 55.6 (major diast), 55.7 (major diast), 55.9 (minor diast), 56.0 (minor diast), 58.5 (minor diast), 60.7 (major diast), 108.5 (major diast), 108.6 (minor diast), 111.5 (minor diast), 111.6 (major diast), 125.5 (minor diast), 125.9 (major diast), 128.1 (major diast), 128.3 (major diast), 128.6 (minor diast), 128.7 (major diast), 128.9 (minor diast), 129.0 (minor diast), 129.9 (minor diast), 130.1 (major diast), 141.3 (minor diast), 142.0 (major diast), 146.9 (both diast), 147.2 (both diast). − MS (EI): *m*/*z* (%) = 311 [M^+] (1), 294 (5), 192 (100), 176 (11), 148 (5), 91 (17). − $C_{20}H_{25}NO_2$ (311.4): calcd. C 77.14, H 8.09, N 4.50; found C 76.83, H 7.88, N 4.25.

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