Highly Diastereoselective Intramolecular α-Amidoalkylation Reactions of Hydroxylactams Derived from *N*-Phenethylimides. Enantioselective Synthesis of Dihydropyrrolo[2,1-*a*] isoquinolones

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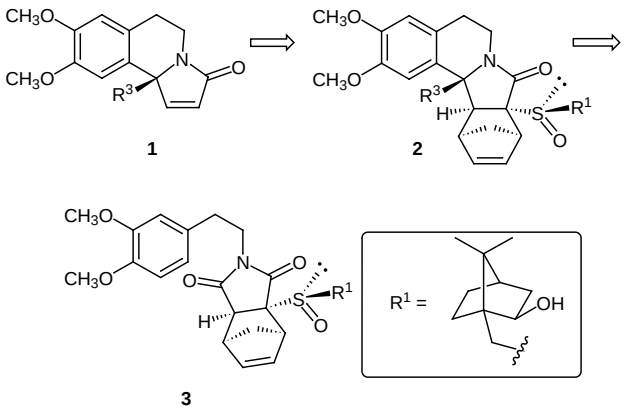
Abstract: α-Hydroxylactams, derived from organolithium addition to an enantiomerically pure *N*-phenethylnorborn-5-en-*endo*-2,3-dicarboxyimide with a 2-*exo*-hydroxy-10-bornylsulfinyl group as chiral auxiliary, undergo efficient and highly diastereoselective *N*-acyliminium ion cyclization. Subsequent removal of the auxiliary and retro-Diels-Alder reaction lead to the enantioselective synthesis of C-10b substituted 5,6-dihydropyrrolo[2,1-*a*]isoquinolines.

Key words: asymmetric synthesis, chiral auxiliaries, organolithium addition, cyclization, *N*-acyliminium ion

The pyrrolo[2,1-*a*]isoquinolines represent a structural fragment of erythrinan alkaloids with significant pharmacological activity. These compounds possess antidepressant,[1] muscarinic agonist,[2] and antileukemic[3] properties. Moreover, they can be used as PET radiotracers for imaging serotonin uptake sites.[4] The importance of the pyrrolo[2,1-*a*]isoquinolines **1** is further enhanced by their utility as advanced intermediates for the synthesis of erythrinan alkaloids.[5] Thus, introduction of a C-4 unit into a dihydropyrroloisqouinoline by the Diels-Alder reaction or a [2+2] photocycloaddition is among the most important procedures for building up the erythrinan ring system.[6] These methods have also been applied to the total synthesis of enantiomerically pure aromatic erythrinan alkaloids, using L-DOPA as precursor of a chiral pyrroloisoquinolone.[7] However, both strategies require several steps for the removal of the carboxyl group of the starting amino acid in the final stages of the synthesis.

On the other hand, we have 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.[8] This methodology has been extended to the use of functionalized organolithium reagents capable of 1,2-addition to the carbonyl group, such as 3-(2-trimethylsilyl-1,3-dithian-2-yl)propyllithium. Thus, the synthesis of C-10b functionalized dihydropyrrolo[2,1-*a*]isoquinolines, immediate precursors for erythrinan alkaloids via intramolecular conjugate additions, has been accomplished.

In this context, our next challenge was to achieve the asymmetric synthesis of these nitrogen heterocycles. Thus, we reasoned that if a chiral auxiliary is appended to the norbornene moiety, enantiomerically pure isoindoloisoquinolines **2** could be obtained. Removal of the chiral auxiliary, followed by retro Diels-Alder reaction would afford enantiopure C-10b substituted dihydropyrrolisoquinolines **1**. This methodology would open up an asymmetric route to erythrinan alkaloids avoiding the release of the carboxyl group required in the above-described protocols.[7] For this purpose, we chose the 2-*exo*-hydroxy-10-bornylsulfinyl group as chiral auxiliary.[9] Thus, our imide precursor would be (2-*exo*-hydroxy-10-bornyl)sulfinylnorbornenimide **3** (Scheme 1).



Scheme 1 Retrosynthetic analysis.

Preparation of imide **3** was carried out using the procedure developed by Arai[9a,b] for related substrates, which relies on an asymmetric Diels-Alder reaction of a sulfinylmaleimide.[10–12] Thus, our first task was the synthesis of *N*-phenethylmaleimide **7**. As depicted in Scheme 2, addition of 10-mercaptoisoborneol to maleimide **4** afforded succinimide **5** as a 95:5 diastereoisomeric mixture in good yield. Treatment with NCS afforded maleimide **6**, which was oxidized with MCPBA to yield sulfinylmaleimide **7** as a single diastereoisomer in excellent yield.[13]

Diels-Alder reaction of sulfinylmaleimide **7** with cyclopentadiene in the presence of $ZnCl_2$ afforded sulfinylnorbornenimide **3** in excellent yield (93%), as a single

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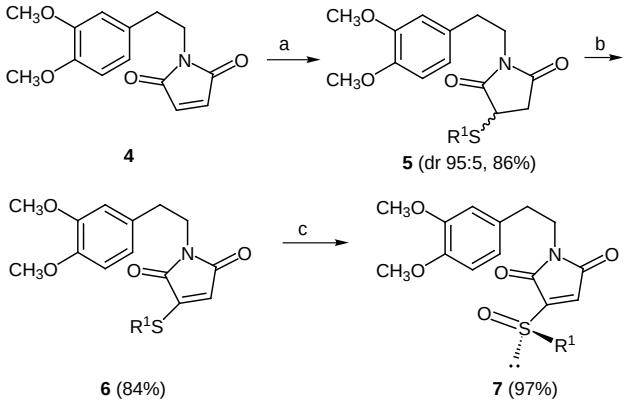


Scheme 2 (a) Mercaptoisoborneol, Et_3N, 0 °C to r.t., 24 h; (b) NCS, CCl_4, reflux, 16 h; (c) MCPBA, CH_2Cl_2, 0 °C, 3 h.

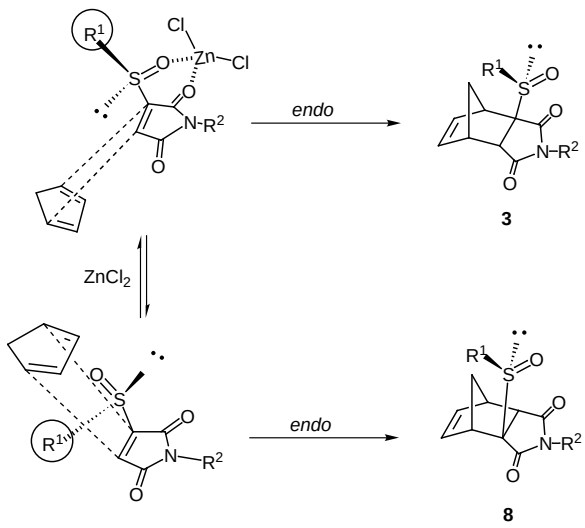
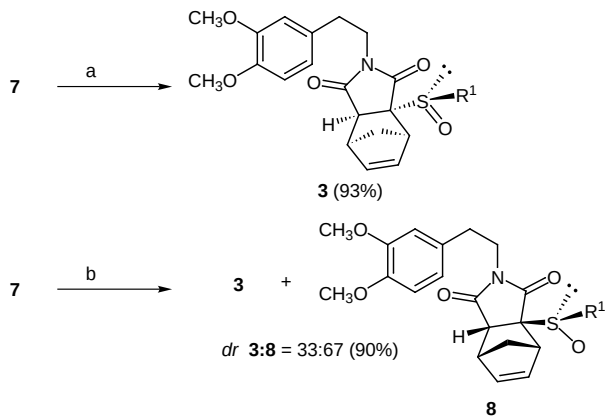


Figure 1 Diels-Alder reaction of **7**.

diastereoisomer (Scheme 3). The stereochemical outcome of the reaction may be explained as shown in Figure 1. 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 **3**. In the absence of $ZnCl_2$, a more stable conformer due to dipole-dipole repulsion would lead to the formation of *endo* product **8**. In fact, when the cycloaddition reaction was carried out in the absence of a Lewis acid, a diastereoisomeric mixture of **3** and **8** was obtained in a 33:67 ratio (90%).

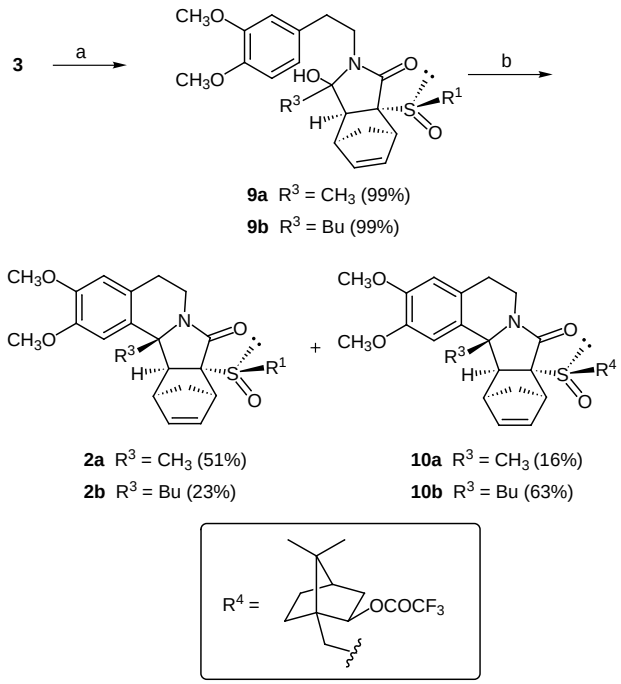


Scheme 3 (a) Cyclopentadiene, $ZnCl_2$, CH_2Cl_2, 0 °C; (b) Cyclopentadiene, CH_2Cl_2, 0 °C.

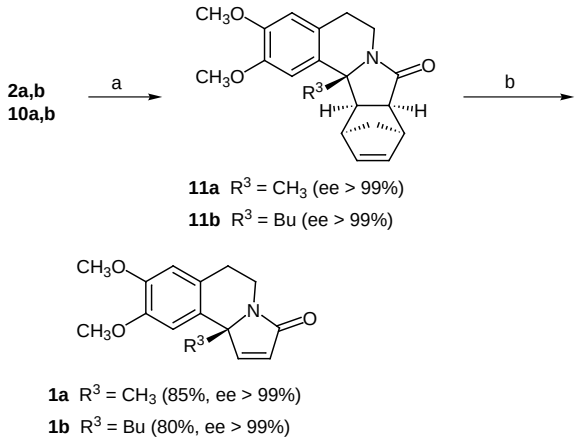
Once the chiral non-racemic imide precursor **3** had been prepared, we studied the stereoselectivity of the organolithium addition-*N*-acyliminium ion cyclization sequence. Thus, addition of MeLi or BuLi (2.3 equiv) to imide **3** afforded α-hydroxylactams **9** in quantitative yields as single diastereoisomers (Scheme 4). As expected, attack of the organolithium took place regioselectively at the less hindered carbonyl group. It was not necessary to determine the stereochemistry of α-hydroxylactams **9**, as a planar *N*-acyliminium ion was going to be generated in the subsequent cyclization. The next step was the construction of the isoquinoline nucleus by an intramolecular α-amidoalkylation reaction. As depicted in Scheme 3, treatment of α-hydroxylactams **9a**,**b** with an excess of TFA at room temperature furnished the expected isoquinoline **2a**,**b**, together with their derivatives **10a**,**b**, in which trifluoroacetylation of the hydroxyl group of the auxiliary had occurred. These products were separated and characterized independently, but as will be discussed later, 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 efficiently afforded the isoquinoline system with complete stereocontrol, as isoindoloisoquinolines **2** and **10** were isolated as single diastereoisomers. 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 C-12b stereogenic centre. In this case, the C10-C11 ethylydene bridge of the endo-norbornene moiety would block the *Re* side.[14]

The chiral auxiliary was reductively removed by treatment with an excess of SmI_2 in the presence of HMPA and *t*-BuOH.[14] Thus, **2a**,**b** and their *O*-trifluoroacetyl derivatives **10a**,**b** were converted separately into the same isoindoloisoquinolines **11a**,**b** in high yields and excellent (>99%) enantiomeric excesses (Scheme 5, Table).[15] Spectroscopic data of **11a** and **11b** were in agreement with those of the corresponding racemates previously reported by us,[8b] which confirms, on one hand, the *endo* stereochemistry of the norbornene moiety, and on the other, the relative stereochemistry of the methyl or butyl groups.

Finally, retro-Diels-Alder reaction[17] of **11a**,**b** using an FVP technique produced the α,β-unsaturated pyrroloisoquinolines **1a**,**b** in high yield and enantiomeric purity, without racemization.[16]



Scheme 4 (a) R^3Li, -78 ºC, THF, 6 h; (b) TFA, CH_2Cl_2, r.t., 3 days.



Scheme 5 (a) SmI_2, HMPA, *t*-BuOH, THF, 1.5 h; (b) 560 °C, 1 mm Hg.

Table Elimination of Chiral Auxiliary. Preparation of **11**.

Entry	Substrate	Product	Yield (%)
1	**2a**	**11a**	96
2	**10a**	**11a**	86
3	**2b**	**11b**	83
4	**10b**	**11b**	83

In summary, we have shown that it is possible to obtain chiral C-10b substituted 5,6-dihydropyrrolo[2,1-*a*]isoquinolines with high optical purity via diastereoselective intramolecular α-amidoalkylation reactions of α-hydroxylactams. In fact, organolithium addition-*N*-acyliminium ion cyclization sequence on an enantiomerically pure *N*-phenethylnorborn-5-en-*endo*-2,3-dicarboxyimide, with a 2-*exo*-hydroxy-10-bornylsulfinyl group as chiral auxiliary, proceeds with high stereocontrol.

Acknowledgement

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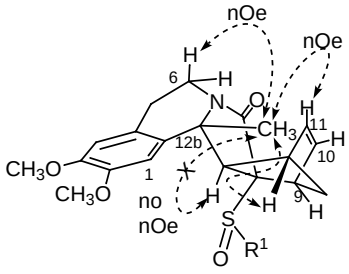
References

(1) (a) Elwan, N. M.; Abelhadi, H. A.; Abdallah, T. A.; Hassaneen, H. M. *Tetrahedron* **1996**, *52*, 3451. (b) McComsey, D. F.; Maryanoff, B. E. *J. Org. Chem.* **2000**, *65*, 4938.
(2) Loesel, W.; Roos, O.; Schnorrenberger, G. U. S. Patent, 4694085, **1987**; *Chem. Abstr.* **1988**, *108*, 204513.
(3) Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem.* **1998**, *31*, 2097.
(4) Suehiro, M.; Greenberg, J. H.; Shine, C. Y.; González, C.; Dembowski, B.; Reivich, M. *Nucl. Med. Biol.* **1996**, *23*, 407; and references cited therein.
(5) (a) Bentley, K. *Nat. Prod. Rep.* **1998**, *15*, 341. (b) Bentley, K. *Nat. Prod. Rep.* **2000**, *17*, 247. (c) Bentley, K. *Nat. Prod. Rep.* **2001**, *18*, 341.
(6) For a review on synthesis and biological properties of Erythrinanes, see: Tsuda, Y.; Sano, T. In *The Alkaloids: Chemistry and Pharmacology*, Vol. 48; Cordell, G. A., Ed.; Academic Press: San Diego, **1996**, Chap. 4, 249.
(7) (a) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087. (c) Sano, T.; Kamiko, M.; Toda, J.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1994**, *42*, 197.
(8) (a) Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *Tetrahedron Lett.* **1996**, *33*, 7841. (b) Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron* **1998**, *54*, 12361.
(9) (a) Arai, Y.; Matsui, M.; Koizumi, T.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 1983. (b) Arai, Y.; Matsui, M.; Fujii, A.; Kontani, T.; Ohno, T.; Koizumi, T.; Shiro, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 25. (c) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Gianneto, P. *J. Org. Chem.* **1997**, *62*, 4376.
(10) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, **1990**.
(11) For reviews on stereoselective Diels-Alder reactions of sulfinyl derivatives, see: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (b) García Ruano, J. L.; Carretero, J. C.; Carreño, M. C.; Martín Cabrejas, L. M.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925.
(12) For some more recent examples, see, for instance: (a) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Gianneto, P.; Panzalorto, M.; Rizzo, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1577. (b) Arai, Y.; Masuda, T.; Masaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2165. (c) Carreño, M. C.; García-Cerrada, S.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **2000**, *65*, 4355. (d) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A. *Chem. Eur. J.* **2000**, *6*, 288. (e) García Ruano, J. L.; Bercial, F.; Fraile, A.; Martín Castro, A. M.; Martín, M. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4737.
(13) The absolute configuration of the sulfoxide was established by correlation with related structures: Arai, Y.; Matsui, M.; Koizumi, T. *Synthesis* **1990**, 320; see also ref.[9b].

(14) Nuclear Overhauser effect difference spectroscopy and ^{1}H-^{1}H decoupling experiments confirmed the stereochemistry of isoquinolines. For instance, isoindoloisoquinoline **2a** (Figure 2) demonstrated an enhancement of the H-11, H-12 and H-6_{ax} 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 and H-13, confirms an *R* configuration for C-12b. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry in each case.



2a

Figure 2

(15) See ref.[9b] For other reagents for reductive desulfinylation, see, for instance: (a) Zn/HOAc: Rusell, G. A.; Mikol, V. *J. Am. Chem. Soc.* **1966**, *88*, 5498. (b) Zn/NH_4Cl: Holton, R. A.; Crouse, D. J.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1987**, *52*, 2317. (c) Raney Ni/$NaPH_2O_2$: Node, M.; Nishide, K.; Shigeta, Y.; Obata, K.; Shiraki, H.; Kunishige, H. *Tetrahedron* **1997**, *53*, 12883.

(16) The enantiomeric excess of **11a**,**b** and **1a**,**b** was determined in each case by CSP HPLC (Chiralcel OD, 20% hexane–2-propanol, 0.4 mL/min) by comparison with the corresponding racemates. The racemates were prepared by an alternate procedure described in ref.[8b]. Representative procedures and characterization data for **1a**, **2a**, **10a**, **11a**:

(8a*R*,9*S*,12*R*,12a*S*,12b*R*)-(+)-8a-[(1*S*,2*R*,4*R*,S*S*)-(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(2a).

To a solution of the imide **3** (1.15 g, 2.2 mmol) in dry THF (45 mL), MeLi (7.6 mL of a 0.66 M solution in pentane, 5 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 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 so obtained hydroxy lactam **9a** (203 mg, 0.4 mmol) in CH_2Cl_2 (10 mL), TFA (2.5 mL, 32.4 mmol) was added 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 column flash chromatography (silica gel, 60% hexane–ethyl acetate), yielding two fractions.

2a (101 mg, 51%): $[\alpha]_D^{23}$ +117.9 (0.5, $CHCl_3$); mp (Et_2O–pentane) 121–122 °C; IR ($CHCl_3$): 3400, 2975, 1673, 1407 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.60 (s, 3 H), 1.04 (s, 3 H), 1.23–1.25 (m, 2 H), 1.48 (s, 3 H), 1.60–1.72 (m, 6 H), 2.1 (d, *J* = 8.3 Hz, 1 H), 2.54 (dd, *J* = 16.2, 4.4 Hz, 1 H), 2.75 (d, *J* = 13.1 Hz, 1 H), 2.81–2.92 (m, 1 H), 3.07 (ddd, *J* = 13.1, 12.3, 4.8 Hz, 1 H), 3.21 (d, *J* = 13.1 Hz, 1 H), 3.32 (d, *J* = 3.6 Hz, 1 H), 3.37 (s, 1 H), 3.74–3.78 (m, 2 H), 3.81–3.89 (m, 1 H),* 3.82 (s, 3 H),* 3.89 (s, 3 H),* 4.18 (dd, *J* = 13.1, 6.3 Hz, 1 H), 6.33–6.37 (m, 1 H), 6.45–6.48 (m, 2 H), 6.60 (s, 1 H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.9, 20.4, 26.5, 27.0, 27.6, 30.5, 35.4, 38.3, 48.7, 44.9, 45.8, 46.5, 48.1, 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).

10a (38 mg, 16%): $[\alpha]_D^{23}$ +95.7 (1, $CHCl_3$); IR ($CHCl_3$): 2950, 1780, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.86 (s, 3 H), 1.04 (s, 3 H), 1.48 (s, 3 H), 1.23–1.25 (m, 2 H), 1.58–1.92 (m, 5 H), 2.1 (d, *J* = 8.3 Hz, 1 H), 2.47 (dd, *J* = 16.0, 3.8 Hz, 1 H), 2.79 (ddd, *J* = 16.0, 12.3, 6.5 Hz, 1 H), 3.03 (td, *J* = 12.6, 4.4 Hz, 1 H), 3.12–3.23 (m, 2 H), 3.28 (s, 1 H), 3.52 (d, *J* = 3.6 Hz, 1 H), 3.59 (s, 1 H), 3.82–3.88 (m, 1 H),* 3.82 (s, 3 H),* 3.89 (s, 3 H),* 4.10 (dd, *J* = 13.1, 6.1 Hz, 1 H), 5.05 (dd, *J* = 7.4, 2.8 Hz, 1 H), 6.31–6.34 (m, 1 H), 6.45–6.49 (m, 2 H), 6.60 (s, 1 H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.6, 20.0, 26.3, 26.7, 27.6, 29.9, 35.7, 38.5, 46.7, 44.8, 45.3, 45.6, 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), 622 (M + 1, 3), 623 (M + 2, 1), 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*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(11a). To a solution of **2a** (100 mg, 0.2 mmol) in dry THF (5 mL), 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) were added sequentially at r.t. The resulting mixture was stirred at this temperature for 1.5 h, 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 (silica gel, ethyl acetate) afforded isoindoloisoquinoline **11a** (59 mg, 96%), whose spectroscopic data are coincidental to those previously reported for the racemate[8b]: $[\alpha]_D^{23}$ +202.8 (1.43, $CHCl_3$); mp (Et_2O) 183–184 °C [Lit.[8a] racemate (Et_2O) 158–160 °C]; ^{1}H NMR ($CDCl_3$) 1.45 (s, 3 H),* 1.41–1.45 (m, 1 H),* 1.64 (d, *J* = 8.3 Hz, 1 H), 2.44 (d, *J* = 11.9 Hz, 1 H), 2.96–2.99 (m, 2 H), 3.09–3.11 (m, 2 H), 3.23–3.25 (m, 2 H), 3.82 (s, 3 H), 3.90 (s, 3 H), 4.10–4.14 (m, 1 H), 6.21–6.23 (m, 2 H), 6.48 (s, 1 H), 6.65 (s, 1 H) (*: partially overlapped signals). The enantiomeric excess was determined by CSP HPLC to be > 99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane–2-propanol, 0.4 mL/min; t_r (*ent*-**11a**) = 18.5 min (< 1%); t_r(**11a**) = 21.2 min (> 99%).

(10b*R*)-(+)-(-8,9-Dimethoxy-10b-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one(1a). Isoindoloisoquinoline **11a** (92 mg, 0.28 mmol) was heated at 560 °C under vacuum (1 mm Hg) for short periods of time (10 min).[18] The evolution of the reaction was monitored by ^{1}H NMR, and the procedure was repeated until complete evolution of starting material was observed. The crude product was purified by column chromatography (silica gel, 80% hexane–EtOAc) (63 mg, 85%), whose spectroscopic

data were coincidental to those previously reported for the racemate.[8b] $[\alpha]^{23}_{D}$ +201.4 (0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.59 (s, 3 H), 2.65 (dd, *J* = 15.8, 3.9 Hz, 1 H), 2.85–2.99 (m, 1 H), 3.22 (td, *J* = 12.0, 4.5 Hz, 1 H), 3.83 (s, 3 H), 3.90 (s, 3 H), 4.4 (dd, *J* = 13.5, 6.3 Hz, 1 H), 6.10 (d, *J* = 5.5 Hz, 1 H), 6.59 (s, 1 H), 6.68 (s, 1 H), 7.34 (d, *J* = 5.9 Hz, 1 H). The enantiomeric excess was determined by CSP HPLC to be > 99%, by comparison with the racemic mixture. Chiralcel OD, 20% hexane–2-propanol, 0.4 mL/min; t_r (*ent*-**1a**) = 14.5 min (< 1%); t_r(**1a**) = 18.2 min (> 99%).

(17) For a review on applications of retro-Diels-Alder reactions in stereoselective synthesis, see: Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev*. **1999**, *99*, 1163.

(18) Continuous heating at 1 mm Hg for longer periods of time resulted in decomposition of starting material.