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Enantiodivergent Synthesis of Pyrrolo[2,1-*a*]isoquinolines Based on Diastereoselective Parham Cyclization and α-Amidoalkylation Reactions

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Enantiodivergent synthesis of C-10b-substituted pyrrolo[2,1-*a*]isoquinolines starting from an enantiomerically pure *N*-phenethylnorborn-5-en-*endo*-2,3-dicarboxyimide **3a**, with a 2-*exo*-hydroxy-10-bornylsulfinyl group as a chiral auxiliary, has been developed. The key transformations are derived from diastereoselective intramolecular cyclization of aryllithiums and α-amidoalkylation reactions, with the ethylidene bridge of the norbornene moiety dictating the stereochemical outcome in both types of reactions. Thus, the organolithium addition−intramolecular α-amidoalkylation sequence on imide **3a** afforded stereoselectively the *R* configuration at C-12b, whereas the tandem Parham cyclization−intermolecular α-amidoalkylation reactions on the corresponding iodinated imide **3b** occurred with complete control of stereoselectivity, leading to the epimer at C-12b. Subsequent reductive removal of the chiral auxiliary and retro-Diels−Alder reaction afforded (10b*S*)- and (10b*R*)-pyrroloisoquinolines **1** in high yields and optical purities (>99% ee).

Introduction

Aryl and heteroaryllithium compounds[1] are interesting building blocks in synthetic organic chemistry because by reaction with carbon electrophiles they produce, together with the formation of a carbon−carbon bond, the transfer of functionality to the electrophilic reagent, and as a result, polyfunctionalized molecules are prepared in one step. Thus, the aromatic metalation−cyclization sequence has become a valuable protocol for the regioselective construction of carbocyclic and heterocyclic systems. However, certain electrophilic groups, such as ketones and imides, do not remain passive during the metalation process, and competitive nucleophilic attack by organolithium base may occur. In these cases, one can take advantage of the very fast rate of metal−halogen exchange[2] compared with nucleophilic addition to carbonyl groups to allow aromatic metalation and subsequent intramolecular cyclization reactions, which are known as Parham cyclizations.[3]

Our work in this field has demonstrated that iodinated *N*-phenethylimides tolerate iodine−lithium exchange, giving rise to the isoquinoline nucleus via a Parham-type cyclization.[4] Since the thus obtained fused isoquinolones possess a α-hydroxylactam function, they represent immediate precursors of bicyclic *N*-acyliminium ions,[5] which can be transformed into a variety of derivatives via intermolecular α-amidoalkylation with different nucleophiles. This has been illustrated in the synthesis of the isoindolo[1,2-*a*]isoquinoline skeleton of nuevamine-type alkaloids.[6] This approach is complementary to the tandem organolithium addition−*N*-acyliminium ion cyclization sequence with *N*-phenethylimides, which also constitutes an effective route to several types of isoquinoline alkaloids. Although intramolecular α-amidoalkylation

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reaction[7] has been widely used in the stereocontrolled synthesis of nitrogen heterocycles, relatively minor effort has been dedicated to stereoselective Parham cyclization. However, its potential as a useful stereoselective cyclization procedure has proven to be extremely interesting.[8] In this context, we have developed a diastereodivergent synthesis of 1,10b-*cis*- and 1,10b-*trans*-thiazolo[4,3-*a*]-isoquinoline systems, based on both types of cyclizations.[9]

On the other hand, pyrrolo[2,1-*a*]isoquinolones[10] have attracted considerable interest because they possess antidepressant,[11] muscarinic agonist,[12] antiplatelet,[13] and anticancer[14] activity. Moreover, they can be used as PET radiotracers for imaging serotonin uptake sites.[15] The importance of these nitrogen heterocycles is further enhanced by their utility as advanced intermediates for the synthesis of alkaloids.[16] In connection with our interest in aromatic lithiation and α-amidoalkylation reactions, our next challenge was to achieve the asymmetric synthesis of the C-10b substituted pyrrolo[2,1-*a*]-isoquinolones **1**.[17] In fact, we have previously reported that *N*-phenethylnorborn-5-en-*endo*-2,3-dicarboxyimide could be considered as a synthetic equivalent of *N*-phenethylmaleimide in the organolithium addition−*N*-acyliminium ion cyclization sequence, as it carries a masked α,β−unsaturated imide moiety, that could be released by a retro-Diels−Alder reaction.[18] Therefore, in contrast to previous approaches,[19] we reasoned that if a chiral auxiliary is appended to the norbornene moiety, enantiomerically pure isoindoloisoquinolines **2** could be obtained. For this purpose, we chose the 2-*exo*-hydroxy-10-bornylsulfinyl group as chiral auxiliary.[20] Thus, our imide precursor would be (2-*exo*-hydroxy-10-bornyl)sulfinylnorbornenedicarboximide **3a** (Figure 1). Organolithium addition would generate a hydroxylactam, whose intramolecular α-amidoalkylation reaction would lead to C-10b-substituted dihydropyrrolisoquinolines (10b*R*)-**1**, after removal of the chiral auxiliary and retro Diels−Alder reaction. The stereochemistry of the stereogenic center on C-10b would be determined in the α-amidoalkylation reaction, in which attack of the aromatic ring onto the *N*-acyliminium ion would occur from the less hindered side. Alternatively, a Parham cyclization on iodinated imide **3b** would afford a 12b-hydroxy isoindoloisoquinoline, precursor of a bicyclic *N*-acyliminium ion. The subsequent intermolecular α-amidoalkylation reaction[21] would occur with complete inversion of configuration at C-12b, which finally would lead to dihydropyrrolisoquinolines (10b*S*)-**1**. We now wish to report the complete details of our investigations,[22] which have culminated in enantiodivergent approaches to the target dihydropyrrolo[2,1-*a*]isoquinolinones **1**.

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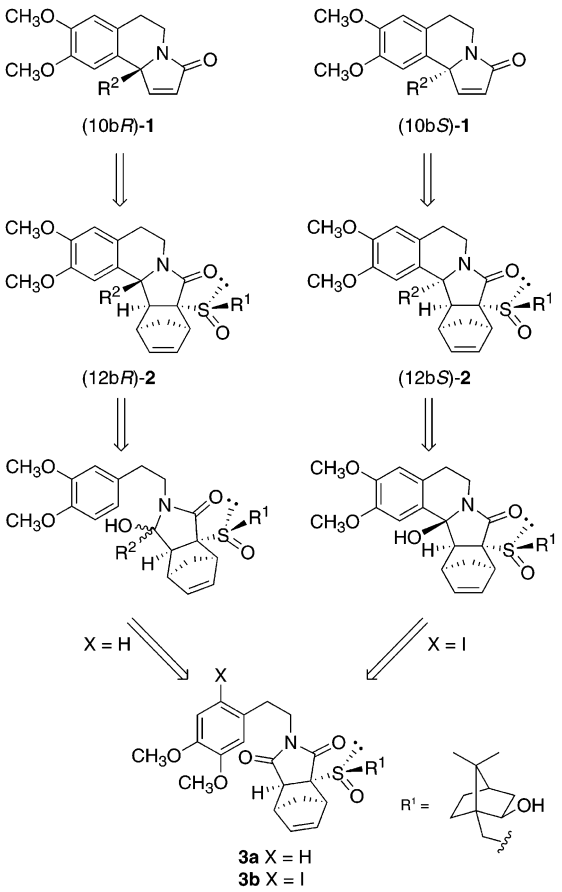
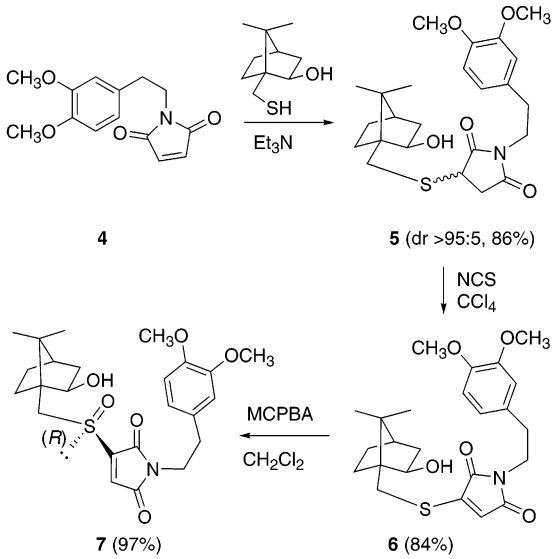


FIGURE 1.

Results and Discussion

Intramolecular α-Amidoalkylation. Preparation of imide **3a** was carried out using the procedure developed by Arai[20] for related substrates, which relies on an asymmetric Diels−Alder reaction[23] of a sulfinylmaleimide. Thus, our first task was the synthesis of *N*-phenethylmaleimide **7**. As shown in Scheme 1, addition of 10-mercaptoisoborneol[24] to maleimide **4**[18b] afforded succinimide **5** in good yield and excellent diastereoselectivity (>95:5 dr). Subsequent treatment with NCS afforded maleimide **6**, which was oxidized with MCPBA to yield sulfinylmaleimide **7** as a single diastereoisomer in quantitative yield. The stereochemical outcome of this type of oxidation has been widely studied.[25] The most accepted proposal is that the oxidation preference is determined by the hydroxyl group of the auxiliary, which participates in a hydrogen bond with the reactive peracid, determining the preferential attack on one of the diastereotopic electron pairs on sulfur. In fact, it has been reported that on similar substrates, oxidation occurs on the same side of the hydroxyl group of the auxiliary, in the preferred conformation.[26] Therefore, in our case, the absolute configuration of the sulfur atom could be assigned as *R*.[27]

SCHEME 1



Once the sulfoxide was efficiently installed, it controlled the stereochemistry of an asymmetric Diels−Alder reaction. Thus, reaction of sulfinylmaleimide **7** with cyclopentadiene in the presence of $ZnCl_2$ afforded sulfinyl norbornenedicarboximide **3a** in excellent yield (93%), as a single diastereoisomer (Scheme 2). In addition, we have observed that when the cycloaddition reaction was carried out in the absence of a Lewis acid, a diastereoisomeric mixture of **3a** and **8** was obtained in a 33:67 ratio (90%). From the stereochemical standpoint, these

(21) Intermolecular α-amidoalkylation reactions of bicyclic *N*-acyliminium ions with different types of nucleophiles (silyl enol ethers, allylsilanes, organocuprates, etc.) usually occur with complete stereoselectivity, as a result of stereoelectronically favored axial attack at the least hindered face. For reviews, see refs 5d,e. For some examples, see: (a) Agami, C.; Amiot, F.; Couty, F.; Dechoux, L.; Kaminsky, C.; Venier, O. *Tetrahedron: Asymmetry* **1998**, *9*, 3955−3958. (b) Dhimane, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhommet, G. *Eur. J. Org. Chem.* **1998**, 1955−1963. (c) Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 275−278. (d) David, M.; Dhimane, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhommet, G. *Heterocycles* **2001**, *55*, 941−949.

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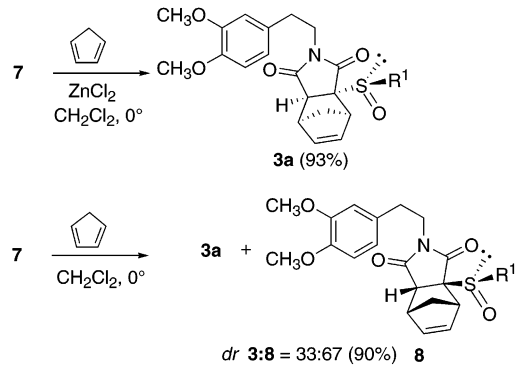
SCHEME 2



results may be explained as shown in Figure 2. In the presence of $ZnCl_2$, formation of a zinc chelate with sulfinyl and carbonyl oxygen atoms would direct the attack of cyclopentadiene from the less hindered side to afford the *endo* product **3a**. In the absence of $ZnCl_2$, a more stable conformer, due to dipole−dipole repulsion, would lead to the formation of *endo* product **8**.

Once the chiral nonracemic imide precursor **3a** had been prepared, we studied the stereoselectivity of the intramolecular α-amidoalkylation route to pyrroloisoquinolines (10b*R*)-**1**. Thus, addition of MeLi or BuLi (2.3 equiv) afforded α-hydroxylactams **9a**,**b** in quantitative yields as single diastereoisomers (Scheme 3). As expected, attack of the organolithium took place regioselectively at the less hindered carbonyl group. Similarly, reduction of imide **3a** was carried out with excess $NaBH_4$ at 0 °C to afford hydroxylactam **9c**. It was not necessary to determine the stereochemistry of α-hydroxylactams **9a**−**c**, as a planar *N*-acyliminium ion was going to be generated in the subsequent cyclization. The next step was the intramolecular α-amidoalkylation reaction. As depicted in Scheme 3, treatment of α-hydroxylactams **9a**−**c** with an excess of TFA at room temperature furnished the expected methaneisoindoloisoquinolines (12b*R*)-**2a**−**c**, together with their derivatives **10a**,**b**, in which trifluoroacetylation of the hydroxyl group of the auxiliary had occurred. Although these products were separated and characterized independently, this side reaction had no relevance in the following steps. Thus, considering the combined yield of both isoquinolines **2** and **10**, the intramolecular α-amidoalkylation reaction

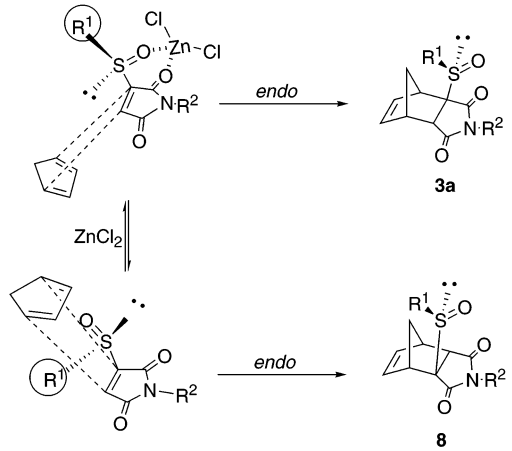
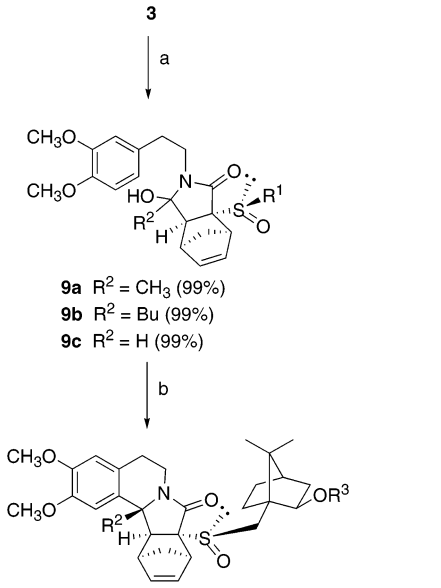


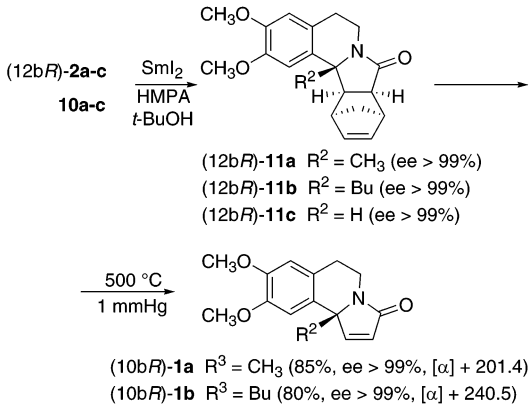
FIGURE 2.

SCHEME 3[a]



[a] Reagents: (a) R^2Li (2.3 equiv), THF, −78 °C (for **a**,**b**); $NaBH_4$, EtOH, 0 °C (for **c**). (b) TFA, CH_2Cl_2, rt.

SCHEME 4



efficiently afforded the isoquinoline system with complete stereocontrol, as isoindoloisoquinolines **2** and **10** were isolated as single diastereoisomers.

Among the methods described in the literature for the reductive desulfinylation, SmI_2 in the presence of HMPA and *t*-BuOH was chosen for the removal of the chiral auxiliary.[28] Thus, (12b*R*)-**2a**,**b** and their *O*-trifluoroacetyl derivatives **10a**,**b** were converted separately into the same isoindoloisoquinolines (12b*R*)-**11a**,**b** in high yields and excellent (>99%) enantiomeric excesses (Scheme 4, Table 1). However, (12b*R*)-**11c** (entry 5) was obtained by desulfinylation of the crude mixture of (12b*R*)-**2c** and **10c**, without purification, due to their instability under chromatographic conditions. It is interesting to point out that

(28) (a) For a general review on applications of samarium diiodide in organic chemistry, see: Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372. (b) For a review on reductions with samarium diiodide, see: Molander, G. A. *Org. React.* **1994**, *46*, 211−305. For related examples of desulfinylation, see refs 20a,b.

TABLE 1. Removal of Chiral Auxiliary: Preparation of (12b*R*)-11

entry	substrate	product	[α]	ee (%)	yield (%)
1	**2a**	(12b*R*)-**11a**	+202.8	>99	83
2	**10a**	(12b*R*)-**11a**		>99	83
3	**2b**	(12b*R*)-**11b**	+200.7	>99	96
4	**10b**	(12b*R*)-**11b**		>99	86
5	**2c**, **10c**	(12b*R*)-**11c**	+176.4	>99	39[a]

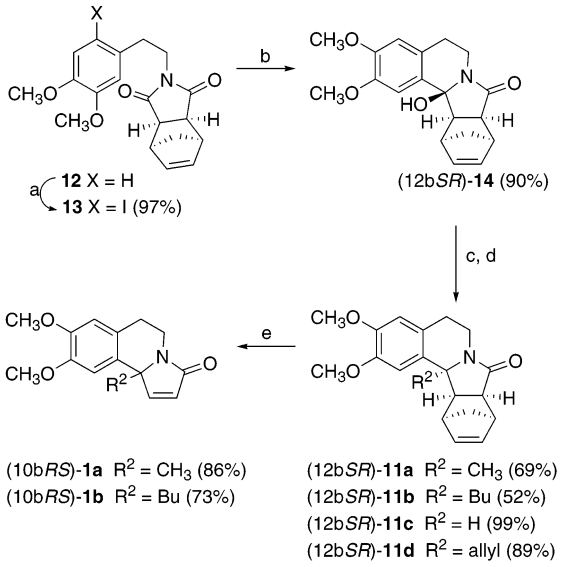
[a] Overall yield of two steps, starting from **9c**.

the reaction is strongly influenced by the amount of HMPA used. Thus, the best results were obtained using an excess of SmI_2 (10 equiv) and HMPA (70 equiv). The yield obtained decreased drastically (from 83 to 47% for **2a**) when less HMPA was used (24 equiv). Spectroscopic data of **11a**−**c** were in agreement with those of the corresponding racemates prepared through an analogous route,[18b] which confirms, on one hand, the *endo* stereochemistry of the norbornene moiety, and on the other, the relative stereochemistry of the substituent on C-12b. Finally, retro-Diels−Alder reaction[29] of **11a**,**b** using a FVP technique produced the α,*β*-unsaturated pyrroloisoquinolines (10b*R*)-**1a**,**b** in high yield and enantiomeric purity, without racemization. Unfortunately, under the conditions tested, **11c** gave only decomposition products.

Tandem Parham Cyclization−Intermolecular α-Amidoalkylation. Once the pyrroloisoquinolines (10b*R*)-**1** had been efficiently prepared, our next concern was the synthesis of enantiomerically pure (10b*S*)-**1** through combined Parham cyclization−intermolecular α-amidoalkylation methodology, followed by retro-Diels Alder reaction. A preliminary study with racemic compounds was carried out to check the diastereoselectivity of this sequence (Scheme 5).

Thus, iodinated imide **13**, obtained regioselectively from **12**,[18b] was submitted to Parham cyclization conditions (*t*-BuLi, −78 °C, 6 h), affording hydroxylactam **14** in excellent yield and with complete diastereoselectivity.[30] Intermolecular α-amidoalkylation reaction was achieved by prior formation of a bicyclic *N*-acyliminium ion by treatment of **14** with $BF_3{\cdot}OEt_2$, followed by alkylation with the corresponding cuprates. Thus, C-12b-substituted isoindoloisoquinolines (12b*SR*)-**11a**,**b** were obtained in good yields as single diastereomers, with complete inversion of configuration at C-12b (Table 2, Scheme 5). In addition, reduction of **14** efficiently furnished (12b*SR*)-**11c** in a stereoselective fashion using $NaBH_4$/TFA, a reagent that has proven to be synthetically valuable for the reduction of hydroxy groups.[31] Other nucleophiles such as allylsilane could also be introduced using this procedure, though in this case it was necessary to use $TiCl_4$ as a Lewis acid (entry 4).[32] Therefore, this approach could be considered as diastereocomplementary to the

SCHEME 5[a]



[a] Reagents: (a) I_2, CF_3CO_2Ag, $CHCl_3$, rt. (b) *t*-BuLi, THF, −78 °C. (c) $BF_3{\cdot}Et_2O$ or $TiCl_4$. (d) $R^2{}_2CuLi$ or $NaBH_4$/TFA. (e) *o*-DCB, reflux.

TABLE 2. Intermolecular α-Amidoalkylation of 14

Lewis acid	conditions	product	yield (%)
$BF_3{\cdot}Et_2O$	MeLi/CuI, −78 °C	(12b*SR*)-**11a**	69
$BF_3{\cdot}Et_2O$	BuLi/CuI, −78 °C	(12b*SR*)-**11b**	52
	$NaBH_4$/TFA, 0 °C to room temperature	(12b*SR*)-**11c**	99
$TiCl_4$	(allyl)TMS, −78 °C to room temperature	(12b*SR*)-**11d**	89

organolithium addition−intramolecular α-amidoalkylation sequence, as methanoisoindoloisoquinolines (12b*SR*)-**11** are epimers at C-12b of those previously reported by us.[18b] To complete the synthesis of racemic pyrroloisoquinolines **1**, retro-Diels−Alder reaction was carried out. However, the application of the FVP procedure described above to (12b*SR*)-**11** only led to decomposition products, and it was necessary to carry out the reaction at reflux of *o*-DCB to obtain the pyrroloisoquinolines; even working under these conditions, only good yields of pyrroloisoquinolines **1a**,**b** were achieved.

Having established that the Parham cyclization−intermolecular α-amidoalkylation sequence was completely stereoselective, we applied this strategy to the enantiomerically pure precursor **3b**, obtained by regioselective iodination of **3a** (Scheme 6). Thus, Parham cyclization of **3b** provided hydroxylactam (12b*S*)-**15** as a single diastereomer, which was submitted to intermolecular α-amidoalkylation with different nucleophiles to afford isoindoloisoquinolines (12b*S*)-**2a**−**d** with complete inversion of configuration at C-12b. Removal of the chiral auxiliary under the previously tested conditions (SmI_2, HMPA, *t*-BuOH) furnished isoindoloisoquinolines (12b*S*)-**11** in good yield and high enantiomeric purity, determined by CSP HPLC (Table 3). Finally, the use of refluxing *o*-DCB to carry out the retro-Diels−Alder

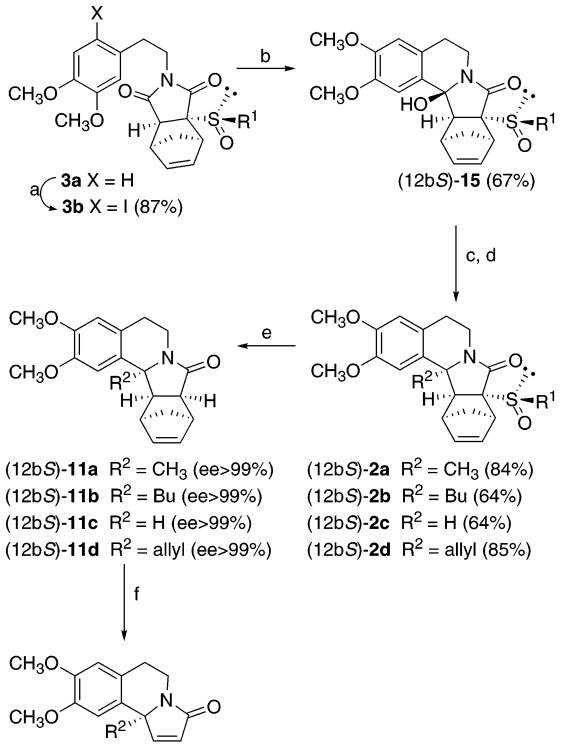
(29) For a review on the concept of transient chirality in the stereoselective synthesis via Retro-Diels−Alder reaction, see: Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **2000**, *99*, 1163−1190.

(30) Hydroxylactam **14** turned out to be unstable under chromatographic purification conditions on silicagel, suffering partial epimerization at C-12b to give the (12b*RS*)-**14′** epimer (see stereochemical discussion and Supporting Information). However, it could be efficiently purified using neutral alumina.

(31) For a review on reduction of alcohols and other functional groups with this reagent, see: Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395. For related examples, see ref 9.

(32) When $BF_3{\cdot}OEt_2$ was used, no α-amidoalkylation reaction was observed. Instead, epimeric hydroxylactam (12b*RS*)-**14′** was recovered as result of water attack to the intermediate *N*-acyliminium ion with inversion of configuration during workup.

SCHEME 6[a]



[a] Reagents: (a) I_2, CF_3CO_2Ag, $CHCl_3$, rt. (b) *t*-BuLi, THF, −78 °C. (c) $BF_3{\cdot}Et_2O$ (d) $R^2{}_2CuLi$ or $NaBH_4$/TFA. (e) SmI_2, HMPA, *t*-BuOH. (f) *o*-DCB, reflux.

TABLE 3. Removal of Chiral Auxiliary: Preparation of (12b*S*)-11

entry	product	[α]	ee (%)	yield (%)
1	(12b*S*)-**11a**	−192.7	>99	79
2	(12b*S*)-**11b**	−220.0	>99	60
3	(12b*S*)-**11c**	−182.4	>99	56
4	(12b*S*)-**11d**	−149.7	>99	60

reaction provided enantiomerically pure pyrroloisoquinolines (10b*S*)-**11a**,**b**. As in the racemic series, under the conditions tested (12b*S*)-**11c**,**d**, gave only decomposition products.

Stereochemical Considerations. Throughout the methodology described above, different types of stereochemical control have been used to achieve the asymmetric synthesis of the targeted pyrroloisoquinolines **1**. Thus, it has been shown that the hydroxyl group in the isoborneol moiety of maleimide **6** controlled the configuration of the sulfoxide of maleimide **7** in the oxidation reaction. Conversely, the sulfinyl group determined the formation of the *endo* adduct **3a** in a chelation-controlled Diels−Alder reaction of **7** with cyclopentadiene. Finally, the ethylidene bridge of the norbornene (and not the chiral auxiliary) moiety controlled the stereochemical outcome of the *N*-acyliminium cyclization of **9a**−**c** to give (12b*R*)-**2a**−**c** as single diastereomers. Thus, the observed stereochemistry is consistent with the aromatic ring approaching the intermediate *N*-acyliminium ion from the less hindered *Si* side, which resulted in an *R* configuration for the newly created stereogenic center at

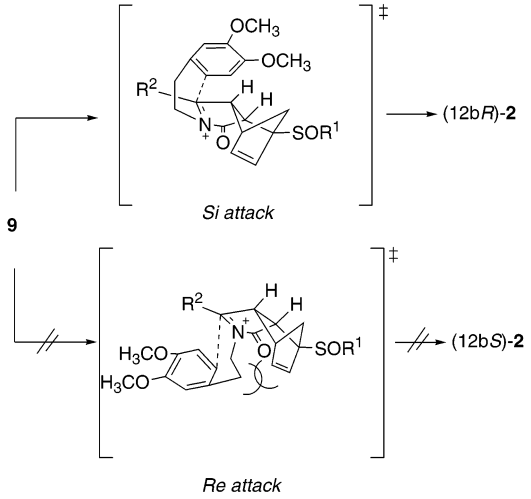
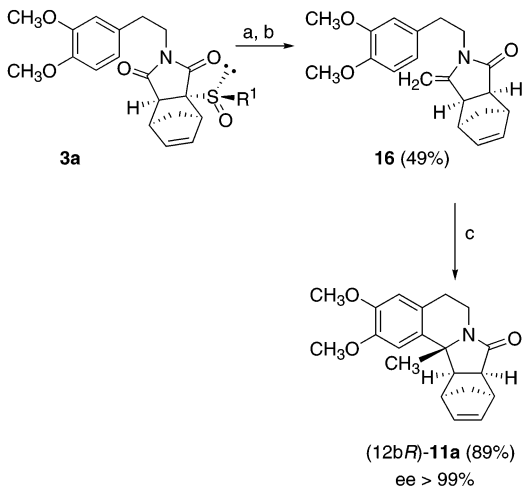


FIGURE 3.

SCHEME 7[a]



[a] Reagents: (a) MeLi, THF, −78 °C. (b) SmI_2, HMPA, *t*-BuOH. (c) TFA, CH_2Cl_2.

C-12b. In this case, the C10−C11 ethylidene bridge of the *endo*-norbornene moiety would block the *Re* side (Figure 3).

To verify that it is the ethylidene bridge that controls the stereochemistry of the cyclization, the chiral auxiliary was removed prior to the cyclization step. Thus, using the organolithium addition conditions (MeLi, THF, −78 °C) on imide **3a** followed by treatment with SmI_2 gave enamide **16**, since the intermediate hydroxylactam dehydrated under reductive desulfinylation conditions. Without further purification, **16** was treated with TFA to provide the isoindoloisoquinoline (12b*R*)-**11a** in good yield and >99% ee, thus confirming our hypothesis.

In a similar fashion, the C10−C11 ethylidene bridge controls the stereochemical outcome of the Parham cyclization−intermolecular α-amidoalkylation sequence. Thus, as depicted in Figure 4, the attack of the aryllithium intermediate would occur from the less hindered *Si* side of the carbonyl group, resulting in an *S* configuration for C-12b. Hydroxylactam **15** is subsequently treated with a Lewis acid, resulting in the formation of a bicyclic *N*-acyliminium intermediate. The attack of the incoming nucleophile would occur from the face opposite

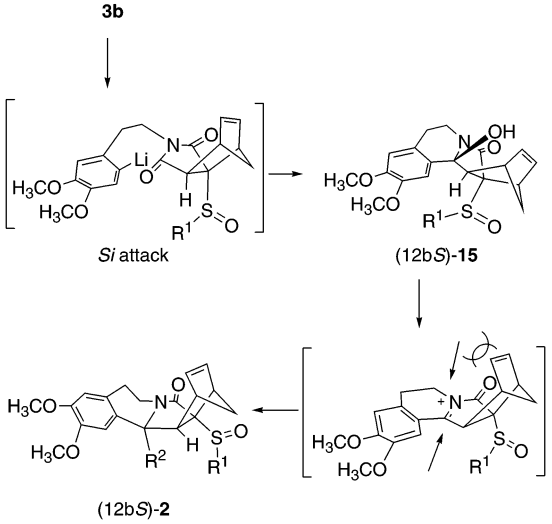


FIGURE 4.

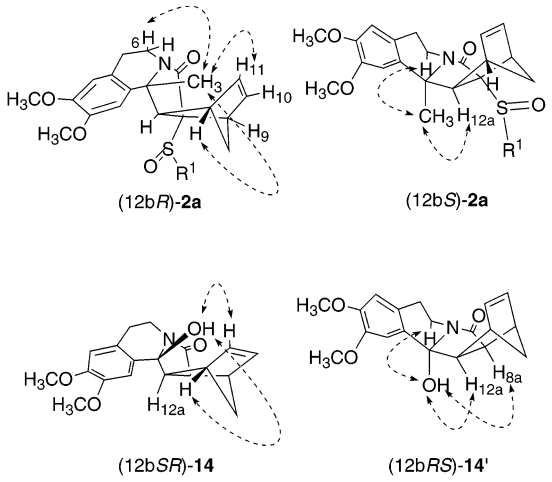


FIGURE 5. Selected NOE enhancements.

to the C10−C11 ethylidene bridge, resulting in an *S* configuration for the stereogenic center at C-12b.

Nuclear Overhauser effect difference spectroscopy and $^1H-^1H$ decoupling experiments confirmed the stereochemistry of all the isoquinoline derivatives. The most significant results obtained with epimeric isoindoloisoquinolines (12b*S*)-**2a** and (12b*R*)-**2a** are shown in Figure 5. For instance, isoindoloisoquinoline (12b*R*)-**2a** demonstrated an enhancement of the H-11, H-12, and H-6ax signals upon irradiation on C-12b methyl hydrogens and vice versa. This fact, together with the absence of NOE between C-12b methyl hydrogens and the protons H-12a, confirms an *R* configuration for C-12b. On the other hand, epimeric (12b*R*)-**2a** showed an enhancement of H-12a and H-6ax upon irradiation of C-12b methyl hydrogens, confirming an *S* configuration for C-12b. Analogous results were obtained with the epimeric hydroxylactams **14** and **14′**.[30] Thus, an enhancement of the signals of *endo* protons H-8a and H-12a was observed upon irradiation on the hydroxyl proton of (12b*RS*)-**14′**, whereas on (12b*SR*)-**14**, the signal of hydroxyl proton showed a NOE enhancement upon irradiation on H-11 and H-12 protons, and vice versa. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry in each case.

In summary, we have developed a stereodivergent route to enantiomerically pure C-10b-substituted 5,6-dihydropyrrolo[2,1-*a*]isoquinolines of *R* and *S* absolute configuration via diastereoselective intra- or intermolecular α-amidoalkylation reactions of α-hydroxylactams. The strategy has as a starting point the preparation of an enantiomerically pure *N*-phenethylnorborn-5-en-*endo*-2,3-dicarboxyimide, with a 2-*exo*-hydroxy-10-bornylsulfinyl group as a chiral auxiliary. Thus, the chiral auxiliary controls the configuration at sulfur, which, in turn, determines the formation of the *endo* adduct in a chelation-controlled Diels−Alder reaction. The application of the organolithium addition−intramolecular α-amidoalkylation sequence on this imide give isoindoloisoquinolines of *R* configuration on C-12b, while (12b*S*)-epimers are obtained via a Parham cyclization−intermolecular α-amidoalkylation sequence. In both sequences, the ethylidene bridge of the norbornene moiety is responsible for the stereochemical control. After reductive elimination of the chiral auxiliary and retro-Diels−Alder reaction (10b*S*)- and (10b*R*)-pyrroloisoquinolines are obtained in high yields and optical purities (>99% ee).

Experimental Section

Intramolecular α-Amidoalkylation. Synthesis of Isoindoloisoquinolines (12*R*)-2a−c. (8a*R*,9*S*,12*R*,12a*S*,12b*R*)-(+)-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-Hydroxy-7,7-dimethylbicyclo-[2.2.1]heptan-1-yl)methylsulfinyl]-2,3-dimethoxy-12b-methyl-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*R*)-2a]. To a solution of compound **3a** (1.15 g, 2.2 mmol) in dry THF (45 mL) was added MeLi (7.6 mL of a 0.66 M solution in pentane, 5 mmol) 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 CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford hydroxy lactam **9a** (1.18 g, 99%), which was used without further purification. To a solution of the thus obtained hydroxy lactam **9a** (203 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) was added TFA (2.5 mL, 32.4 mmol), and the resulting solution was stirred at room temperature 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 flash column chromatography (silicagel, 60% hexane/ethyl acetate), yielding two fractions. **2a** (101 mg, 51%): $[\alpha]^{23}_D$ + 117.9 (0.5, $CHCl_3$); mp (Et_2O) 93−94 °C; IR ($CHCl_3$) 3400, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60 (s, 3H), 1.04 (s, 3H), 1.23−1.25 (m, 2H), 1.48 (s, 3H), 1.60−1.72 (m, 6H), 2.1 (d, J = 8.3 Hz, 1H), 2.54 (dd, J = 16.2, 4.4 Hz, 1H), 2.75 (d, J = 13.1 Hz, 1H), 2.81−2.92 (m, 1H), 3.07 (ddd, J = 13.1, 12.3, 4.8 Hz, 1H), 3.21 (d, J = 13.1 Hz, 1H), 3.32 (d, J = 3.6 Hz, 1H), 3.37 (s, 1H), 3.74−3.78 (m, 2H), 3.81−3.89 (m, 1H)*, 3.82 (s, 3H)*, 3.89 (s, 3H)*, 4.18 (dd, J = 13.1, 6.3 Hz, 1H), 6.33−6.37 (m, 1H), 6.45−6.48 (m, 2H), 6.60 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.4, 26.5, 27.0, 27.6, 30.5, 35.4, 38.3, 44.9, 45.8, 46.5, 48.1, 48.7, 50.2, 51.0, 52.5, 55.7, 56.2, 60.6, 75.4, 76.8, 107.4, 112.0, 124.1, 135.3, 135.8, 139.2, 147.9, 148.0, 168.4; MS (EI) *m*/*z* (rel intensity) 526 (M^+ + 1, 2), 525 (M^+, 1), 373 (47), 325 (19), 324 (23), 310 (16), 308 (25), 307 (100), 292 (21), 290 (27), 258 (26), 206 (16), 164 (8), 119 (35), 91 (26). Anal. Calcd for

$C_{30}H_{39}NO_5S$: C, 68.54; H, 7.47; N, 2.66. Found: C, 68.81; H, 7.42; N, 2.70. **10a** (38 mg, 16%): $[\alpha]^{23}_D$ + 95.7 (1, $CHCl_3$); IR ($CHCl_3$) 1780, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.04 (s, 3H), 1.48 (s, 3H), 1.23−1.25 (m, 2H), 1.58−1.92 (m, 5H), 2.1 (d, J = 8.3 Hz, 1H), 2.47 (dd, J = 16.0, 3.8 Hz, 1H), 2.79 (ddd, J = 16.0, 12.3, 6.5 Hz, 1H), 3.03 (td, J = 12.6, 4.4 Hz, 1H), 3.12−3.23 (m, 2H), 3.28 (s, 1 H), 3.52 (d, J = 3.6 Hz, 1H), 3.59 (s, 1H), 3.82−3.88 (m, 1H)*, 3.82 (s, 3H)*, 3.89 (s, 3H)*, 4.10 (dd, J = 13.1, 6.1 Hz, 1H), 5.05 (dd, J = 7.4, 2.8 Hz, 1H), 6.31−6.34 (m, 1H), 6.45−6.49 (m, 2H), 6.60 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 19.6, 20.0, 26.3, 26.7, 27.6, 29.9, 35.7, 38.5, 44.8, 45.3, 45.6, 46.7, 49.2, 50.2, 50.4, 52.6, 55.7, 56.2, 60.7, 75.7, 82.0, 107.6, 111.7, 110.7, 124.0, 135.4, 136.2, 139.7, 147.8, 147.9, 155.6, 169.2; MS (EI) m/z (rel intensity) 621 (M^+, 6), 325 (5), 324 (100), 308 (17), 307 (18), 290 (12), 258 (15), 206 (15), 164 (13), 135 (10), 119 (52), 93 (11), 91 (20).

(8a*R*,9*S*,12*R*,12a*S*,12b*R*)-(+)-12b-Butyl-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)-methylsulfinyl]-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*R*)-2b]. To a solution of compound **3a** (969 mg, 1.7 mmol) in dry THF (37 mL) was added *n*-BuLi (3.1 mL of a 1.44 M solution in hexane, 4.3 mmol) at −78 °C. The resulting mixture was stirred at this temperature for 6 h, quenched by the addition of saturated NH_4Cl (15 mL), and allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford hydroxy lactam **9b** (1.05 g, 99%), which was used without further purification. To a solution of the thus obtained hydroxy lactam **9b** (844 mg, 1.14 mmol) in CH_2Cl_2 (40 mL) was added TFA (10 mL, 130 mmol), and the resulting solution was stirred at room temperature 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 flash column chromatography (silicagel, 60% hexane/ethyl acetate), yielding two fractions. **2b** (187 mg, 21%): $[\alpha]^{23}_D$ + 660 (0.05, $CHCl_3$); IR ($CHCl_3$) 3408, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (s, 3H), 0.87 (t, J = 6.5 Hz, 3H), 1.05 (s, 3H), 1.19−1.41 (m, 8H), 1.66−1.75 (m, 6H), 2.08 (d, J = 8.7 Hz, 1H), 2.61 (dd, J = 17.2, 5.3 Hz, 1H), 2.76−2.94 (m, 2H), 3.19−3.37 (m, 2H), 3.41−3.47 (m, 2H), 3.73 (m, 1H), 3.82 (s, 3H)*, 3.88 (s, 3H)*, 3.83−3.85 (m, 2H)*, 4.18 (dd, J = 13.5, 7.9 Hz, 1H), 6.34−6.36 (m, 1H), 6.45−6.47 (m, 1H), 6.51 (s, 1H), 6.68 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.9, 20.4, 23.3, 26.9, 27.0, 28.0, 30.5, 35.4, 37.9, 38.3, 44.9, 45.6, 46.3, 48.1, 48.9, 50.3, 51.0, 51.5, 55.6, 56.3, 63.2, 75.4, 76.8, 108.7, 112.0, 125.3, 132.3, 135.9, 138.9, 147.9, 149.9, 168.7; MS (EI) m/z (rel intensity) 510 (M^+ − Bu, 5), 416 (20), 415 (75), 366 (45), 350 (21), 349 (94), 310 (33), 309 (25), 301 (27), 292 (100), 164 (35), 119 (52), 93 (26), 55 (25). **10b** (604 mg, 57%): $[\alpha]^{23}_D$ +100.9 (0.03, $CHCl_3$); IR ($CHCl_3$) 1783, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86−0.98 (m, 6H), 1.05 (s, 3H), 1.11−1.42 (m, 6H), 1.57−1.93 (m, 7H), 2.07 (d, J = 8.3 Hz, 1H), 2.5 (dd, J = 16.8, 5.3 Hz, 1H), 2.76−2.90 (m, 1H), 3.10−3.27 (m, 4H), 3.57−3.58 (m, 2H), 3.84 (s, 3H)*, 3.90 (s, 3H)*, 3.84−3.90 (m, 1H)*, 4.10 (dd, J = 13.5, 7.3 Hz, 1H), 5.05 (dd, J = 7.5, 2.7 Hz, 1H), 6.30−6.33 (m, 1H), 6.45−6.48 (m, 2H), 6.70 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.6, 20.1, 23.3, 26.6, 26.8, 27.9, 29.8, 35.6, 37.6, 38.5, 44.7, 45.1, 45.5, 46.6, 49.2, 50.2, 50.3, 51.3, 55.6, 56.1, 63.3, 75.6, 82.1, 108.8, 111.7, 111.0, 125.1, 132.4, 136.3, 139.3, 146.9, 147.8, 155.9, 169.4; MS (EI) m/z (rel intensity) 663 (M^+, <1), 569 (14), 568 (36), 415 (84), 366 (84), 350 (23), 349 (100), 309 (40), 308 (75), 292 (98), 276 (20), 248 (33), 244 (24), 119 (52), 91 (47), 57 (10), 55 (24).

(8a*R*,9*S*,12*R*,12a*S*,12b*R*)-(+)-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methylsulfinyl]-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*R*)-2c]. To a solution of the imide **3a** (160 mg, 0.3 mmol) in dry EtOH (12 mL) was added $NaBH_4$ (214 mg, 5.6 mmol) in portions at 0 °C. The resulting mixture was stirred at this temperature for 1 h and allowed to warm to room temperature. After 4 h, the reaction was quenched by the addition of saturated NH_4Cl (10 mL). 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 lactam **9c** (148 mg, 92%), which was used without further purification. To a solution of the thus obtained hydroxy lactam **9c** (148 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) was added TFA (4 mL, 52 mmol), and the resulting solution was stirred at room temperature 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 flash column chromatography (silicagel, ethyl acetate), yielding two fractions: **2c** (45 mg, 26%) and **10c** (24.6 mg, 17%). These isoindoloisoquinolines were too unstable to be fully characterized and in subsequent experiments were submitted to reductive desulfinylation without purification.

Parham Cyclization of Iodinated Imide 3b. Synthesis of (8a*R*,9*S*,12*R*,12a*S*,12b*S*)-(+)-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methylsulfinyl]-12b-hydroxy-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one (15). To a solution of the imide **3b** (121 mg, 0.18 mmol) in dry THF (15 mL) was added *t*-BuLi (0.63 mL of a 1.17 M solution in pentane, 0.74 mmol) at −78 °C. The resulting mixture was stirred at this temperature for 5 h, quenched by the addition of saturated NH_4Cl (5 mL), and allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford hydroxylactam **15**, which was crystallized from Et_2O (66 mg, 67%): $[\alpha]^{23}_D$ + 203.3 (0.4, $CHCl_3$); mp (Et_2O) 198−200 °C; IR ($CHCl_3$) 3667, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.41 (s, 3H), 0.98 (s, 3H), 1.15−1.28 (m, 3H), 1.58−1.73 (m, 5H), 2.10 (d, J = 9.1 Hz, 1H), 2.31 (d, J = 12.7 Hz, 1H), 2.60 (dd, J = 16.4, 4.2 Hz, 1H), 2.75−2.88 (m, 2H), 3.12−3.27 (m, 3H), 3.41−3.47 (m, 1H), 3.70−3.77 (m, 2H), 3.82 (s, 3H)*, 3.91 (s, 3H)*, 3.82−3.90 (m, 1H)*, 4.16 (dd, J = 13.3, 5.7 Hz, 1H), 6.27−6.29 (m, 1H), 6.30−6.56 (m, 2H), 6.84 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 20.0, 20.1, 27.0, 28.0, 30.6, 34.5, 38.3, 44.7, 46.3, 46.7, 47.9, 48.1, 49.1, 51.0, 52.8, 55.8, 56.2, 75.4, 76.7, 84.9, 107.8, 111.7, 125.9, 130.8, 133.9, 140.2, 148.6, 149.5, 166.5; MS (EI) m/z (rel intensity) 528 (M^+ + 1, 1), 527 (M^+, 1), 309 (100), 375 (47), 376 (10), 327 (26), 325 (73), 292 (19), 291 (31). Anal. Calcd for $C_{29}H_{37}NO_6S$: C, 66.01; H, 7.07; N, 2.65. Found: C, 66.07; H, 7.01; N, 2.40.

Intermolecular α-Amidoalkylation Reactions of 15. Synthesis of Isoindoloisoquinolines (12*S*)-2a−d. (8a*R*,9*S*,12*R*,12a*S*,12b*S*)-(−)-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methylsulfinyl]-2,3-dimethoxy-12b-methyl-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*S*)-2a]. MeLi (1.42 mL of a 1.6 M solution in pentane, 2.28 mmol) was added at 0 °C to suspension of CuI (217 mg, 1.14 mmol) in dry THF (10 mL), and the solution was stirred at this temperature for 1 h. A solution of the hydroxylactam **15** (100 mg, 0.19 mmol) in dry THF (10 mL) at 0 °C was treated with $BF_3{\cdot}Et_20$ (0.07 mL, 0.57 mmol), and after 30 min, the reaction mixture was added via cannula over the organocuprate previously formed at 0 °C. The resulting mixture was stirred at this temperature for 3 days, quenched by the addition of NH_3 (12% aq, 10 mL), and allowed to warm to room temperature.

The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 15 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude reaction mixture was purified by flash column chromatography (silicagel, ethyl acetate) to afford (12b*S*)-**2a** (85 mg, 84%): $[\alpha]^{23}_D$ −101.6 (1.1, $CHCl_3$); mp (pentane) 114−115 °C; IR ($CHCl_3$) 3421, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.17−1.27 (m, 4H), 1.38−1.85 (m, 10H), 2.04 (d, J = 8.3 Hz, 1H), 2.49−2.71 (m, 2H), 2.89−3.01 (m, 2H), 3.39−3.56 (m, 4H), 3.86 (s, 3H)*, 3.91 (s, 3H)*, 3.86−3.94 (m, 1H)*, 4.04−4.15 (m, 2H), 5.14 (dd, J = 5.1, 2.6 Hz, 1H), 6.04 (dd, J = 5.1, 3.2 Hz, 1H), 6.51 (s, 1H), 6.64 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.5, 27.1, 28.5, 30.8, 32.4, 35.3, 38.5, 45.0, 46.3, 46.5, 48.3, 48.6, 49.5, 51.0, 53.7, 55.8, 56.1, 61.2, 75.6, 77.2, 109.4, 111.0, 125.8, 130.7, 135.3, 138.3, 147.5, 147.9, 166.5; MS (EI) *m*/*z* (rel intensity) 526 (M^+ + 1, 5), 373 (31), 325 (28), 324 (28), 310 (44), 309 (14), 308 (26), 307 (100), 292 (11), 290 (44), 258 (21), 164 (6). Anal. Calcd for $C_{30}H_{39}NO_5S$: C, 68.54; H, 7.48; N, 2.66. Found: C, 68.49; H, 7.42; N, 2.41.

(8a*R*,9*S*,12*R*,12a*S*,12b*S*)-(−)-12b-Butyl-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methylsulfinyl]-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*S*)-2b]. *n*-BuLi (1.42 mL of a 1.18 M solution in hexane, 3.51 mmol) was added at 0 °C to suspension of CuI (333 mg, 1.75 mmol) in dry THF (10 mL), and the solution was stirred at this temperature for 1 h. A solution of the hydroxylactam **15** (154 mg, 0.29 mmol) in dry THF (10 mL) at 0 °C was treated with $BF_3{\cdot}Et_20$ (0.11 mL, 0.88 mmol), and after 30 min, the reaction mixture was added via cannula over the organocuprate previously formed at 0 °C. The resulting mixture was stirred at this temperature for 3 days, quenched by the addition of NH_3 (12% aq, 15 mL), and allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 15 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude reaction mixture was purified by flash column chromatography (silicagel, ethyl acetate) to afford (12b*S*)-**2b** as an oil (105 mg, 64%): $[\alpha]^{23}_D$ −94.2 (0.26, $CHCl_3$); IR ($CHCl_3$) 3421, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H), 0.92 (s, 3H), 1.13−1.24 (m, 6H), 1.34−1.95 (m, 9H), 1.97−2.06 (m, 3H), 2.49−2.70 (m, 2H), 2.94−3.10 (m, 2H), 3.40−3.60 (m, 4H), 3.88 (s, 3H)*, 3.92 (s, 3H)*, 3.86−3.90 (m, 1H)*, 4.06−4.08 (m, 2H), 4.15 (dd, J = 12.7, 5.5 Hz, 1H), 5.05 (dd, J = 5.5, 2.4 Hz, 1H), 5.90 (dd, J = 5.1, 3.2 Hz, 1H), 6.5 (s, 1H), 6.6 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.9, 20.4, 23.0, 27.1, 27.5, 28.5, 30.9, 36.8, 38.5, 45.0, 46.1, 46.5, 46.8, 48.3, 48.6, 49.6, 51.0, 53.0, 55.7, 56.1, 64.5, 75.3, 77.1, 109.4, 111.0, 126.5, 129.8, 134.6, 138.9, 147.4, 147.8, 167.9; MS (EI) *m*/*z* (rel intensity) 568 (M^+ + 1, 13), 511 (10), 510 (28), 349 (33), 366 (15), 309 (33), 308 (100), 292 (51), 291 (29), 164 (22), 109 (13), 107 (17), 93 (22), 91 (17), 57 (12).

(8a*R*,9*S*,12*R*,12a*S*,12b*S*)-(−)-8a-[(1*S*,2*R*,4*R*,S*R*)-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methylsulfinyl]-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*S*)-2c]. A solution of the hydroxylactam **15** (118 mg, 0.22 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C to a mixture of $NaBH_4$ (70 mg, 1.81 mmol) and TFA (0.4 mL, 5.37 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched by the addition of NaOH (10% aq, 10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude reaction mixture was purified by flash column chromatography (silicagel, ethyl acetate) to afford (12b*S*)-**2b** as a white solid (73 mg, 64%): $[\alpha]^{23}_D$ −126.6 (0.75, $CHCl_3$); mp (AcOEt) 123−125 °C; IR ($CHCl_3$) 3425, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 3H), 1.16−1.27 (m, 4H), 1.44−1.84 (m, 7H), 2.03 (d, J = 8.7 Hz, 1H), 2.49−2.70 (m, 2H), 2.84 (ddd, J = 12.7, 11.5, 4.7 Hz, 1H), 2.98 (s, 1H), 3.31 (d, J = 13.1 Hz, 1H), 3.42 (d, J = 13.1 Hz, 1H), 3.61−3.66 (m, 2H), 3.86 (s, 3H)*, 3.90 (s, 3H)*, 3.86−3.90 (m, 1H)*, 4.04−4.22 (m, 2H), 4.97 (d, J = 8.7 Hz, 1H), 5.23−5.26 (m, 1H), 6.07 (dd, J = 4.8, 3.2 Hz, 1H), 6.55 (s, 1H), 6.63 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.5, 27.1, 28.2, 30.9, 38.0, 38.5, 45.0, 45.4, 45.9, 46.5, 48.2, 48.6, 49.2, 51.0, 55.7, 55.8, 56.0, 76.0, 77.1, 108.6, 111.4, 125.5, 126.5, 135.2, 138.0, 147.8, 147.9, 167.3; MS (EI) *m*/*z* (rel intensity) 512 (M^+ + 1, 6), 359 (22), 311 (22), 310 (88), 309 (100), 294 (25), 293 (90), 277 (12), 276 (33), 245 (12), 244 (32), 192 (4). Anal. Calcd for $C_{29}H_{37}NO_5S$: C, 68.07; H, 7.29; N, 2.74. Found: C, 67.98; H, 7.27; N, 2.69.

(8a*R*,9*S*,12*R*,12a*S*,12b*S*)-(−)-8a-[(1*S*,2*R*,4*R*,S*R*)-12b-Allyl-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)-methylsulfinyl]-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*S*)-2d]. Allylmagnesium chloride (1.1 mL of a 2 M solution in THF, 2.2 mmol) was added at −20 °C to a suspension of CuI (207 mg, 1.09 mmol) in dry THF (10 mL), and the solution was stirred at this temperature for 20 min. A solution of the hydroxylactam **15** (41 mg, 0.08 mmol) in dry THF (5 mL) was treated with $BF_3{\cdot}Et_20$ (0.03 mL, 0.23 mmol), and after 30 min, the reaction mixture was added via cannula over the organocuprate previously formed at −20 °C. The resulting mixture was stirred at this temperature for 30 min and then at 0 °C for 5 days. The reaction was quenched by the addition of NH_3 (12% aq, 10 mL) and allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude reaction mixture was purified by flash column chromatography (silicagel, ethyl acetate) to afford (12b*S*)-**2c** as an oil (36 mg, 85%): $[\alpha]^{23}_D$ −134.4 (0.68, $CHCl_3$); IR ($CHCl_3$) 3400, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.16 (s, 3H), 1.22−2.05 (m, 8H), 2.03 (d, J = 8.3 Hz, 1H), 2.48−3.20 (m, 6H), 3.37−3.54 (m, 3H), 3.64 (s, 1H), 3.85 (s, 3H)*, 3.90 (s, 3H)*, 3.85−3.90 (m, 1H)*, 4.04−4.11 (m, 2H), 5.04−5.15 (m, 3H), 5.57−5.70 (m, 1H), 5.98 (dd, J = 5.1, 3.2 Hz, 1H), 6.51 (s, 1H), 6.65 (s, 1H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.4, 27.1, 28.4, 30.8, 36.4, 38.5, 45.0, 46.5, 46.7, 48.3, 48.6, 49.5, 50.1, 51.0, 52.2, 55.7, 56.1, 64.1, 75.3, 77.1, 109.6, 111.0, 119.9, 126.6, 128.9, 132.9, 134.7, 138.8, 147.3, 147.9, 167.7; MS (EI) *m*/*z* (rel intensity) 510 (M^+ − allyl, 22), 358 (10), 309 (31), 308 (100), 292 (33), 291 (3), 260 (8), 164 (1).

Removal of Chiral Auxiliary by Reductive Desulfinylation. Synthesis of (12b*R*)-(+)-11a−c and (12b*S*)-(−)-11a−d. General Procedure. To a solution of isoindolisoquinolines (12b*R*)-(+)-**2** or (12b*S*)-(−)-**2** (1 mmol) in dry THF (5 mL) were added SmI_2 (10 mmol), *t*-BuOH (10 mmol), and HMPA (70 mmol) sequentially at room temperature. The resulting mixture was stirred at this temperature for 1.5 h (for the 12b*R* series) or 2.5 h (for the 12b*S* series) and quenched by the addition of cold HCl (15 mL of a 1 M solution). The organic layer was separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (3 × 10 mL) and with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography afforded isoindoloisoquinolines (12b*R*)-(+)-**11a**−**c** or (12b*S*)-(−)-**11a**−**d**.

(8a*S*,9*S*,12*R*,12a*S*,12b*R*)-(+)-2,3-Dimethoxy-12b-methyl-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one [(12b*R*)-11a]. According to General Procedure, (12b*R*)-(+)-**2a** (100 mg, 0.2 mmol) was treated sequentially with SmI_2 (20 mL of a 0.1 M solution in THF, 2 mmol), *t*-BuOH (0.2 mL, 2.1 mmol), and HMPA (2.5 mL, 15 mmol). After workup, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*R*)-**11a** (59 mg, 83%), whose spectroscopic data are identical to those previously reported for the racemate:[18b] $[\alpha]^{23}_D$ + 202.8 (1.43, $CHCl_3$); mp (Et_2O) 183−184 °C [lit. racemate[18b]

(Et_2O) 158−160 °C]; ^1H NMR ($CDCl_3$) δ 1.36 (d, J = 8.2 Hz, 1H), 1.37 (s, 3H), 1.55 (d, J = 8.2 Hz, 1H), 2.29−2.42 (m, 1H), 2.80−2.98 (m, 2H), 3.00−3.08 (m, 2H), 3.10−3.20 (m, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 4.01−4.10 (m, 1H), 6.10−6.16 (m, 2H), 6.41 (s, 1H), 6.59 (s, 1H) (* designates partially overlapped signals). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.5 mL/min; t_r[(12b*R*)-**11a**] = 18.4 min (>99%); t_r(*ent*) = 22.4 min (<1%).

(8a*S*,9*S*,12*R*,12a*S*,12b*R*)-(+)-12b-Butyl-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]-isoquinolin-8-one [(12b*R*)-11b]. According to General Procedure, (12b*R*)−(+)-**2b** (129 mg, 0.2 mmol) was treated sequentially with SmI_2 (20 mL of a 0.1 M solution in THF, 2 mmol), *t*-BuOH (0.2 mL, 2.1 mmol), and HMPA (2.5 mL, 15 mmol). After work up, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*R*)-**11b** (69 mg, 86%), whose spectroscopic data are identical to those previously reported for the racemate:[18b] $[\alpha]^{23}_D$ + 200.7 (0.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.43 (d, J = 8.3 Hz, 1H), 1.18−1.53 (m, 4H), 1.62 (d, J = 8.3 Hz, 1H), 1.73−1.85 (m, 2H), 2.78 (dd, J = 16.4, 6.3 Hz, 1H), 3.06 (ddd, J = 13.4, 10.2, 9.5 Hz, 1H), 3.30−3.40 (m, 3H), 3.41 (broad s, 1H), 3.48−3.51 (m, 1H), 3.86 (s, 3H), 3.92 (s, 3H), 4.17 (dd, J = 13.4, 7.4 Hz, 1H), 6.20 (dd, J = 5.5, 2.5 Hz, 1H), 6.31 (dd, J = 5.5, 2.1 Hz, 1H), 6.61 (s, 1H), 6.76 (s, 1H). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.5 mL/min; t_r[(12b*R*)-**11b**] = 12.5 min (>99%); t_r(*ent*) = 17.5 min (<1%).

(8a*S*,9*S*,12*R*,12a*S*,12b*R*)-(+)-2,3-Dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]-isoquinolin-8-one [(12b*R*)-11c]. According to General Procedure, a mixture of isoindoloisoquinolines (12b*R*)-(+)-**2c** and **10c** (124 mg, 0.22 mmol) (obtained from the intramolecular α-amidoalkylation reaction and used without further purification) was treated sequentially with SmI_2 (22 mL of a 0.1 M solution in THF, 2.2 mmol), *t*-BuOH (0.2 mL, 2.1 mmol), and HMPA (2.8 mL, 16.4 mmol). After workup, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*R*)-**11c** (22 mg, 39% overall for two steps): $[\alpha]^{23}_D$ + 176.4 (0.1, $CHCl_3$); mp oil; mp (racemate, AcOEt) 155−156 °C; ^1H NMR ($CDCl_3$) δ 1.47 (d, J = 8.3 Hz, 1H), 1.68 (d, J = 8.3 Hz, 1H), 2.50−2.60 (m, 1H), 2.78−2.93 (m, 3H), 3.12 (dd, J = 9.4, 4.1 Hz, 1H), 3.28 (broad s, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 4.03 (broad s, 1H), 4.16−4.29 (m, 1H), 6.23−6.26 (m, 1H), 6.3−6.32 (m, 1H), 6.54 (s, 1H), 6.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.4, 36.9, 44.2, 45.4, 46.2, 50.9, 51.0, 55.6, 55.8, 59.1, 107.3, 111.3, 125.3, 130.0, 133.9, 136.5, 147.4, 147.6, 172.7; MS (EI) *m*/*z* (rel intensity) 312 (M^+ + 1, 1), 311 (M^+, 4), 246 (15), 245 (100), 244 (44), 217 (6), 216 (7), 214 (3), 200 (4). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.98; H, 6.78; N, 4.10. The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 15% hexane/2-propanol, 0.4 mL/min; t_r[(12b*R*)-**11c**] = 30 min (>99%); t_r(*ent*) = 46.6 min (<1%).

(8a*S*,9*S*,12*R*,12a*S*,12b*S*)-(−)-2,3-Dimethoxy-12b-methyl-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]-isoquinolin-8-one [(12b*S*)-11a]. According to General Procedure, (12b*S*)-(−)-**2a** (71 mg, 0.13 mmol) was treated sequentially with SmI_2 (13.5 mL of a 0.1 M solution in THF, 1.35 mmol), *t*-BuOH (0.13 mL, 1.3 mmol), and HMPA (1.38 mL, 8.1 mmol). After workup, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*S*)-**11a** (35 mg, 79%) as an oil: $[\alpha]^{23}_D$ −192.7 (0.60, $CHCl_3$); IR ($CHCl_3$) 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 8.3 Hz, 1H), 1.38 (d, J = 8.5 Hz, 1H), 1.52 (s, 3H), 2.44−2.66 (m, 2H), 2.81−2.93 (m, 3H), 3.24 (broad s, 1H), 3.33−3.38 (m, 1H), 3.84 (s, 3H), 3.90 (s, 3H), 4.10−4.17 (m, 1H), 4.81−4.83 (m, 1H), 5.88−5.92 (m, 1H), 6.49 (s, 1H), 6.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.8, 32.3, 34.5, 45.7, 46.7, 49.6, 50.1, 50.6, 55.7, 56.0, 61.7, 109.4, 111.1, 126.2, 132.5, 133.2, 134.1, 147.2, 147.5, 172.8; MS (EI) *m*/*z* (rel intensity) 325 (M^+, 5), 311 (11), 310 (52), 245 (19), 244 (100), 200 (4), 85 (2), 83 (2). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.44; H, 6.95; N, 4.22. The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 3% hexane/2-propanol, 1 mL/min; t_r(*ent*) = 38.1 min (<1%); t_r[(12b*S*)-**11a**] = 41.4 min (>99%).

(8a*S*,9*S*,12*R*,12a*S*,12b*S*)-(−)-12b-Butyl-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]-isoquinolin-8-one [(12b*S*)-11b]. According to General Procedure, (12b*S*)-(−)-**2b** (72 mg, 0.13 mmol) was treated sequentially with SmI_2 (13 mL of a 0.1 M solution in THF, 1.3 mmol), *t*-BuOH (0.13 mL, 1.3 mmol), and HMPA (1.33 mL, 7.8 mmol). After workup, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*S*)-**11b** (41 mg, 60%): $[\alpha]^{23}_D$ −220.0 (0.10, $CHCl_3$); IR ($CHCl_3$) 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 6.9 Hz, 3H), 1.11−1.23 (m, 4H), 1.30 (d, J = 8.2 Hz, 1H), 1.39 (d, J = 8.2 Hz, 1H), 1.73−1.94 (m, 2H), 2.45−2.52 (m, 1H), 2.53−2.67 (m, 1H), 2.80 (td, J = 12.5, 4.5 Hz, 1H), 2.91−2.95 (m, 2H), 3.20 (broad s, 1H), 3.25−3.30 (m, 1H), 3.84 (s, 3H), 3.91 (s, 3H), 4.15 (dd, J = 12.5, 5.3 Hz, 1H), 4.75−4.77 (m, 1H), 5.88−5.91 (m, 1H), 6.48 (s, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.8, 25.8, 28.6, 34.5, 43.9, 45.5, 47.0, 48.1, 50.2, 50.9, 55.7, 56.0, 64.7, 109.3, 111.1, 125.9, 132.7, 133.7, 134.0, 147.0, 147.3, 173.5; MS (EI) *m*/*z* (rel intensity) 311 (10), 310 (40), 246 (2), 245 (15), 244 (100), 200 (3). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.86; H, 8.03; N, 3.56. The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 3% hexane/2-propanol, 1 mL/min; t_r(*ent*) = 44.2 min (<1%); t_r[(12b*S*)-**11b**] = 50.6 min (>99%).

(8a*S*,9*S*,12*R*,12a*S*,12b*S*)-(−)-2,3-Dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]-isoquinolin-8-one [(12b*S*)-11c]. According to General Procedure, (12b*S*)-(−)-**2c** (36.5 mg, 0.07 mmol) was treated sequentially with SmI_2 (7.1 mL of a 0.1 M solution in THF, 0.71 mmol), *t*-BuOH (0.07 mL, 0.71 mmol), and HMPA (0.48 mL, 2.84 mmol). After workup, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*S*)-**11b** (12.4 mg, 56%): $[\alpha]^{23}_D$ −182.4 (0.12, $CHCl_3$); IR ($CHCl_3$) 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 8.3 Hz, 1H), 1.43 (d, J = 8.1 Hz, 1H), 2.47−2.66 (m, 2H), 2.77 (td, J = 11.8, 4.2 Hz, 1H), 2.93 (m, 1H), 3.21−3.33 (m, 2H), 3.35−3.38 (m, 1H), 3.85 (s, 3H), 3.91 (s, 3H), 4.19−4.26 (m, 1H), 4.84 (d, J = 8.5 Hz, 1H), 4.89−4.92 (m, 1H), 5.91−5.94 (m, 1H), 6.53 (s, 1H), 6.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 37.4, 42.0, 45.7, 45.8, 50.2, 50.4, 55.8, 56.0, 57.3, 108.6, 111.4, 126.7, 127.5, 133.6, 134.0, 147.5, 173.5; MS (EI) *m*/*z* (rel intensity) 311 (M^+, 62), 310 (25), 246 (9), 245 (60), 244 (100), 230 (10), 217 (7), 216 (15), 215 (11), 214 (65), 202 (5), 200 (8), 192 (15), 191 (9), 176 (7), 91 (11), 77 (6), 66 (11), 65 (6). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 10% hexane/2-propanol, 0.8 mL/min; t_r(*ent*) = 23.4 min (<1%); t_r[(12b*S*)-**11c**] = 26.5 min (>99%).

(8a*S*,9*S*,12*R*,12a*S*,12b*S*)-(−)-12b-Allyl-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]-isoquinolin-8-one [(12b*S*)-11d]. According to General Procedure, (12b*S*)-(−)-**2d** (36.5 mg, 0.06 mmol) was treated sequentially with SmI_2 (6.6 mL of a 0.1 M solution in THF, 0.66 mmol), *t*-BuOH (0.06 mL, 0.66 mmol), and HMPA (0.85 mL, 4.96 mmol). After workup, purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinoline (12b*S*)-**11d** (14 mg, 60%) $[\alpha]^{23}_D$ −149.7 (0.3, $CHCl_3$); IR ($CHCl_3$) 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, J = 8.7 Hz, 1H), 1.40 (d, J = 8.7 Hz, 1H), 2.43−2.57 (m, 2H), 2.60−2.70 (m, 2H), 2.84−2.90 (m, 2H), 2.95−3.00 (m, 1H), 3.21−3.26 (m, 2H), 3.86 (s, 3H), 3.92 (s, 3H), 4.18 (dd, J = 13.0, 4.6 Hz, 1H), 4.79−4.81 (m, 1H), 5.11−5.16 (m, 2H), 5.64−5.80 (m, 1H), 5.89−5.92 (m, 1H), 6.51 (s, 1H), 6.66 (s, 1H); ^{13}C

NMR ($CDCl_3$) δ 28.5, 34.4, 45.4, 46.7, 47.9, 48.0, 50.1, 50.6, 55.6, 56.0, 64.5, 109.2, 111.1, 119.5, 126.2, 131.6, 132.4, 133.6, 134.1, 147.0, 147.4, 173.6; MS (EI) *m*/*z* (rel intensity) 311 (5), 310 (22), 245 (17), 244 (100), 228 (4), 200 (12), 77 (4), 66 (8), 65 (5); HRMS calcd for $C_{19}H_{20}NO_3$ (M^+ − allyl) 310.1443, found 310.1433. The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 3% hexane/2-propanol, 1 mL/min; t_r(*ent*) = 26.1 min (<1%); t_r[(12b*S*)-**11d**] = 31.4 min (>99%).

Retro Diels−Alder Reactions. Synthesis of Enantiomerically Pure Isoquinolines (10b*R*)-1a,b or (10b*S*)-1a,b. (10b*R*)-(+)-8,9-Dimethoxy-10b-methyl-5,6dihydropyrrolo-[2,1-*a*]isoquinolin-3-one [(10b*R*)-1a]. Isoindoloisoquinoline (12b*R*)-**11a** (92 mg, 0.28 mmol) was heated at 560 °C under vacuum (1 mmHg) for short periods of time (10 min). The evolution of the reaction was monitored by ^{1}H NMR, and the procedure was repeated until complete consumption of starting material was observed. The crude product was purified by flash column chromatography (silicagel, 80% hexane/ethyl acetate) (63 mg, 85%), whose spectroscopic data were identical to those previously reported for the racemate:[18b] $[\alpha]^{23}_D$ +201.4 (0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.52 (dd, *J* = 16.4, 2 Hz, 1H), 2.71−2.85 (m, 1H), 3.09 (td, *J* = 13.1, 4.2 Hz, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 4.26 (dd, *J* = 13.1, 7.0 Hz, 1H), 5.94 (d, *J* = 5.7 Hz, 1H), 6.47 (s, 1H), 6.62 (s, 1H), 7.29 (d, *J* = 5.7 Hz, 1H). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.4 mL/min; t_r[10b*S*)-**1a**] = 14.5 min (<1%); t_r[(10b*R*)-**1a**] = 18.6 min (>99%).

(10b*R*)-(+)-10b-Butyl-8,9-dimethoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinolin-3-one [(10b*R*)-1b]. Isoindoloisoquinoline (12b*R*)-**11b** (129 mg, 0.35 mmol) was heated at 560 °C under vacuum (1 mmHg) for short periods of time (10 min). The evolution of the reaction was monitored by ^{1}H NMR and the procedure was repeated until complete consumption of starting material was observed. The crude product was purified by column chromatography (silicagel, 80% hexane/ethyl acetate) (84 mg, 80%), whose spectroscopic data coincided with those previously reported for the racemate:[18b] $[\alpha]^{23}_D$ + 240.5 (0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J* = 7.1 Hz, 3H), 1.08−1.26 (m, 4H), 1.85−1.96 (m, 2H), 2.64 (dd, *J* = 16.2, 4.1 Hz, 1H), 2.91 (td, *J* = 16.2, 6.7 Hz, 1H), 3.15 (td, *J* = 12.4, 4.1 Hz, 1H), 3.83 (s, 3H), 3.88 (s, 3H), 4.41 (dd, *J* = 12.4, 6.7 Hz, 1H), 6.13 (d, *J* = 5.7 Hz, 1H), 6.59 (s, 1H), 6.69 (s, 1H), 7.22 (d, *J* = 5.7 Hz, 1H). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.4 mL/min; t_r[10b*R*)-**1b**] = 17.5 min (>99%); t_r[(10b*S*)-**1b**] = 19 min (<1%).

(10b*S*)-(−)-8,9-Dimethoxy-10b-methyl-5,6dihydropyrrolo[2,1-*a*]isoquinolin-3-one [(10b*S*)-1a]. A solution of isoindoloisoquinoline (12b*S*)-**11a** (35 mg, 0.11 mmol) in *o*-DCB (5 mL) was refluxed for 9 days. The evolution of the reaction was monitored by ^{1}H NMR. The crude product was purified by column chromatography (silica gel, 80% hexane/ethyl acetate) (10 mg, 50%), whose spectroscopic data were identical to those previously reported for the racemate:[18b] $[\alpha]^{23}_D$ −220.6 (0.29, $CHCl_3$). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.4 mL/min; t_r[10b*S*)-**1a**] = 14.5 min (>99%); t_r[(10b*R*)-**1a**] = 18.6 min (<1%).

(10b*S*)-(−)-10b-Butyl-8,9-dimethoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinolin-3-one [(10b*S*)-1b]. A solution of isoindoloisoquinoline (12b*S*)-**11b** (21 mg, 0.06 mmol) in *o*-DCB (3 mL) was refluxed for 10 days. The evolution of the reaction was monitored by ^{1}H NMR. The crude product was purified by column chromatography (silica gel, 80% hexane/ethyl acetate) (12 mg, 70%), whose spectroscopic data were identical to those previously reported for the racemate:[18b] $[\alpha]^{23}_D$ − 245.4 (0.20, $CHCl_3$). The enantiomeric excess determined by CSP HPLC was >99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.4 mL/min; t_r[10b*R*)-**1b**] = 17.5 min (<1%); t_r[(10b*S*)-**1b**] = 19 min (>99%).

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Supporting Information Available: Experimental procedures and full characterization data for compounds **3a**,**b**, **4**−**7**, **13**, **14**, and **14′** and 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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