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Diastereoselective Intramolecular α-Amidoalkylation Reactions of L-DOPA Derivatives. Asymmetric Synthesis of Pyrrolo[2,1-*a*]isoquinolines

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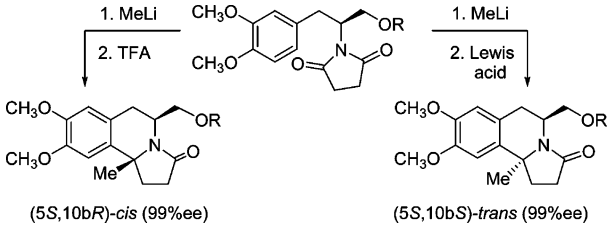

Stereocontrolled intramolecular α-amidoalkylation reactions of L-DOPA-derived succinimides have been studied. Addition of MeLi to nonracemic succinimides **9a**−**d** yields oxoamides, which are cyclized upon treatment with Lewis or protic acids to afford (5*S*,10b*S*)-*trans* **11** or (5*S*,10b*R*)-*cis* **12** pyrroloisoquinolines with variable diastereoselectivities, but with high enantiomerical purities (ee 99%).

Introduction

N-Acyliminium ions are extremely versatile intermediates in organic synthesis. In the context of the intramolecular α-amidoalkylation reactions in carbon−carbon bond-forming processes, considerable work has been done in the area of reactions of cyclic *N*-acyliminium ions with π-nucleophiles, leading to alkaloids and other nitrogen-containing biologically active compounds.[1] Diastereoselectivity in these intramolecular α-amidoalkylations can be achieved by the steric control of the substituents already present in the cyclic *N*-acyliminium ion (R^1) or along the chain connecting the π-nucleophiles and the nitrogen atom (R^2) (Figure 1).[2]

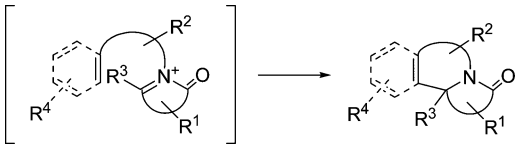

FIGURE 1. Intramolecular reaction of cyclic *N*-acyliminium ions with π-nucleophiles.

For example, we have described a tandem organolithium addition, *N*-acyliminium ion cyclization sequence

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(1) For reviews on *N*-acyliminium ion chemistry, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416. (b) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, pp 271−339. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047−1082. (d) de Koning, H.; Speckamp, W. N. In *Stereoselective Synthesis [Houben-Weyl]*; Helmchen, G., Hoffmann, R. W., Muzler, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Workbench ed. E21, Vol. 3, pp 1952−2010. (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (f) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311−2352. (g) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628. (h) Dobbs, A. P.; Rossiter, S. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 3, pp 419−450.

(2) For reviews, see ref 1. For some selected examples of diastereoselective intramolecular α-amidoalkylation reactions of cyclic *N*-acyliminium ions, see the following references. Steric control by the substituents in the ring: (a) Ostendorf, M.; van der Neut, S.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, *65*, 115−124. (b) Consonni, A.; Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Silvani, A. *Eur. J. Org. Chem.* **2001**, *66*, 1377−1383. (c) Hwang, D. J.; Kang, S. S.; Lee, J. Y.; Choi, J. H.; Park, H.; Lee, Y. S. *Synth. Commun.* **2002**, *32*, 2499−2505. (d) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, 47−62. (e) Kaluza, Z.; Mostowicz, D. *Tetrahedron: Asymmetry* **2003**, *14*, 225−232. (f) Mostowicz, D.; Wójcik, R.; Dolega, G.; Kahuza, Z. *Tetrahedron Lett.* **2004**, *45*, 6011−6015. (g) Siwicka, A.; Wojasiewicz, K.; Rosiek, B.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 975−993. (h) Hanessian, S.; Tremblay, M.; Marzi, M.; del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070−5085. Steric control by the substituents along the chain connecting the π-nucleophiles and the nitrogen atom: (i) Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1446−1451. (j) Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148−152. (k) Nielsen, T. E.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765−3773. (l) Ardeo, A.; García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2003**, *44*, 8445−8448.

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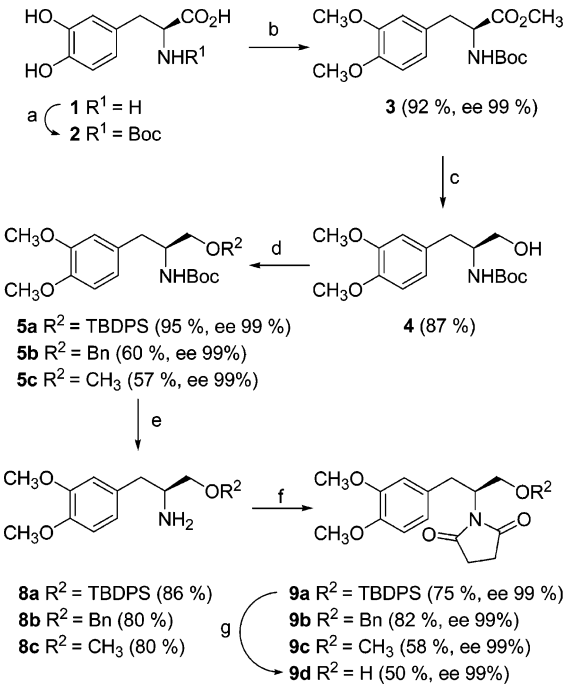
with *N*-phenethylimides, which constitutes an effective route to several types of isoquinoline alkaloids.[3] Our approach can be used to generate cyclic *N*-acyliminium ions with a substituent adjacent to the iminium carbon, whose cyclization leads to the diastereoselective synthesis of 1,10b-*cis* thiazoloisoquinolines.[4] This methodology has recently been directed toward the enantioselective synthesis of pyrrolo[2,1-*a*]isoquinolones via stereocontrolled α-amidoalkylation reactions starting from an enantiopure *N*-phenethylnorborn-5-en-2,3-dicarboximide with a 2-*exo*-hydroxy-10-bornylsulfinyl group as chiral auxiliary.[5]

We were also interested in the effect of a stereogenic center α to the nitrogen atom on this type of *N*-acyliminium cyclizations. Thus, in a preliminary communication, we have reported that addition of organolithiums to chiral nonracemic L-DOPA-derived succinimide yields oxoamides, which are cyclized diastereoselectively upon treatment with $BF_3{\cdot}OEt_2$, to afford 5,10b-*trans* pyrroloisoquinolones in high ee (99%), but in moderate overall yields (34−36%).[6] Although the resulting pyrroloisoquinolones were isolated as single 5,10b-*trans* diastereomers, not detecting the presence of the corresponding cis diastereomers, the moderate yields obtained did not allow us to conclude that the cyclization reactions were completely diastereoselective. Shortly thereafter, Allin and co-workers[7] reported a related stereoselective approach to the pyrroloisoquinoline ring system based on the intramolecular α-amidoalkylation reaction of a bicyclic lactam derived from (*S*)-phenylalaninol. In this case, the cyclization with $TiCl_4$ led to a mixture of product diastereoisomers in high yield (87%) in a 2:1 ratio also in favor of the 5,10b-*trans* product.

With these precedents we decided to reinvestigate the stereoselectivity of this type of intramolecular α-amidoalkylation reaction, using of a series of L-DOPA-derived *N*-phenethylsuccinimides with different substituents in the α-position to the nitrogen atom, and protic and Lewis acids to carry out the intramolecular α-amidoalkylation reaction. We disclose here full details of our investigations that ultimately led to a successful approach toward the asymmetric synthesis of pyrrolo[2,1-*a*]isoquinolones.[8]

SCHEME 1[a]



[a] Reagents: (a) $(Boc)_2O$, 50% dioxane/H_2O, Et_3N, rt. (b) Me_2SO_4, K_2CO_3, acetone, reflux. (c) $LiAlH_4$, 50% Et_2O/THF, reflux. (d) TBDPSiCl, imidazole, CH_2Cl_2, rt (for **5a**); BnBr, NaH, THF, 0 °C to rt (for **5b**); KOH, DMSO, MeI, rt (for **5c**). (e) TFA, CH_2Cl_2, rt. (f) Succinic anhydride, Et_2O, reflux. Then, Ac_2O, NaOAc, 85 °C. (g) TBAF, THF, 0 °C to rt.

Results and Discussion

Our first task was the synthesis of *N*-phenethylsuccinimides **9a**−**d**, which were prepared from L-DOPA **1** by standard functional group manipulation, as outlined in Scheme 1. Thus, protection of the amino group of L-DOPA **1** with $(Boc)_2O$, followed by methylation with dimethyl sulfate, yielded methyl ester **3**, which was submitted to $LiAlH_4$ reduction to give the phenylalanilol **4**. Derivatization of the primary hydroxyl group was achieved using TBDPSCl, benzyl bromide, and iodomethane to give ethers **5a**−**c**.[9] Hydrolysis of Boc amides **5a**−**c** with TFA in dichloromethane at room temperature afforded the corresponding amines **8a**−**c**. Treatment of these amines with succinic anhydride led to the corresponding amido acids, which, without further purification, were cyclized with Ac_2O and NaAcO to give succinimides **9a**−**c** in good yields. Finally, **9d** was prepared by hydrolysis of the *O*-silyl ether of imide **9a** with TBAF. Thus, succinimides **9a**−**d** were prepared in moderate to good overall yields from L-DOPA without epimerization of the stereogenic center, as imides **9a**−**d** showed an enantiomeric excess equal to starting amino acid (99% ee), determined by chiral phase HPLC.

(3) (a) Lete, E.; Egiarte, A.; Sotomayor, N.; Vicente, T.; Villa, M. J. *Synlett* **1993**, 41−42. (b) Collado, M. I.; Lete, E.; Sotomayor, N.; Villa, M. J. *Tetrahedron* **1995**, *51*, 4701−4710. (c) Collado, M. I.; Sotomayor, N.; Villa, M. J.; Lete, E. *Tetrahedron Lett*. **1996**, *37*, 6193−6196. (d) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem*. **1997**, *62*, 2080−2092. (e) Osante, I.; García, E.; Ardeo, A.; Arrasate, S.; Lete, E.; Sotomayor, N. *Recent Res. Dev. Org. Chem.* **2002**, *6*, 103−111.

(4) (a) Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Synlett* **2000**, 101−103. (b) Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2001**, 1267−1277.

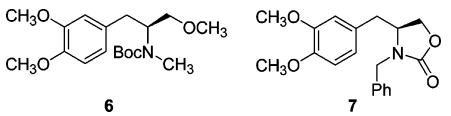
(5) (a) González-Temprano, I.; Sotomayor, N.; Lete, E. *Synlett* **2002**, 593−597. (b) González-Temprano, I.; Osante, I.; Sotomayor, N.; Lete, E. *J. Org. Chem*. **2004**, *69*, 3875−3885.

(6) García, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2001**, *42*, 1511−1513.

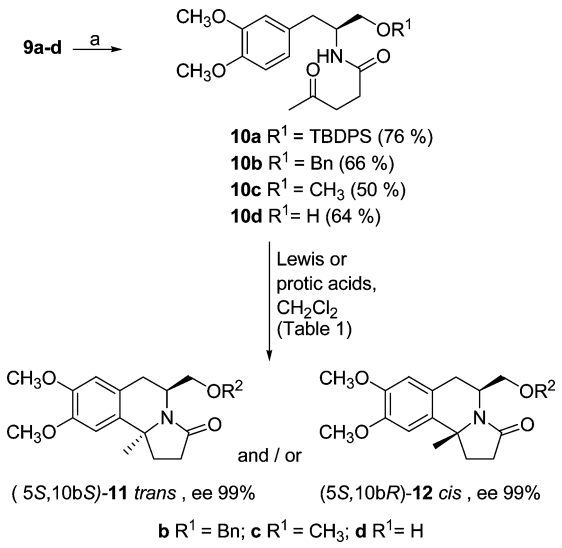
(7) (a) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D. *Tetrahedron Lett*. **2001**, *42*, 3943−3946. (b) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D.; Elsegood, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3029−3036.

(8) Pyrrolo[2,1-*a*]isoquinolones have attracted considerable interest because they possess antidepressant, muscarinic agonist, antiplatelet, and anticancer activity. Moreover, they can be used as PET radiotracers for imaging serotonin uptake sites. The importance of these nitrogen heterocycles is further enhanced by their utility as advanced intermediates for the synthesis of alkaloids. For a general review on properties, synthesis, and reactivity of pyrrolo[2,1-*a*]isoquinolines, see: Mikhailovskii, A. G.; Shklyaev, V. S. *Chem. Heterocycl. Compd.* **1997**, *33*, 243−265; Transl. *Khim. Geterotsikl. Soedin*.

(9) *O*-Silylation of **4** was carried out with imidazole and TBDPSCl to give **5a** in excellent yield (95%). However, the yields of the benzyl and methyl ethers **5b** and **5c** were only moderate due to the formation of side products **6** (35%) and **7** (30%), respectively. Several attempts to improve these yields failed. See Supporting Information.



SCHEME 2[a]



[a] Reagents: (a) MeLi (4 equiv), −78 °C, 6 h.

TABLE 1. Intramolecular α-Amidoalkylation Reaction of Oxoamides 10a−d

			product		dr
entry	subs	acid	yield (%)	R^2	**11** trans/**12** cis
1	**10a**	$BF_3{\cdot}Et_2O$[a]	92	H	2:1
2	**10b**	$BF_3{\cdot}Et_2O$[a]	33	H	>95:5
3	**10d**	$BF_3{\cdot}Et_2O$[a]	81	H	2:1
4	**10a**	$TiCl_4$[b]	13[d]	H	2:1
5	**10b**	$TiCl_4$[b]	15[d]	H	2:1
6	**10d**	$TiCl_4$[b]	48[d]	H	2:1
7	**10a**	TFA[c]	67	H	1:1.3
8	**10b**	TFA[c]	92	Bn	1:1
9	**10c**	TFA[c]	80	Me	1:2
10	**10d**	TFA[c]	88	H	1:4

[a] (a) $BF_3{\cdot}Et_2O$ (10 equiv), 0 °C. (b) Reflux, 4 days. (c) $BF_3{\cdot}Et_2O$ (10 equiv), reflux, 3 days. [b] (a) $TiCl_4$ (4 equiv) at −78 °C. (b) → −10 °C, 3 h. (c) → rt, 6 days. [c] TFA (34 equiv), reflux, 1 day. [d] Variable yields (10−60%) of deprotected oxoamide **10d** were isolated.

The synthesis of key *N*-acyliminium ion precursors **10** was accomplished by reaction with organolithium reagents.[3] Thus, succinimides **9a−d** were treated with MeLi to afford the corresponding oxoamides **10a−d** (Scheme 2). An excess of the organometallic (4 equiv) was required to achieve the reported yields.[10] Oxoamide **10d** was also prepared by hydrolysis of the silyl ether of **10a** with TBAF.

The results of the intramolecular α-amidoalkylation reactions are listed in Table 1. We started studying intramolecular α-amidoalkylation of oxoamide **10a** (R^1 = TBDPS) using $BF_3{\cdot}Et_2O$ as Lewis acid to generate the *N*-acyliminium ion. We had reported[6] that when **10a** was treated with $BF_3{\cdot}OEt_2$ (12 equiv, reflux), 5,10b-*trans* pyrroloisoquinolone **11d** (R^2 = H) was isolated in high ee (99%), but in moderate overall yields (34−36%). Although complete conversion of oxoamide **10a** was observed, it was not possible to isolate and characterize any of the byproducts formed. Optimization experiments have allowed us to enhance the yield of pyrroloisoquinoline **11d** to 92% (entry 1) and to isolate the minor 5,10b-*cis* diastereomer **12d** (R^2 = H). The main experimental differences were the portionwise addition of a larger excess of the Lewis acid and longer reaction times. Thus, $BF_3{\cdot}Et_2O$ (12 mmol) was added to a solution of **10a** in CH_2Cl_2 at 0 °C under argon atmosphere, and after allowing the reaction mixture to reach room temperature, it was heated under reflux for 4 days. Then, the reaction mixture was cooled, treated again with $BF_3{\cdot}Et_2O$ (12 mmol), and refluxed for 3 days, affording the pyrroloisoquinolones **11d/12d** as a trans/cis diastereomer mixture in a 2:1 ratio in favor of the trans isomer (see Table 1, entries 1−3). The yields are given for isolated and purified products, since the diastereomers were separable on a preparative scale by flash column chromatography. Both isomers were stable, and we have not observed any equilibration under the reaction conditions. Additionally, the cyclization took place without epimerization since both diastereomers were enantiopure (99% ee).[11]

The formation of **11d** (R^2 = H) under these reaction conditions suggested that the silyl ether was hydrolyzed to alcohol prior to cyclization, since Allin and co-workers[7b] obtained the same level of diastereoselectivity in the cyclization with $TiCl_4$ of a similar substrate that has a free hydroxyl group. In fact, monitoring of the reaction by ^1H NMR spectroscopy allowed us to detect the unprotected oxoamide **10d**. Moreover, on treating oxoamide **10d** (R^1 = H, Table 1, entry 3) with $BF_3{\cdot}Et_2O$ as Lewis acid, we obtained the diastereomeric mixture of pyrroloisoquinolines **11d/12d** in the same ratio and comparable yield.

With these results in hand, we pursued the *N*-acyliminium cyclization of *O*-alkyl-substituted oxoamide **10b** (R^1 = Bn). However, under a range of conditions, the reaction was sluggish, and we could only isolate the *trans*-pyrroloisoquinoline **11d** (R^2 = H) in low yield (33%). Because of the low yield obtained, the diastereomeric ratio indicated in Table 1 is not indicative of a stereoselective cyclization. Therefore, we did not apply these Lewis acid conditions to **10c** (R^1 = Me).

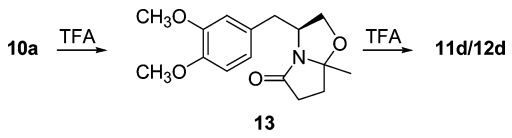
Modest yields and same diastereoselectivities were obtained when oxoamides **10a** (R^1 = TBDPS), **10b** (R^1 = Bn), and **10d** (R^1 = H) were cyclized employing $TiCl_4$ as Lewis acid (entries 4−6). The best results were observed when oxoamides were treated with $TiCl_4$ (4 equiv) in CH_2Cl_2 at −78 °C for 1 h, at −10 °C for 3 h, and at room temperature for 6 days. Despite the long reaction times and the excess of Lewis acid used, in all cases the conversion was low and unprotected oxoamide **10d** (R^1 = H) was isolated (10−60%), obtaining only low yields of pyrroloisoquinolines **11d/12d** (R^2 = H). The observed diastereoselectivity (2:1) is identical to that obtained with $BF_3{\cdot}Et_2O$ and the same for all substrates, which indicates that deprotection occurs prior to cyclization.

Then we decided to test protic acid conditions. Thus, oxoamide **10a** (R^1 = TBDPS) was treated with an excess of TFA in refluxing CH_2Cl_2 for 3 h, isolating oxazolone **13** (14%), together with a low yield of pyrroloisoquinoline

(10) The use of 1, 2, or 3 equiv of MeLi led to lower yields of the oxoamides and starting material. The requirement of more than stoichiometric amounts of organolithiums has been attributed to coordination of the organolithium to oxygenated groups. See: Sardina, F. J.; Blanco, M. *J. Org. Chem.* **1996**, *61*, 4748−4755.

(11) All enantiomeric excesses were checked by chiral stationary phase HPLC by comparison with the corresponding racemates, obtained by analogous routes from racemic D,L-DOPA.

SCHEME 3



11d (R^2 = H, 5%), and a mixture of starting material, its cyclic tautomer, and dehydrated products (Scheme 3). Because Allin and co-workers[7b] had used this oxazolone as an acyliminium ion precursor, we thought that longer reaction times would favor the final α-amidoalkylation reaction. Thus, when oxoamide **10a** (R^1 = TBDPS) was treated with TFA for 1 day, a mixture of pyrroloisoquinolines **11d/12d** (R^2 = H) was obtained in good yield (entry 7). Significantly, reversal of the stereochemistry was observed and the (5*S*,10b*R*)-*cis* diastereomer **12d** was the major diastereomer obtained, although with poor diastereoselectivity. These conditions were applied to oxoamides **10b** (R^1 = Bn) and **10c** (R^1 = Me) (entries 8 and 9). Hydrolysis of methyl or benzyl ether did not occur, and cyclization took place in high yields, but no significant improvement in diastereoselectivity was observed. Only with the unprotected amide **10d** (R^1 = H) a reasonable stereoselectivity was found obtaining the **12d**-*cis* (R^2 = H) diastereomer as the major product (4:1) (entry 10).

In summary, the Lewis acid-promoted cyclization of oxoamides **10a**−**d** is moderately stereoselective, producing the *trans* (5*S*,10b*S*)-**11d** (R^2 = H) as the major diastereomer in a 2:1 diastereomeric ratio. This fact, together with the isolation of deprotected oxoamides, indicates that deprotection occurs prior to cyclization, and thus the protecting group has no relevance for the stereochemical course of the reaction. However, when a protic acid (TFA) is used, a reversal of the stereoselectivity is observed, obtaining mainly the (5*S*,10b*R*)-*cis* products **12**. In these cases, the size of the substituent at the α-position to the nitrogen atom seems to play an important role. Thus, as the size of the C-5 substituent decreases, the cis selectivity improves.

The stereochemical outcome of the cyclization may be explained as a result of conformational factors in the transition state. To explain these results, we propose the conformational models and the transition states depicted in Figure 2. In most examples described in the literature, the most favored transition state would minimize $A^{(1,3)}$ strain, according to Hart's model.[12] Thus, for intramolecular cyclizations of π-nucleophiles on *N*-acyliminium ions with substituents adjacent to the nitrogen atom, an axial orientation is preferred to avoid $A^{(1,3)}$ strain between the substituent and the carbonyl of the *N*-acyl group.[13] This results in the preferred formation of cis diastereomers of, for instance, 5-phenyltetrahydro[2,1-*a*]isoquinolones,[14] 5-aryl-10b-butyltetrahydro[2,1-*a*]isoquinolones,[15] indolizidines,[16] β-carboline derivatives,[17] benzo[*a*]quinolizidines,[18] or polycyclic isoindolinone derivatives.[19] However, in all these cases, the iminium carbon is unsubstituted.

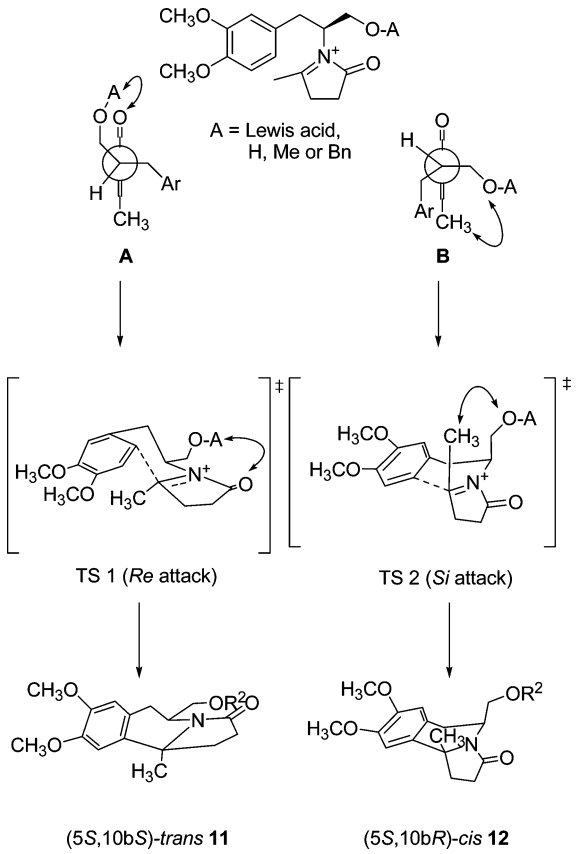
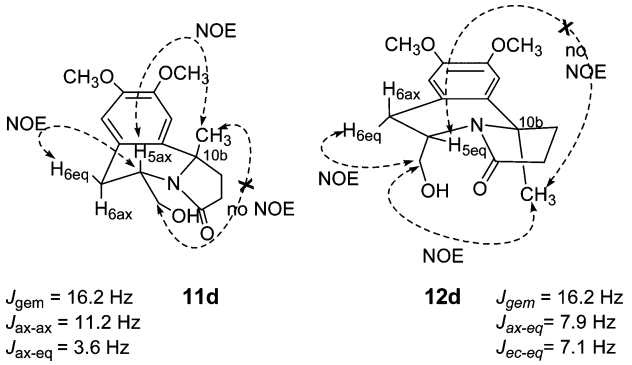


FIGURE 2. Stereochemical outcome of the α-amidoalkylation.

In our case, the iminium carbon bears a methyl group and, as deprotection occurs prior to cyclization, the Lewis acid would probably be coordinated to the hydroxyl group, and thus it can be considered as a large group. The acyliminium ion could adopt two possible conformations **A** and **B**, which allow the attack of the aromatic ring from the *Re* or *Si* faces, through transition states 1 and 2, respectively (Figure 2). A balance between $A^{(1,3)}$ strain in **A** and severe syn axial 1,3-interactions between both substituents in the transition state 2 (TS2) would favor the pseudo-equatorial disposition for C-5 substituent in the transition state 1 (TS1). Thus, attack of the aromatic ring onto the *Re* face of the *N*-acyliminium ion leads to the observed stereochemistry, in which the substituent in 10b (Me) assumes a pseudo-axial position leading to trans diastereomer **11**. Additionally, the formation of a chelate with a Lewis acid, as $TiCl_4$, cannot be ruled out. In this context, Allin and co-workers[7b] had reported the synthesis of pyrroloisoquinolines through a $TiCl_4$-promoted α-amidoalkylation reaction of oxazolones, which are likely to proceed through the same *N*-acyliminium intermediate depicted in Figure 2, obtaining the same

(12) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397−398.
(13) Mooiveer, H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 4627−4636.
(14) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062−5074.
(15) Collado, M. I.; Lete, E.; Sotomayor, N.; Villa, M. J. *Tetrahedron* **1995**, *51*, 4701−4710.
(16) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661−1664.
(17) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **2000**, *41*, 1993−1996.
(18) Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817−2820.
(19) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905−4908.



J_{gem} = 16.2 Hz
$J_{ax\text{-}ax}$ = 11.2 Hz
$J_{ax\text{-}eq}$ = 3.6 Hz

11d **12d**

J_{gem} = 16.2 Hz
$J_{ax\text{-}eq}$ = 7.9 Hz
$J_{ec\text{-}eq}$ = 7.1 Hz

FIGURE 3. Selected NOE enhancements.

level of diastereoselectivity. The stereochemical outcome is explained also by conformational factors in the transition state. Interestingly, when the acyliminium is unsubstituted (H instead of CH_3), the cis diastereomer was obtained. This result is in agreement with our proposal.

When a protic acid is used, the stereoselectivity is lost, or it is inverted in favor of the cis isomer. In this case, there is no metal to coordinate the oxygen atom on the C-5 substituent, and therefore the balance between $A^{(1,3)}$ strain and syn axial 1,3 interactions would favor the conformation that leads to TS2 again, affording the cis diastereomers **12**. Thus, the cis selectivity improves as the size of the substituent on C-5 decreases from Bn to Me and H.

Similar effects have been described for related structures that led to reversal of diastereoselectivity as a result of competing steric interactions.[20] These results are in agreement with those obtained in the synthesis of isoindolinone systems, where a variation of the cis/trans ratio was observed, depending on the nature of the acid used for the cyclization.[19]

Nuclear Overhauser effect difference spectroscopy and $^1H-^1H$ decoupling experiments confirmed the stereochemistry of all the pyrroloisoquinoline derivatives **11** and **12**. The most significant results obtained with diasteromeric pyrroloisoquinolines (5*S*,10b*S*)-**11d** and (5*S*,10b*R*)-**12d** are shown in Figure 3. Thus, for **11d**, the *J* values of the ABX system formed by H-5 and H-6 protons indicate that H-5 is in a pseudo-axial position. Additionally, NOE difference spectroscopy showed an enhancement between H-5 and the methyl group in 10b. These data are consistent with a preferred half-chair conformation in which the substituents in C-10b and in C-5 are in pseudo-axial and pseudo-equatorial positions, respectively. Thus, the configuration was assigned as 5*S*,-10b*S*. On the other hand, for the cis diastereomer **12d**, the *J* values of the ABX system formed by H-5 and H-6 protons indicate that H-5 is in a pseudo-equatorial position. In this case, the absence of NOE enhancement between methyl protons on C-10b and H-5 and the enhancement observed between methyl protons on C-10b and methylene on the C-5 substituent confirmed that both substituents were in a cis disposition, resulting in a 5*S*,10b*R* configuration. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry in each case, and both pyrroloisoquinolones were isolated with high enantiomeric purity (99%).

In summary, a diastereodivergent synthesis of enantiomerically pure pyrrolo[2,1-*a*]isoquinolones via tandem organolithium addition−*N*-acyliminium ion cyclization has been achieved. The stereoselectivity of the intramolecular α-amidoalkylation reaction depends both on the nature of the substituent on the chain connecting the nitrogen atom with the nucleophile and on the nature of the acid used for the generation of the *N*-acyliminium ion. Thus, (5*S*,10b*S*)-*trans* **11** and (5*S*,10b*R*)-*cis* **12** could be obtained from the same succinimide precursor with modest selectivities but in high enantiomerical purity using Lewis or protic acids.

Experimental Section

Synthesis of Oxoamides 10a−d. General Procedure. To a solution of succinimides **9a−d** (1 mmol) in dry THF (20 mL), MeLi (4 mmol) was added at −78 °C. The resulting mixture was stirred at this temperature for 6 h, quenched by the addition of saturated NH_4Cl (20 mL), and allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (10 mL) and with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford oxoamides **10a−d**, which were purified by flash column chromatography.

(*S*)-(−)-*N*-[1-(*t*-Butyldiphenylsilyloxymethyl)-2-(3,4-dimethoxyphenyl)ethyl]-4-oxopentanamide (10a). According to the general procedure, imide **9a** (270 mg, 0.52 mmol) was treated with MeLi (2 mL of a 1 M solution in pentane, 2.0 mmol), yielding oxoamide **10a** that was purified by flash column chromatography (silica gel, 50% hexane/ethyl acetate) (229 mg, 76%): $[\alpha]^{20}_D$ −34 (0.07, CH_2Cl_2); mp (*n*-pentane) 78−80 °C; IR ($CHCl_3$) 3340, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 1.11 (s, 9H), 2.14 (s, 3H), 2.22−2.38 (m, 2H), 2.67−2.74 (m, 2H), 2.86 (d, J = 7.1 Hz, 2H), 3.60−3.62 (m, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 4.10−4.21 (m, 1H), 5.87 (d, J = 8.7 Hz, 1H), 6.67−6.75 (m, 3H), 7.37−7.45 (m, 6H), 7.60−7.65 (m, 4H); ^{13}C NMR ($CDCl_3$) 19.4, 26.9, 29.8, 29.9, 36.6, 38.5, 51.5, 55.7, 55.8, 63.4, 110.9, 112.2, 121.3, 127.7, 127.8, 129.8, 130.4, 133.0, 133.1, 135.5, 147.4, 148.7, 171.1, 207.5; MS (EI) *m/z* (relative intensity) 547 (M^+, 2), 490 (90), 432 (36), 375 (24), 319 (8), 256 (29), 240 (9), 199 (93), 177 (76), 151 (100), 135 (33), 91 (37), 71 (20), 57 (47). Anal. Calcd for $C_{32}H_{41}NO_5Si$: C, 70.17; H, 7.54; N, 2.56. Found: C, 70.03; H, 7.63; N, 2.49.

(*S*)-(−)-*N*-[1-(Benzyloxymethyl)-2-(3,4-dimethoxyphenyl)ethyl]-4-oxopentanamide (10b). According to the general procedure, imide **9b** (215 mg, 0.56 mmol) was treated with MeLi (3.75 mL of a 0.6 M solution in pentane, 2.25 mmol), yielding oxoamide **10b** that was purified by flash column chromatography (silica gel, ethyl acetate) (148 mg, 66%): IR ($CHCl_3$) 3313, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.39 (t, J = 6.3 Hz, 2H), 2.75 (t, J = 6.3 Hz, 2H), 3.38−3.39 (m, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 4.21−4.24 (m, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 5.97 (d, J = 8.7 Hz, 1H), 6.67−6.78 (m, 3H), 7.29−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 29.9, 30.0, 36.9, 38.4, 50.2, 55.8, 69.6, 73.2, 110.9, 112.4, 121.3, 127.7, 127.8, 130.5, 137.9, 147.4, 148.5, 171.2, 207.5; MS (EI) *m/z* (relative intensity) 381 (M^+ − 18, 2), 366 (28), 290 (13), 260 (100), 244 (20), 204 (9), 91 (69), 77 (8), 65 (16).

(*S*)-(−)-*N*-[2-(3,4-Dimethoxyphenyl)-1-methoxymethylethyl]-4-oxopentanamide (10c). According to the general procedure, imide **9c** (177 mg, 0.58 mmol) was treated with MeLi (1.65 mL of a 1.4 M solution in pentane, 2.30 mmol), yielding oxoamide **10c** that was purified by flash column chromatography (silica gel, ethyl acetate) (93 mg, 50%): IR ($CHCl_3$) 3303, 1717, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.36 (t, J = 6.3 Hz, 2H), 2.71 (t, J = 6.3 Hz, 2H)*, 2.65−2.78 (m, 1H)*, 3.22 (d, J = 3.9 Hz, 2H), 3.34 (s, 3H)*, 3.31−

(20) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S. *J. Org. Chem.* **1986**, *51*, 1341−1346.

3.37 (m, 1H)*, 3.79 (s, 3H), 3.81 (s, 3H), 4.06−4.18 (m, 1H), 5.99 (d, J = 8.3 Hz, 1H), 6.64−6.75 (m, 3H) (*designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 29.8, 30.5, 36.6, 38.3, 50.0, 55.6, 55.8, 71.8, 110.8, 112.2, 121.2, 130.3, 147.3, 148.5, 171.1, 207.5; MS (EI) *m/z* (relative intensity) 323 (M^+, 4), 290 (1), 208 (100), 193 (3), 177 (24), 151 (9), 99 (26), 74 (44).

(*S*)-(−)-*N*-[2-(3,4-Dimethoxyphenyl)-1-hydroxymethylethyl]-4-oxopentanamide (10d). According to the general procedure, imide **9d** (202 mg, 0.69 mmol) was treated with MeLi (1.97 mL of a 1.4 M solution in pentane, 2.76 mmol), yielding oxoamide **10d** that was purified by flash column chromatography (silica gel, ethyl acetate) (137 mg, 64%): $[\alpha]^{20}_D$ −25 (0.135, CH_2Cl_2); mp (hexane/AcOEt 50%) 90 °C; IR ($CHCl_3$) 3302, 1700, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (bs, 1H), 2.16 (s, 3H), 2.38 (t, J = 6.3 Hz, 2H), 2.66−2.89 (m, 2H)*, 2.79 (t, J = 6.0 Hz, 2H)*, 3.56 (dd, J = 11.1, 5.0 Hz, 1H), 3.69 (dd, J = 11.1, 3.2 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.08−4.14 (m, 1H), 5.9 (d, J = 7.5 Hz, 1H), 6.72−6.81 (m, 3H) (*designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 29.7, 29.8, 36.3, 38.4, 52.6, 55.7, 63.3, 110.9, 112.2, 121.1, 130.1, 147.4, 148.7, 172.4, 208.3; MS (EI) *m/z* (relative intensity) 309 (M^+, 5), 194 (100), 166 (13), 151 (30), 138 (12), 99 (30), 83 (28), 60 (40). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.87; H, 7.21; N, 4.46.

Intramolecular α-Amidoalkylation. Synthesis of (5*S*,10b*S*)-(−)-5-Hydroxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (11d) and (5*S*,10b*R*)-(+)-5-Hydroxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (12d). Procedure A (with BF_3·EtO_2). To a solution of oxoamide **10a** (410 mg, 0.74 mmol) in CH_2Cl_2 (20 mL), BF_3·EtO_2 (0.88 mL, 7.4 mmol) was added at 0 °C, and the resulting solution was allowed to reach room temperature and then refluxed for 4 days. Then, another portion of BF_3·EtO_2 (0.88 mL, 7.4 mmol) was added again, and the resulting mixture was refluxed for 3 days. The reaction mixture was treated with saturated aqueous $NaHCO_3$, 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. The resulting crude reaction mixture was purified by column chromatography (silicagel, hexane/ethyl acetate/methanol 5:3:2), yielding pyrroloisoquinolines **11d** and **12d** in a 2:1 ratio.

(5*S*,10b*S*)-(−)-5-Hydroxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (11d) (128 mg, 60%): $[\alpha]^{20}_D$ −203 (0.046, CH_2Cl_2); mp (*n*-pentane) 124−126 °C; IR (KBr) 3392, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H), 2.05−2.19 (m, 1H), 2.31−2.47 (m, 2H), 2.59 (dd, J = 16.2, 3.6 Hz, 1H), 2.59−2.73 (m, 1H), 3.02 (dd, J = 16.2, 11.2 Hz, 1H), 3.55−3.67 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.98−4.03 (m, 2H), 4.92 (t, J = 7.1 Hz, 1H), 6.52 (s, 1H), 6.69 (s, 1H); ^{13}C NMR ($CDCl_3$) 27.3, 31.1, 31.3, 34.9, 53.9, 55.8, 56.1, 62.4, 64.4, 107.4, 112.2, 124.3, 133.9, 147.8, 148.0, 174.0; MS (EI) *m/z* (relative intensity) 291 (M^+, 8), 277 (17), 276 (100), 260 (40), 244 (11), 143 (9), 130 (10), 71 (10), 57 (15). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.77; H, 7.53; N, 4.67. ee > 99% (Chiralcel OJ, hexane/2-propanol 90:10, 1 mL/min, t_r (5*S*,10b*S*) = 30.2 min > 99%, t_r (5*R*,10b*R*) = 34.8 min < 1%).

(5*S*,10b*R*)-(+)-5-Hydroxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (12d) (74 mg, 32%): $[\alpha]^{20}_D$ +38 (0.078, CH_2Cl_2); mp (hexane/AcOEt 50%) 140 °C; IR (KBr) 3392, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3H), 2.21−2.47 (m, 3H), 2.68−2.82 (m, 1H), 2.75 (dd, J = 16.2, 7.9 Hz, 1H), 2.98 (dd, J = 16.2, 7.1 Hz, 1H), 3.58 (bs, 1H), 3.67−3.84 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.21−4.32 (m, 1H), 6.62 (s, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.8, 29.2, 30.4, 35.3, 51.8, 55.8, 56.1, 62.4, 66.8, 106.8, 111.3, 123.5, 134.2, 147.9, 148.0, 175.7; MS (EI) *m/z* (relative intensity) 292 (M^+ + 1, 3), 291 (M^+, 12), 276 (100), 260 (28), 244 (8), 204 (4), 85 (20), 83 (35), 71 (4), 57 (3). ee > 99% (Chiralcel OD, hexane/2-propanol 85:15, 0.6 mL/min, t_r (5*R*,10b*S*) = 29.1 min < 1%. t_r (5*S*,10b*R*) = 30.2 min > 99%).

Procedure B (with $TiCl_4$). To a solution of oxoamide **10a** (512 mg, 0.93 mmol) in CH_2Cl_2 (20 mL), $TiCl_4$ (0.41 mL, 3.7 mmol) was added at −78 °C, and the resulting solution was allowed to reach −10 °C and was stirred for 3 h. Then, the reaction mixture was allowed to reach room temperature and stirred for 6 days. After workup and purification as described in procedure A, pyrroloisoquinolines **11d** and **12d** were obtained in a 2:1 ratio (34 mg, 13%).

Procedure C (with TFA). To a solution of oxoamide **10a** (208 mg, 0.38 mmol) in CH_2Cl_2 (15 mL), TFA (1 mL, 12.9 mmol) was added at room temperature, and the mixture was refluxed for 3 h. After workup as described in procedure A, the crude reaction mixture was purified by column chromatography (silicagel, ethyl acetate) to afford (3*S*)-3-(3,4-dimethoxyphenylmethyl)-7a-methylperhydropyrrolo[2,*b*][1,3]oxazol-5-ona (**13**), whose data were coincidental to those described in the literature[7b] (15 mg, 14%): ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.05−2.22 (m, 1H), 2.40−2.52 (m, 1H), 2.71 (dd, J = 13.9, 9.5 Hz, 1H)*, 2.67−2.78 (m, 1H), 3.09 (dd, J = 13.9, 5.5 Hz, 1H), 3.79−3.91 (m, 1H)*, 3.85 (s, 3H)*, 3.86 (s, 3H)*, 4.03 (t, J = 7.1 Hz, 1H), 4.15−4.33 (m, 1H), 6.73−6.81 (m, 3H) (*designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 24.9, 33.3, 34.6, 39.7, 55.6, 55.8, 55.9, 71.3, 100, 111.0, 112.1, 129.5, 147.7, 148.8, 178.3.

In successive experiments, the cyclization was carried out without the isolation of this intermediate, as follows: To a solution of oxoamide **10a** (270 mg, 0.49 mmol) in CH_2Cl_2 (15 mL), TFA (1.5 mL, 19.5 mmol) was added at room temperature, and the mixture was refluxed for 1 day. After workup as described in procedure A, the crude reaction mixture was purified by column chromatography to afford a mixture of pyrroloisoquinolines **11d/12d** in a 1:1.3 ratio, determined by ^{1}H NMR (96 mg, 67%).

Synthesis of (5*S*,10b*S*)-5-Benzyloxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]-isoquinolin-3-one (11b) and (5*S*,10b*R*)-5-Benzyloxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (12b). To a solution of oxoamide **10b** (205 mg, 0.52 mmol) in CH_2Cl_2 (15 mL), TFA (1 mL, 12.9 mmol) was added at room temperature, and the mixture was refluxed for 1 day. After workup as described in procedure A, the crude reaction mixture was purified by column chromatography to afford a mixture of pyrroloisoquinolines **11b/12b** in a 1:1 ratio, determined by ^{1}H NMR, that could not be separated. Data of the mixture are given (180 mg, 92%): IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.45 (s, 3H trans diastereomer), 1.49 (s, 3H cis diastereomer), 2.04−2.44 (m, 6H both diastereomers), 2.58−2.70 (m, 2H both diastereomers), 2.89 (dd, J = 16.4, 4.0 Hz, 1H trans diastereomer), 2.97 (dd, J = 16.3, 6.73 Hz, 1H cis diastereomer), 3.06−3.16 (m, 3H both diastereomers), 3.60 (d, J = 6.7 Hz, 2H cis diastereomer), 3.87 (s, 12H both diastereomers), 3.87−3.90 (m, 1H trans diastereomer), 4.19−4.25 (m, 1H trans diastereomer), 4.41 (d, J = 12.0 Hz, 1H trans diastereomer), 4.54 (bs, 2H both diastereomers), 4.59 (d, J = 12.0 Hz, 1H cis diastereomer), 4.63−4.69 (m, 1H cis diastereomer); 6.59 (s, 2H cis diastereomer), 6.60 (s, 1H trans diastereomer), 6.66 (s, 1H trans diastereomer); ^{13}C NMR ($CDCl_3$) 27.8 (trans diastereomer), 29.05 (cis diastereomer), 29.5, 30.8 (both diastereomers), 34.3 (trans diastereomer), 36.3 (cis diastereomer), 46.4 (trans diastereomer), 49.3 (cis diastereomer), 55.8 (trans diastereomer), 55.9 (cis diastereomer), 61.0 (trans diastereomer), 62.5 (cis diastereomer), 68.4, 70.2 (both diastereomers), 72.8 (both diastereomers), 106.4, 111.7 (both diastereomers), 107.2, 112.2 (trans diastereomer), 123.1 (cis diastereomer), 124.8 (trans diastereomer), 127.5, 128.3 (both diastereomers), 133.7, 135 (both diastereomers), 138.1, 138.3 (both diastereomers), 147.8 (both diastereomers), 173.8 (both diastereomers). The diastereomers were separated by GC−MS, and the MS spectra obtained separately, confirming a 1:1 ratio: one isomer MS

(EI) *m/z* (relative intensity) 381 (M^+, 2), 366 (32), 290 (14), 260 (100), 261 (17), 244 (24), 204 (11), 91 (81), 77 (11), 65 (21), 55 (11). Other isomer MS (EI) *m/z* (relative intensity) 381 (M^+, 2), 366 (23), 290 (12), 260 (100), 261 (17), 244 (23), 204 (11), 91 (69), 77 (9), 65 (17), 55 (9).

Synthesis of (5*S*,10b*S*)-5-Methoxymethyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (11c) and (5*S*,10b*R*)-5-Methoxymethyl-10b-methyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo-[2,1-*a*]isoquinolin-3-one (12c). To a solution of oxoamide **10c** (87 mg, 0.26 mmol) in CH_2Cl_2 (15 mL), TFA (1 mL, 12.9 mmol) was added at room temperature, and the mixture was refluxed for 1 day. After workup as described in procedure A, the crude reaction mixture was purified by column chromatography to afford a mixture of pyrroloisoquinolines **11c/12c** in a 1:2 ratio, determined by ^{1}H NMR, that could not be separated. Data of the mixture are given (65 mg, 80%): IR ($CHCl_3$) 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H trans diastereomer), 1.46 (s, 3H cis diastereomer), 1.95−2.38 (m, 6H both diastereomers), 2.53−2.76 (m, 4H both diastereomers), 2.85−299 (m, 2H both diastereomers), 3.27 (s, 3H trans diastereomer), 3.29 (s, 3H cis diastereomer), 3.43 (d, J = 7.1 Hz, 2H cis diastereomer), 3.72 (dd, J = 9.1, 3.7 Hz, 1H trans diastereomer), 3.80 (s, 6H trans diastereomer), 3.82 (s, 6H cis diastereomer), 3.85−3.89 (m, 1H trans diastereomer), 4.04−4.13 (m, 1H trans diastereomer), 4.54−4.63 (m, 1H cis diastereomer), 6.54, 6.57, 6.65 (3s, 6H both diastereomers); ^{13}C NMR ($CDCl_3$) 27.8 (trans diastereomer), 28.9 (cis diastereomer), 29.3, 30.7, 30.8 (both diastereomers), 34.2 (trans diastereomer), 36.4 (cis diastereomer), 45.9 (cis diastereomer), 49.0 (trans diastereomer), 55.7 (both diastereomers), 55.8 (trans diastereomer), 55.9 (cis diastereomer), 60.7 (cis diastereomer), 62.5 (trans diastereomer), 68.4 (trans diastereomer), 72.4 (cis diastereomer), 106.4, 107.2, 111.6, 112.1 (both diastereomers), 122.8, 124.7 (both diastereomers), 133.5, 134.9 (both diastereomers), 147.7, 147.8, 147.9 (both diastereomers), 173.6 (both diastereomers). The diastereomers were separated by GC−MS, and the MS spectra obtained separately, confirming a 1:2 ratio: minor trans isomer: MS (EI) *m/z* (relative intensity) 305 (M^+, 5), 291 (14), 290 (77), 261 (17), 260 (100), 244 (20), 204 (10), 160 (5), 122 (7), 91 (5), 77 (6), 65 (17), 55 (9). Major cis isomer: MS (EI) *m/z* (relative intensity) 305 (M^+, 8), 291 (14), 290 (77), 261 (17), 260 (100), 244 (22), 204 (12), 160 (5), 122 (8), 91 (5), 77 (6), 65 (3), 55 (9).

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Supporting Information Available: Experimental procedures and full characterization data for compounds **3**−**9**. Copies of ^{1}H and ^{13}C NMR spectra of compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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