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Enantioselective Synthesis of Spirocyclic Aminochroman Derivatives According to the CN(*R*,*S*) Strategy

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Enantiomerically pure (3′*R*)- and (3′*S*)-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran]s (*R*)-**10** and (*S*)-**10** were successfully synthesized according to the CN(*R*,*S*) methodology with the aim of serving as a pattern for the generation of related spirocyclic compounds. Two different synthetic pathways were studied starting from 2-cyano-6-phenyloxazolopiperidine (−)-**2**. One of them was selected and used for the preparation of amines (*R*)-**17** and (*S*)-**17** starting from (−)-**2** and (+)-**2**, respectively. The enantiomeric purity of all final aminochroman derivatives was determinated by capillary electrophoresis using β-cyclodextrin as the chiral selector.

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter of the central nervous system that is involved in many physiological and pathophysiological processes in the brain. These processes are mediated by the specific interaction of 5-HT with several different receptors.[1,2] The dysfunction of the serotoninergic system has been linked to various behavioral problems involving memory, thermoregulation, sleep, and sexual behavior. Moreover, serotonin is also implicated in numerous neuropsychiatry disorders such as anxiety, depression, schizophrenia, or Alzheimer's disease.[3−5] Due to the role of 5-HT_{1A} receptors in anxiety and depression, the synthesis of 5-HT_{1A} agonists appears to be very attractive. In our laboratory, previous works[6−9] have led to new potential therapeutic agents that demonstrated a good affinity and a high selectivity for the 5-HT_{1A} receptors. Among them, compound **1b** (**S 22178**) (Figure 1) showed an 8.8 nmol affinity toward this receptor.[7] The synthesis of both enantiomers of **1b** was achieved for pharmacological purposes.

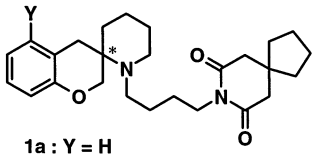

FIGURE 1.

At the present time, just one pathway leading only to racemic 3-aminochroman derivatives has been described.[7] To define an easy and enantioselective approach to this type of compound, a model study was performed. The key step of the synthetic pathway controls the stereochemistry of the spirocyclic center. It was generated using the CN(*R*,*S*) method[10] developed by Husson et al. from 2-cyano-6-phenyloxazolopiperidine (−)-**2**.[11] Indeed, the α-aminonitrile function of this chiral precursor could be used to generate the required spirocyclic system. By this approach, each enantiomer of target compound **1a** was synthesized in two different ways starting from (−)-**2**. Finally, one pathway was selected and used to prepare both enantiomers of the methoxylated derivative **1b** starting from isomers (−)-**2** and (+)-**2**.

Results and Discussion

Synthesis of Amine (*S*)-12a. Compound **2** was found to be a good candidate for triggering the asymmetric

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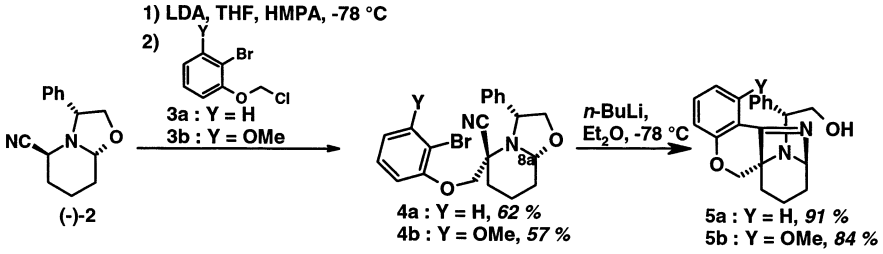
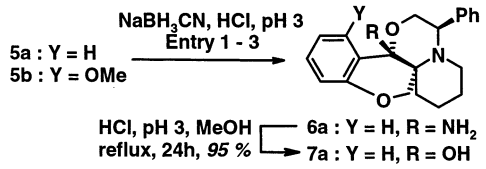
SCHEME 1



SCHEME 2



Entry	Y	Conditions	R	Product	Yield (%)
1	H	THF, reflux, 4h	NH_2	6a	*80*
2	H	MeOH, reflux, 36 h	OH	7a	*84*
3	OMe	MeOH, reflux, 36 h	OH	7b	*96*

synthesis of dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] derivatives for an asymmetric synthesis by the CN(*R*,*S*) method. The alkylation of the anion derived from (−)-**2** with 1-bromo-2-(chloromethoxy)benzene[12] (**3a**) (LDA, THF, −78 °C) led to the formation of **4a** as a single product. This compound was isolated in 62% yield after flash chromatography (Scheme 1). Then compound **4a** was submitted to halogen/metal exchange using *n*-BuLi in THF at −78 °C. The lithiated intermediate led to a single isomer of imine **5a** (91% yield). According to the literature,[13] the formation of this imine can be explained by the intramolecular addition of the aryllithium species onto the nitrile function followed by the attack of an intermediate imine salt on the C-8a atom of the potential iminium ion. The ^{1}H NMR spectrum of **5a** presents a narrow triplet at δ 5.03 (J = 2.1 Hz) assigned to the bridgehead proton.

At this stage, only a reduction of **5a** with sodium cyanoborohydride at pH 3 (1 N HCl) gave satisfactory results (Scheme 2). Initially, as described by Froelich et al.,[13] the reaction was conducted in methanol/THF (1:1), giving a mixture of hemiaminal **6a** and hemiacetal **7a**, each one as a single isomer. A study of the solvent influence gave interesting results. As depicted in Scheme 2, when the reaction was performed in refluxing THF for 4 h, only **6a** was obtained in 80% yield. When the reaction was performed in refluxing methanol for 36 h, only **7a** was obtained in 84% yield. Moreover, the hydrolysis of **6a** in refluxing methanol performed in the presence of 1 N hydrochloric acid at pH 3 for 24 h gave **7a**, indicating

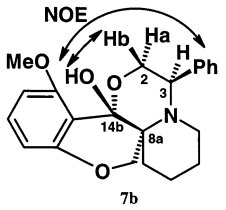


FIGURE 2. NOE connectivities on compound **7b**.

that the hemiaminal **6a** is an intermediate during the reductive reaction of **5a** to **7a**. The absolute configuration of **6a** was deduced according to the literature.[13] During the reduction stage, the restricted imine is attacked by the primary alcohol function on its accessible face. Hence, only one isomer can be formed. The absolute configuration of **7a** was deduced from ^{1}H NMR data of compound **7b**. Indeed, the H-2b signal was inferred by the Karplus theory: H-2a, δ 3.55 (dd, J_{cis} = 3.8 Hz, J_{gem} = 11.0 Hz); H-2b, δ 4.28 (t, J_{trans} = 11.0 Hz, J_{gem} = 11.0 Hz); H-3, δ 3.93 (dd, J_{cis} = 3.8 Hz, J_{trans} = 11.0 Hz). Then, an NOE experiment conducted on **7b** indicated a relationship between H-2b and OH (Figure 2). In addition, the NOE experiment showed a connectivity between OH and protons of the phenyl group. From these results, it was possible to assign unambiguously the (3*S*,8a*R*,14b*S*) absolute configuration for **7a**, fixing the chirality of the spiro center.

The next step consisted in reducing compounds **6a** and **7a** by the couple $LiAlH_4/AlCl_3$, in a suspension in THF. This sequence gave compounds **8a** and **9a** in 99% and 88% yield, respectively (Scheme 3). As explained by Husson et al.,[13] the reduction of such compounds occurred via a retention mechanism as proposed for ketals[14] and oxazolidines.[15] Finally, diamine **10a** and amino alcohol **11a** were obtained by hydrogenolysis of the chiral appendage in **8a** and **9a**, in 96% and 97% yield, respectively. The spatial group determined from the X-ray crystal structure of **11a** indicated that there is only one isomer. This result can be used, in conjunction with the previous NOE data, to establish the absolute configuration of **11a** and, consequently, absolute configuration of the related compounds **9a**, **9b**, and **11b**.

The reduction of the primary amine function of compound **10a** to its corresponding methylene was achieved by hydroxylaminesulfonic acid (NH_2OSO_3H),[16] in the presence of 20% sodium hydroxide in ethanol at reflux

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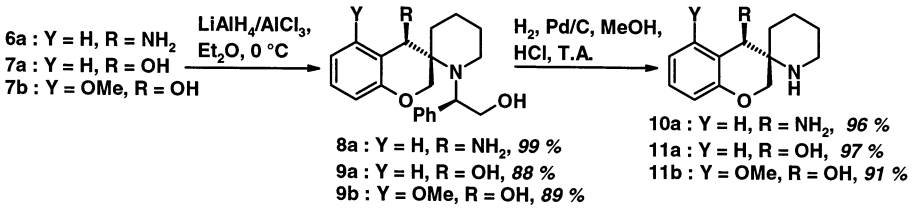
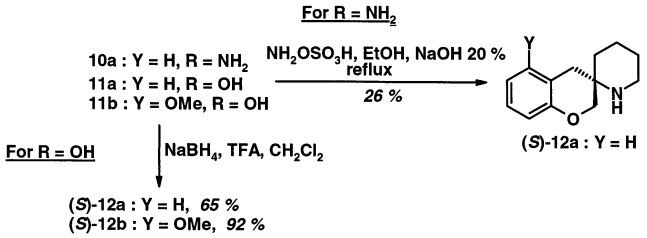
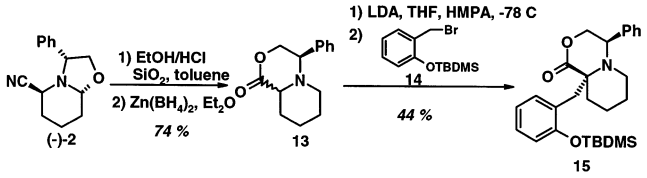
SCHEME 3



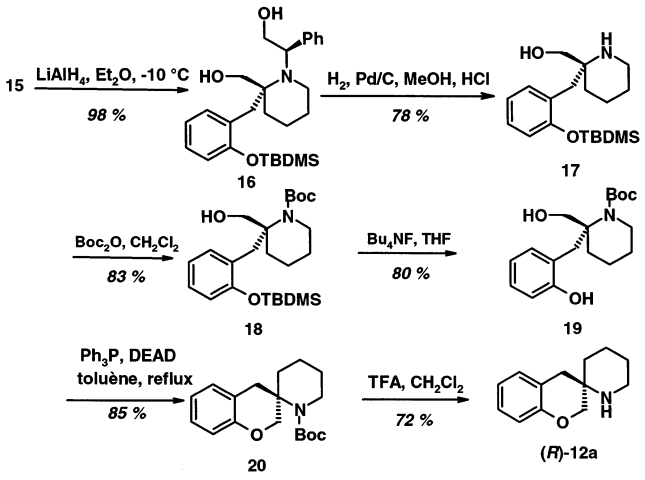
SCHEME 4



SCHEME 5



SCHEME 6



(Scheme 4). Hence, the amine (*S*)-**12a** was obtained in moderate yield (26%).

To increase the accessibility to amine (*S*)-**12a**, the alcohol function of **11a** was reduced in corresponding methylene by adding sodium borohydride in portions to a solution of amino alcohol **11a** in a mixture of TFA/CH_2Cl_2.[17] After a basic treatment and subsequent purification, amine (*S*)-**12a** was obtained in 65% yield. No racemization was observed during the reduction of the alcohol function. In this way, (3′*S*)-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((*S*)-**12a**) was synthesized in six steps in 27% overall yield starting from the nitrile (−)-**2**. The absolute configuration of (*S*)-**12a** was deduced from its precursor **11a**.

Synthesis of Amine (*R*)-12a. Complementary to the previous work, the synthesis of the *R* enantiomer was carried out with a different pathway, starting from the same synthon (−)-**2**. To invert the spirocyclic stereogenic center, we applied the method used for the synthesis of pipecolic acid derivatives.[18] Lactone **13** (7:3 epimeric mixture, Scheme 5) was synthesized in two steps from (−)-**2** in 74% overall yield. The enolate of compound **13** (LDA, THF, −78 °C) was alkylated with 2-(*tert*-butyldimethylsiloxy)benzyl bromide[19] (**14**) to furnish only the alkylated compound **15** in 44% yield. This compound exhibited (4*R*,9a*R*) absolute configuration in accordance with a mechanism described in the literature[18] involving the fact that the electrophile came on the more stable enolate conformer bearing an equatorial phenyl group.

Reduction of lactone **15** with a $LiAlH_4$ suspension in Et_2O gave diol **16** in 86% yield (Scheme 6). The chiral appendage in **16** was cleaved by hydrogenolysis (H_2, Pd/C, MeOH, HCl_{aq}) to furnish **17** in 78% yield. At this stage, according to our synthetic pathway, the amino function must be protected. Consequently, **17** reacted with Boc_2O in CH_2Cl_2 to afford **18** in 83% yield. The phenol function was regenerated by Bu_4NF in THF in 80% yield, and the obtained diol **19** was engaged in a Mitsunobu reaction. Cyclizated product **20** was thus obtained by using Ph_3P and DEAD in dry toluene in 85% yield. The synthesis finished by cleavage of the protecting group by TFA in CH_2Cl_2 to give (*R*)-**12a** in 72% yield. In this way (3′*R*)-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((*R*)-**12a**) was synthesized in nine steps in 8.8% overall yield starting from (−)-**2**.

The absolute configuration of (*S*)-**12a** was unambiguously determined from its optical rotation, opposite that of (*R*)-**12a**. Enantiomeric purities of aminochromans (*S*)-**12a** and (*R*)-**12a** were determinated by capillary electrophoresis using *β*-cyclodextrin as the chiral selector. Both enantiomers (*S*)-**12a** and (*R*)-**12a** were obtained in 99.6% and 99.3% enantiomeric purity, respectively.

Synthesis of Amines (*S*)-12b and (*R*)-12b. To obtain both enantiomers of the compound **1b** (**S 22178**), a synthetic pathway should be selected. As described above, amine (*S*)-**12a** was obtained in six steps in 27% overall yield, whereas amine (*R*)-**12a** was synthesized in nine steps in 8.8% overall yield. In both processes, nitrile (−)-**2** was used as the starting material. By extrapolating these results, it was supposed that amine (*S*)-**12b** could be so obtained starting from (−)-**2**, and conversely (+)-**2** could

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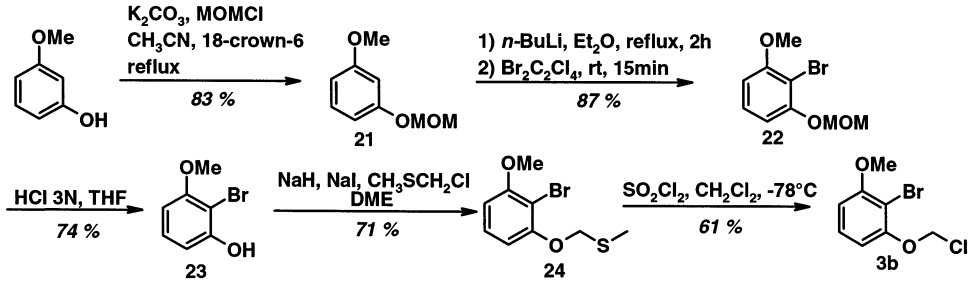
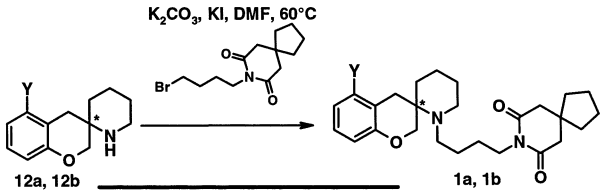
(21) Supplementary X-ray crystallographic data: University Chemical Lab, Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, U.K. E-mail: http:/www.deposit@chemcrys.cam.ac.uk.

SCHEME 7



SCHEME 8

SCHEME 9



Amine	Y	Product	Yield (%)
(*S*)-12a	H	(*S*)-1a	*66*
(*R*)-12a	H	(*R*)-1a	*76*
(*S*)-12b	OMe	(*S*)-1b	*64*
(*R*)-12b	OMe	(*R*)-1b	*72*

furnish amine (*R*)-**12b**. Consequently, we investigated the synthesis of both enantiomers of compound **1b** (**S 22178**)-with the first pathway starting from (−)-**2** for (+)-**S 22178** and (+)-**2** for (−)-**S 22178**.

As depicted in Scheme 7, alkylating agent **3b** used in the first step was obtained starting from 3-methoxyphenol. The phenol function was protected with a methoxymethyl group to afford **21** in 83% yield. The bromination of **21** was performed by using *n*-BuLi and $Br_2C_2Cl_4$ in Et_2O, giving **22** in 87% yield. Phenol **23** was regenerated with 3 N hydrochloric acid in THF in 74% yield. The phenolate (K_2CO_3, CH_3CN) of **23** was reacted with chloromethyl methyl sulfide to give thioacetal **24** in 71% yield. Finally, compound **3b** was obtained from thio compound **24** by action of sulfuryl chloride in dichloromethane at −78 °C in 61% yield, after crystallization in pentane.

As described for the generation of (*S*)-**12b**, the nitrile (−)-**2** was engaged in an anionic reaction using LDA in THF at −78 °C. The obtained anion was alkylated by **3b** to give **4b** as a single isomer. The synthetic pathway described for (*S*)-**12a** was used to generate amine (*S*)-**12b**. Compounds **4b**, **5b**, **7b**, **9b**, **11b**, and (*S*)-**12b** were obtained in similar yields compared to the generation of (*S*)-**12a**. Thus, both enantiomers (*S*)-**12b** and (*R*)-**12b** (Scheme 8) were synthesized starting from (−)-**2** and (+)-**2** in 34% and 32% overall yield, respectively.

Determination of the enantiomeric excess of (*S*)-**12b** and (*R*)-**12b** was performed by capillary electrophoresis using *β*-cyclodextrin as the chiral selector. Amines (*S*)-**12b** and (*R*)-**12b** were obtained in enantiomeric purity higher than 99.5%.

As depicted in Scheme 9, both enantiomers of **1a** and **1b** were synthesized according to the literature[7] in 66% and 76% yield starting from (*S*)-**12a** and (*R*)-**12a**, respectively, and in 64% and 72% yield starting from (*S*)-**12b** and (*R*)-**12b**, respectively.

Conclusion

In this work was reported the efficient synthesis of both enantiomers of compound **1b** (**S 22178**). First, amines (*S*)-**12a** and (*R*)-**12a** were synthesized as models, according to the CN(*R*,*S*) method in two different ways in 27% and 8.8% overall yield, respectively. The former way was used to generate amines (*S*)-**12b** and (*R*)-**12b** obtained in 32% and 34% overall yield, respectively. The enantiomeric purity of (*S*)-**12a** and (*R*)-**12a** was assessed by capillary electrophoresis, showing an enantiomeric purity superior to 99%. The same analytical procedure was applied to (*S*)-**12b** and (*R*)-**12b**, indicating an enantiomeric purity higher than 99.5%.

Experimental Section

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. Anhydrous solvents (Et_2O and THF) were freshly distilled from sodium/benzophenone under nitrogen prior to use. ^1H and ^{13}C NMR spectra were obtained at 250.131 and 62.9 MHz, respectively. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in hertz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Infrared spectra were recorded using NaCl film or KBr pellets. Mass spectroscopy (MS) was performed by ion spray (IS). Optical rotations were determined at rt and are referenced to the D-line of sodium. Melting points (mp's) were determinated in an open capillary tube and are uncorrected. Analytical thin-layer chromatography was performed on $60F_{254}$ silica gel precoated plates. Flash chromatography was performed using silica gel 40−70 μm (230−400 mesh).

(3*R*,5*S*,8a*R*)-5-[(2-Bromophenoxy)methyl]-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile (4a). To a solution of nitrile (−)-**2** (4 g., 17.5 mmol) in 50 mL of THF at −78 °C was added an LDA solution (2 M in hexane, 18.3 mL, 35.0 mmol). After 30 min of stirring, HMPA (8 mL, 35.0 mmol) and then 1-bromo-2-(chloromethoxy)-benzene (**3a**) (7.8 g, 35.0 mmol) in THF were added dropwise. The mixture was stirred for 3 h and then hydrolyzed by a saturated aq NH_4Cl solution. The reaction was extracted with CH_2Cl_2. Organic extracts were washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 98:2) to give **4a** (colorless oil, 4.48 g, 62% yield): $[\alpha]^{20}_D = -96$ (*c* 1.0, $CHCl_3$); IR (film) 2222 cm^{-1}; MS (IS) *m*/*z* 413 (M + 1, $^{79}Br)^+$, 415 (M +

1, $^{81}Br)^+$; ^1H NMR ($CDCl_3$) δ 1.67−2.37 (m, 6H), 3.38 (d, 1H, J = 9.1 Hz), 3.71 (d, 1H, J = 9.1 Hz), 3.78 (dd, 1H, J = 7.9 Hz, J' = 4.9 Hz), 4.16 (dd, 1H, J = 7.9 Hz, J' = 4.9 Hz), 4.25 (dd, 1H, J = 9.8 Hz, J' = 2.8 Hz), 4.28 (t, 1H, J = 7.9 Hz), 5.92 (dd, 1H, J = 7.9 Hz, J' = 1.2 Hz), 6.76 (td, 1H, J = 7.9 Hz, J' = 1.2 Hz), 7.00 (td, 1H, J = 7.9 Hz, J' = 1.2 Hz), 7.17−7.44 (m, 5H), 7.46 (dd, 1H, J = 7.9, J' = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 18.9, 28.7, 32.6, 61.1, 61.6, 71.2, 73.7, 91.0, 111.2, 116.1, 121.6, 126.4, 127.0, 127.4, 127.8, 132.6, 141.7, 152.9. Anal. Calcd for $C_{21}H_{21}N_2O_2Br$: C, 61.03; H, 5.12; N, 6.78; Br, 19.33. Found: C, 61.15; H, 5.03; N, 6.87; Br, 19.01.

(2*R*)-2-[(1*S*,12*S*)-10-Oxa-2,16-diazatetracyclo-[10.3.1.0^{3,12}.0^{4,9}]hexadeca-2,4(9),5,7-tetraen-16-yl]-2-phenyl-1-ethanol (5a). To a solution of **4a** (3.7 g, 8.9 mmol) in 40 mL of anhydrous Et_2O at −78 °C was added dropwise 11.2 mL (17.9 mmol) of *n*-BuLi (1.6 M in hexane). After 2 h of stirring, the reaction mixture was hydrolyzed, extracted with AcOEt, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, compound **5a** was isolated by flash chromatography (SiO_2; petroleum ether/AcOEt, 7:3) as an amorphous white solid (2.74 g, 91% yield): mp 73−75 °C; $[\alpha]^{20}_D$ = −16 (*c* 1.0, $CHCl_3$); IR (KBr) 3624−3122 cm^{-1}; MS (IS) *m*/*z* 335.5 (M + 1)$^+$; ^1H NMR ($CDCl_3$) δ 1.32−1.87 (m, 7H), 3.70−3.74 (m, 2H), 3.99 (t, 1H, J = 4.6 Hz), 4.06 (d, 1H, J = 10.7 Hz), 4.21 (d, 1H, J = 10.7 Hz), 5.03 (t, 1H, J = 2.1 Hz), 6.93 (d, 1H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.29−7.48 (m, 6H), 8.03 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.9, 20.7, 62.1, 65.7, 66.3, 74.0, 83.6, 116.7, 117.9, 122.2, 126.3, 128.4, 128.5, 129.2, 133.8, 140.4, 157.9, 168.1. Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.39; H, 6.67; N, 8.51.

(3*S*,8a*R*,14b*S*)-3-Phenyl-2,3,5,6,7,8-hexahydro-14b*H*-chromeno[4,3-*b*]pyrido[2,1-*c*][1,4]oxazin-14b-amine (6a). To a solution of imine **5a** (0.9 g, 2.7 mmol) in THF (20 mL) acidified with 1 N aq HCl (pH 3) was added portionwise $NaBH_3CN$ (0.186 g, 2.9 mmol). The reaction mixture was maintained at pH 3, refluxed for 4 h, neutralized at pH 7 with saturated aq $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 7:3) to give **6a** in 80% yield (0.72 g) as a white foam: $[\alpha]^{20}_D$ = −7 (*c* 1.0, $CHCl_3$); IR (film) 3540−3113 cm^{-1}; MS (IS) *m*/*z* 337.5 (M + 1)$^+$, 320.0 (M − NH_2)$^+$; ^1H NMR ($CDCl_3$) δ 1.50−1.80 (m, 6H), 2.30 (td, 1H, J = 11.9 Hz, J' = 3.7 Hz), 2.56 (dt, 1H, J = 11.9 Hz, J' = 3.7 Hz), 2.60 (br s, 2H), 3.58−3.70 (m, 1H), 3.87−3.99 (m, 2H), 4.62 (d, 1H, J = 10.7 Hz), 4.95 (d, 1H, J = 10.7 Hz), 6.83 (dd, 1H, J = 8.0 Hz, J' = 0.9 Hz), 6.95 (td, 1H, J = 8.0 Hz, J' = 0.9 Hz), 7.28−7.38 (m, 5H), 7.21 (td, 1H, J = 8.0 Hz, J' = 0.9 Hz), 7.43 (dd, 1H, J = 8.0 Hz, J' = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 26.0, 27.9, 45.8, 56.3, 60.0, 61.0, 66.4, 82.7, 116.9, 121.3, 125.6, 125.8, 127.9, 128.8, 129.7, 140.3, 152.4. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.03; H, 7.15; N, 8.45.

(3*S*,8a*R*,14b*S*)-3-Phenyl-2,3,5,6,7,8-hexahydro-14b*H*-chromeno[4,3-*b*]pyrido[2,1-*c*][1,4]oxazin-14b-ol (7a). Reduction of **5a**, in the manner described for the preparation of **6a**, but using MeOH as solvent and 36 h for the reflux, affords **7a** in 84% yield: white foam; $[\alpha]^{20}_D$ = −24 (*c* 1.0, $CHCl_3$); IR (film) 3524 cm^{-1}; MS (IS) *m*/*z* 338 (M + 1)$^+$, 320 (M − OH)$^+$; ^1H NMR ($CDCl_3$) δ 1.40−1.83 (m, 7H), 2.28 (td, 1H, J = 12.2 Hz, J' = 3.3 Hz), 2.56−2.62 (m, 1H), 3.61−3.73 (m, 1H), 3.91−4.03 (m, 2H), 4.44 (s, 1H), 4.62 (d, 1H, J = 10.6 Hz), 4.96 (dd, 1H, J = 10.6 Hz, J' = 1.2 Hz), 6.81 (dd, 1H, J = 7.6 Hz, J' = 0.9 Hz), 6.96 (td, 1H, J = 7.6 Hz, J' = 0.9 Hz), 7.16−7.49 (m, 6H), 7.63 (dd, 1H, J = 7.6 Hz, J' = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5, 25.8, 27.5, 45.6, 56.5, 60.6, 60.8, 66.5, 92.9, 116.3, 121.1, 124.0, 126.3, 128.1, 130.1, 139.4, 152.6. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.81; H, 6.84; N, 4.30.

(3′*S*,4′*R*)-[(1*R*)-2-Hydroxy-1-phenylethyl]-4′-amino-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] (8a). To a suspension of $LiAlH_4$ (0.485 mg, 12.8 mmol) and $AlCl_3$ (1.7 g, 12.8 mmol) in THF (15 mL) at 0 °C was added a solution of amino ether **6a** (0.86 g, 2.5 mmol) in THF (15 mL). The reaction mixture was stirred for 3 h at this temperature. A solution of NaOH (10%) (0.5 mL) was added, followed by addition of water (0.5 mL). After being stirred for 18 h, the mixture was filtrated through a Celite pad and concentrated. The residue was purified by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5), affording **8a** (0.85 g, 99%) as a white foam: $[\alpha]^{20}_D$ = −90 (*c* 1.0, $CHCl_3$); IR (film) 3624−3126 cm^{-1}; MS (IS) *m*/*z* 339.5 (M + 1)$^+$, 322.0 (M − NH_2)$^+$; ^1H NMR ($CDCl_3$) δ 1.36−1.74 (m, 6H), 2.54−2.59 (m, 1H), 2.63 (br s, 2H), 3.05−3.17 (m, 1H), 3.47 (dd, 1H, J = 10.3 Hz, J' = 4.5 Hz), 3.78 (d, 1H, J = 11.3 Hz), 3.95 (t, 1H, J = 10.3 Hz), 4.19 (d, 1H, J = 11.3 Hz), 4.44 (dd, 1H, J = 10.3 Hz, J' = 4.5 Hz), 4.77 (br s, 1H), 6.73 (d, 1H, J = 7.6 Hz), 6.95 (t, 1H, J = 7.6 Hz), 7.15 (t, 1H, J = 7.6 Hz), 7.21−7.32 (m, 5H), 7.48 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 22.8, 25.4, 31.6, 48.7, 54.3, 56.9, 62.7, 63.4, 64.0, 109.9, 120.3, 126.7, 126.8, 127.4, 127.8, 130.1, 146.0, 130.1. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.48; H,7.81; N, 8.45.

(3′*S*,4′*R*)-[(1*R*)-2-Hydroxy-1-phenylethyl]-4′-hydoxy-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] (9a). Following the same procedure described for product **8a**, **7a** (1.2 g, 3.5 mmol) was reduced with a suspension of $LiAlH_4$ (0.607 g, 16.0 mmol) and $AlCl_3$ (2.14 g, 16.0 mmol) in THF (15 mL) at 0 °C to furnish **9a** as a white foam (1.06 g, 88%): $[\alpha]^{20}_D$ = −65 (*c* 1.0, $CHCl_3$); IR (film) 3405 cm^{-1}; MS (IS) *m*/*z* 340 (M + 1)$^+$, 322.0 (M − OH)$^+$; ^1H NMR ($CDCl_3$) δ 1.48−1.68 (m, 6H), 2.54−2.62 (m, 1H), 3.04−3.09 (m, 1H), 3.52 (dd, 1H, J = 10.6 Hz, J' = 4.6 Hz), 3.85−3.98 (m, 3H), 4.15 (d, 1H, J = 11.6 Hz), 4.53 (dd, 1H, J = 10.6, J' = 4.6 Hz), 6.73 (dd, 1H, J = 7.9 Hz, J' = 0.9 Hz), 6.95 (td, 1H, J = 7.9 Hz, J' = 0.9 Hz), 7.11−7.36 (m, 6H), 7.55 (d, 1H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 25.1, 25.3, 40.4, 26.8, 60.2, 61.4, 62.5, 66.2, 102.7, 109.9, 113.0, 126.4, 127.4, 128.4, 129.0, 129.2, 140.0, 155.9. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.28; H, 7.48; N, 4.31.

(3′*S*,4′*R*)-4′-Amino-3′,4′-dihydrospiro[piperidine-2,3′-(2′*H*)-benzopyran] (10a). Hydrogenolysis of compound **8a** (0.96 g, 2.8 mmol) in MeOH (10 mL) in the presence of 2 drops of HCl (37%) and 10% Pd/C (100 mg) for 4 h afforded a compound which, after filtration and concentration, was disolved in CH_2Cl_2 and washed by a saturated aq solution of K_2CO_3. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2). The diamine **10a** (0.59 g, 96%) was obtained as a green oil: $[\alpha]^{20}_D$ = −101 (*c* 1.0, $CHCl_3$); IR (film) 3684−3103 cm^{-1}; MS (IS) *m*/*z* 219 (M + 1)$^+$, 202 (M − NH_2)$^+$; ^1H NMR ($CDCl_3$) δ 1.54−1.90 (m, 9H), 2.85−2.90 (m, 2H), 3.74 (br s, 1H), 4.05 (d, 1H, J = 11.1 Hz), 4.21 (d, 1H, J = 11.1 Hz), 6.82 (d, 1H, J = 7.9 Hz), 6.91 (t, 1H, J = 7.9 Hz), 7.16 (t, 1H, J = 7.9 Hz), 7.27 (d, 1H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 26.5, 27.1, 41.6, 52.0, 54.7, 66.3, 116.8, 121.3, 127.3, 129.0, 130.4, 153.7. Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.48; H, 8.28; N, 12.99.

(3′*S*,4′*R*)-4′-Hydroxy-3′,4′-dihydrospiro[piperidine-2,3′-(2′*H*)-benzopyran] (11a). Following the same procedure as for product **10a**, hydrogenolysis of **9a** (0.50 g, 1.5 mmol) afforded **11a** (0.31 g, 97%) as a white solid: mp 122−123 °C; $[\alpha]^{20}_D$ = −37 (*c* 1.0, $CHCl_3$); IR (KBr) 3354, 3328−3003 cm^{-1}; MS (IS) *m*/*z* 220 (M + 1)$^+$, 202 (M − OH)$^+$; ^1H NMR ($CDCl_3$) δ 1.54−1.78 (m, 6H), 2.84−2.92 (m, 1H), 3.18−3.23 (m, 1H), 4.29 (d, 1H, J = 11.6 Hz), 4.35 (d, 1H, J = 11.6 Hz), 4.99 (s, 1H), 6.16 (br s, 2H), 6.79 (d, 1H, J = 7.9 Hz), 6.94 (t, 1H, J = 7.9 Hz), 7.18 (t, 1H, J = 7.9 Hz), 7.39 (d, 1H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6, 23.3, 23.6, 40.8, 55.2, 64.9, 69.0, 116.2, 121.7, 122.7, 129.2, 129.5, 152.9. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.25; H, 7.79; N, 6.48.

(3′*S*)-3′,4′-Dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((S)-12a). The diamine **10a** (0.1 g, 0.46 mmol) was dissolved in a refluxing mixture of EtOH/NaOH (10%, 1:1, 4 mL). NH_2OSO_3H (1.0 g, 9.16 mmol) was added portionwise over 30 min. After 3 h of stirring, the reaction was extracted

with CH_2Cl_2 and dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) to furnish amine (*S*)-**12a** (0.024 mg, 26%) as a colorless oil: $[\alpha]^{20}_D = -37$ (*c* 1.0, $CHCl_3$); IR (film) 3684−3035 cm^{-1}; MS (IS) *m*/*z* 204 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.48−1.78 (m, 6H), 2.71 (d, 1H, $J = 16.4$ Hz), 2.79−2.85 (m, 3H), 3.85 (d, 1H, $J = 10.9$ Hz), 4.09 (dd, 1H, $J = 10.9$ Hz, $J' = 2.1$ Hz), 6.81−6.89 (m, 2H), 7.02−7.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.4, 26.4, 33.0, 36.6, 41.1, 48.4, 71.5, 116.5, 120.5, 120.9, 127.5, 130.6, 153.9. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.74; H, 8.38; N, 6.93.

Reduction of Amino Alcohol 11a to Amine (*S*)-12a. To a suspension of the amino alcohol **11a** (0.1 g, 0.4 mmol) and $NaBH_4$ (0.14 g, 4 mmol) in CH_2Cl_2 was added dropwise over 30 min 2 mL of TFA. The mixture was refluxed for 42 h and then hydrolyzed by a solution of saturated K_2CO_3. Extraction and flash chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) gave amine (*S*)-**12a** (0.06 g, 65%) with the same characteristics as described above.

(4*R*,9a*R*)-9a-(2-*tert*-Butyldimethylsiloxybenzyl)-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1(6H)-one (15). To a solution of lactone **13** (0.51 g, 2.2 mmol) in 50 mL of THF at −78 °C was added an LDA solution (2.2 mL, 4.4 mmol). After 30 min of stirring, HMPA (1.0 mL, 4.4 mmol) and then 2-(*tert*-butyldimethylsiloxy)benzyl bromide (**14**) (1.55 g, 4.4 mmol) in THF were added dropwise. The mixture was stirred for 3 h and then hydrolyzed by a saturated aq NH_4Cl solution. The reaction was extracted with CH_2Cl_2, and the organic layers were washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 98:2) to give **15** (colorless oil, 0.44 g, 44%): $[\alpha]^{20}_D = -61$ (*c* 1.0, $CHCl_3$); IR (film) 1731 cm^{-1}; MS (IS) *m*/*z* 452.5 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 0.25 (s, 3H), 0.26 (s, 3H), 1.01 (s, 9H), 1.40−1.85 (m, 6H), 2.41−2.49 (m, 1H), 2.65−2.76 (m, 1H), 3.18 (d, 1H, $J = 13.7$ Hz), 3.56 (d, 1H, $J = 13.7$ Hz), 4.12 (dd, 1H, $J = 8.8$ Hz, $J' = 3.6$ Hz), 4.26−4.37 (m, 2H), 6.81−6.88 (m, 2H), 7.09−7.37 (m, 7H); ^{13}C NMR ($CDCl_3$) δ −3.8, −3.4, 18.7, 22.3, 26.1, 26.9, 34.6, 38.3, 49.4, 64.2, 66.7, 74.8, 111.8, 120.2, 126.4, 126.7, 127.1, 127.5, 127.6, 129.7, 143.9, 158.5, 171.7. Anal. Calcd for $C_{27}H_{37}NO_3Si$: C, 71.80; H, 8.26; N, 3.10. Found: C, 71.98; H, 8.45; N, 3.15.

(2*R*)-2-[(2*R*)-2-(2-*tert*-Butyldimethylsilyloxybenzyl)-2-(hydroxymethyl)tetrahydro-1(2*H*)-pyridinyl]-2-phenyl-1-ethanol (16). To a suspension of $LiAlH_4$ (0.240 mg, 6.2 mmol) in Et_2O (10 mL) at −10 °C was added a solution of lactone **15** (0.56 g, 1.24 mmol) in Et_2O (10 mL). The reaction mixture was stirred for 3 h at rt. A solution of NaOH (10%) (0.25 mL) was added, followed by addition of water (0.5 mL). After being stirred for 4 h, the mixture was filtrated through a Celite pad and concentrated. The crude product was purified by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5), affording **16** (0.55 g, 98%) as a white foam: $[\alpha]^{20}_D = -48$ (*c* 1.0, $CHCl_3$); IR (film) 3688−3028 cm^{-1}; MS (IS) *m*/*z* 456.5 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 0.22 (s, 3H), 0.32 (s, 3H), 1.02 (s, 9H), 1.41−1.84 (m, 6H), 2.82 (d, 1H, $J = 13.4$ Hz), 2.83−2.89 (m, 1H), 2.91 (d, 1H, $J = 13.4$ Hz), 3.19−3.23 (m, 1H), 3.68 (dd, 1H, $J = 10.6$ Hz, $J' = 4.9$ Hz), 3.72 (d, 1H, $J = 12.2$ Hz), 3.92 (d, 1H, $J = 12.2$ Hz), 4.00 (t, 1H, $J = 10.6$ Hz), 4.28 (br s, 2H), 4.85 (dd, 1H, $J = 10.6$ Hz, $J' = 4.9$ Hz), 6.84−6.94 (m, 2H), 7.08−7.23 (m, 2H), 7.30−7.53 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −3.8, −3.4, 18.7, 20.9, 26.2, 27.2, 30.7, 31.5, 41.3, 61.0, 62.6, 62.7, 66.3, 119.4, 121.2, 127.1, 127.3, 128.3, 128.9, 129.2, 132.4, 140.3, 153.9. Anal. Calcd for $C_{27}H_{41}NO_3Si$: C, 71.16; H, 9.07; N, 3.07. Found: C, 71.23; H, 9.09; N, 3.11.

[(2*R*)-2-(2-*tert*-Butyldimethylsilyloxybenzyl)hexahydro-2-pyridinyl]methanol (17). Hydrogenolysis of compound **16** (0.35 g, 0.77 mmol) in MeOH (15 mL) in the presence of 2 drops of HCl (37%) and 10% Pd/C (40 mg) for 1 h afforded a compound which, after filtration and concentration, was disolved in CH_2Cl_2 and washed by a saturated aq solution of K_2CO_3. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5). The amino alcohol **17** (0.20 g, 78%) was isolated as a green oil: $[\alpha]^{20}_D = -8$ (*c* 1.0, $CHCl_3$); IR (film) 3401−3088 cm^{-1}; MS (IS) 336.5 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 0.27 (s, 3H), 0.29 (s, 3H), 0.99 (s, 9H), 1.52−1.98 (m, 6H), 3.14−3.39 (m, 4H), 3.45 (d, 1H, $J = 12.5$ Hz), 3.79 (d, 1H, $J = 12.5$ Hz), 5.97 (br s, 2H), 6.84 (dd, 1H, $J = 7.9$ Hz, $J' = 1.2$ Hz), 6.92 (td, 1H, $J = 7.9$ Hz, $J' = 1.2$ Hz), 7.13 (td, 1H, $J = 7.9$ Hz, $J' = 1.2$ Hz), 7.29 (dd, 1H, $J = 7.9$ Hz, $J' = 1.2$ Hz); ^{13}C NMR ($CDCl_3$) δ −3.6, −3.5, 18.6, 18.7, 22.6, 26.2, 27.1, 30.0, 40.3, 61.5, 64.0, 119.7, 121.8, 125.4, 128.3, 132.7, 154.3. Anal. Calcd for $C_{19}H_{33}NO_2Si$: C, 68.01; H, 9.91; N, 4.17. Found: C, 67.94; H, 9.87; N, 4.23.

***tert*-Butyl (2*R*)-2-(2-*tert*-Butyldimethylsilyloxybenzyl)-2-(hydroxymethyl)tetrahydro-1(2*H*)-pyridinecarboxylate (18).** To a solution of amino alcohol **17** (0.152 g, 0.45 mmol) in CH_2Cl_2 (4 mL) in the presence of Et_3N (0.13 mL, 0.90 mmol) was added 0.153 g (0.68 mmol) of Boc_2O. The solution was stirred for 72 h, then hydrolyzed, extracted by CH_2Cl_2, and dried over $MgSO_4$. Purification was achieved by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) to furnish **18** (0.163 g, 83%) as a colorless oil: $[\alpha]^{20}_D = +26$ (*c* 1.0, $CHCl_3$); IR (film) 3405−3105, 1736 cm^{-1}; MS (IS) *m*/*z* 436.5 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 0.22 (s, 3H), 0.23 (s, 3H), 1.01 (s, 9H), 1.41 (s, 9H), 1.52−1.98 (m, 6H), 2.88−3.12 (m, 3H), 3.55 (dd, 1H, $J = 12.2$ Hz, $J' = 7.0$ Hz), 3.93−4.04 (m, 2H), 4.22 (br s, 1H), 6.79 (dd, 1H, $J = 7.6$ Hz, $J' = 1.2$ Hz), 6.83 (td, 1H, $J = 7.6$ Hz, $J' = 1.2$ Hz), 7.04 (dd, 1H, $J = 7.6$ Hz, $J' = 1.2$ Hz), 7.13 (dd, 1H, $J = 7.6$ Hz, $J' = 1.2$ Hz); ^{13}C NMR ($CDCl_3$) δ −3.9, −3.8, 18.5, 18.9, 24.6, 26.1, 27.8, 28.6, 30.1, 32.7, 42.5, 63.8, 69.6, 80.2, 118.8, 121.3, 127.3, 128.4, 131.7, 154.3, 156.6. Anal. Calcd for $C_{24}H_{41}NO_4Si$: C, 66.16; H, 9.49; N, 3.21. Found: C, 66.45; H, 9.60; N, 3.25.

***tert*-Butyl (2*R*)-2-(2-Hydroxybenzyl)-2-(hydroxymethyl)tetrahydro-1(2*H*)-pyridinecarboxylate (19).** To a solution of alcohol **18** (0.2 g, 0.46 mmol) in CH_2Cl_2 (8 mL) was added 0.92 mL (0.92 mmol) of a 1 M solution of Bu_4NF in THF. The solution was stirred for 4 h, then hydrolyzed, extracted by CH_2Cl_2, and dried over $MgSO_4$. Flash chromatography (SiO_2, CH_2Cl_2) gave diol **18** as a colorless oil (0.117 g, 80%): $[\alpha]^{20}_D = +40$ (*c* 1.0, $CHCl_3$); IR (film) 3644−3105, 1756 cm^{-1}; MS (IS) *m*/*z* 322 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.45−1.85 (m, 6H), 2.87 (d, 1H, $J = 14.0$ Hz), 3.01−3.12 (m, 1H), 3.19 (dd, 1H, $J = 13.1$ Hz, $J' = 11.3$ Hz), 3.28 (d, 1H, $J = 14.0$ Hz), 3.77 (d, 1H, $J = 13.1$ Hz), 4.04−4.11 (m, 1H), 6.79 (td, 1H, $J = 7.9$ Hz, $J' = 1.2$ Hz), 6.91 (dd, 1H, $J = 7.9$ Hz, $J' = 1.2$ Hz), 7.09−7.17 (m, 2H), 7.88 (dd, 1H, $J = 11.3$ Hz, $J' = 1.8$ Hz), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.1, 24.8, 28.5, 30.0, 31.1, 43.1, 63.7, 68.3, 81.5, 118.6, 119.6, 122.8, 128.6, 132.6, 156.8, 157.4. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.48; H, 8.62; N, 4.41.

***tert*-Butyl (3′*R*)-3′,4′-Dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran]carboxylate (20).** To a solution of diol **19** (0.055 g, 0.17 mmol) in dry toluene (5 mL) were added successively Ph_3P (0.055 g, 0.19 mmol) and DEAD (0.035 mL, 0.19 mmol). After the solution was stirred at reflux for 18 h, the solvent was evaporated, and the crude product was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 95:5) to furnish benzopyran **20** (0.045 g, 85%) as a white solid: mp 75−77 °C; $[\alpha]^{20}_D = -44$ (*c* 1.0, $CHCl_3$); IR (KBr) 1695 cm^{-1}; MS (IS) *m*/*z* 304 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.44−1.78 (m, 6H), 2.88 (dd, 1H, $J = 16.0$ Hz, $J' = 2.2$ Hz), 3.31−3.41 (m, 1H), 3.57 (d, 1H, $J = 16.2$ Hz), 3.69−3.78 (m, 1H), 4.07 (dd, 1H, $J = 10.7$ Hz, $J' = 2.5$ Hz), 4.78 (d, 1H, $J = 10.7$ Hz), 6.79−6.89 (m, 2H), 7.02−7.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.9, 23.9, 28.6, 29.8, 33.6, 41.6, 54.9, 70.8, 80.2, 116.6, 120.8, 121.7, 127.2, 130.2, 153.6, 155.5. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.19; H, 8.26; N, 4.65.

(3′*R*)-3′,4′-Dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((*R*)-12a). To a solution of protected amine **20** (0.1 g, 0.33 mmol) in CH_2Cl_2 was added TFA (0.31 mL, 3.96 mmol), and the mixture was stirred for 18 h. A saturated aq solution of K_2CO_3 was then added, and the product was extracted by CH_2Cl_2 and dried over $MgSO_4$. After concentration under reduced

pressure, purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) to give amine (*R*)-**12a** (0.048 g, 72%) with the same characteristics as described for (*S*)-**12a**: $[\alpha]^{20}_D = +37$ (*c* 1.0, $CHCl_3$).

1-Methoxy-3-(methoxymethoxy)benzene (21). To a solution of 3-methoxyphenol (10 g, 80.5 mmol) in CH_3CN (250 mL) was added under nitrogen at 0 °C dry K_2CO_3 (22 g, 161.0 mmol). After 15 min, 18-crown-6 (3 g, 21.7 mmol) and MOMCl (7 mL, 92.2 mmol) were added. The mixture was stirred for 18 h at rt and then filtrated. The filtrate was evaporated under reduced pressure and purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 98:2), giving **21** as a colorless oil (11.3 g, 83%): IR (film) 1283 cm^{-1}; MS (IS) *m*/*z* 169 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 3.47 (s, 3H), 3.78 (s, 3H), 5.15 (s, 2H), 6.56−6.64 (m, 3H), 7.20 (t, 1H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 55.2, 55.9, 94.4, 102.6, 107.4, 108.3, 129.8, 158.4, 160.7.

2-Bromo-1-methoxy-3-(methoxymethoxy)benzene (22). To a solution of **21** (2 g, 11.9 mmol) in Et_2O (40 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 8.8 mL, 14.3 mmol), and the resulting solution was refluxed for 2 h. After the solution was cooled at rt, 4.64 g (14.3 mmol) of $Br_2C_2Cl_4$ was added in portions, and the resulting mixture was stirred for 15 min. The mixture was hydrolyzed and extracted by AcOEt. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 95:5) to furnish **22** as a yellow oil (87%, 2.57 g): IR (film) 1258 cm^{-1}; MS (IS) *m*/*z* 247 $(M + 1, {}^{79}Br)^+$, 249 $(M + 1, {}^{81}Br)^+$; ^1H NMR ($CDCl_3$) δ 3.52 (s, 3H), 3.90 (s, 3H), 5.25 (s, 2H), 6.61 (d, 1H, $J = 8.4$ Hz), 6.80 (d, 1H, $J = 8.4$ Hz), 7.21 (t, 1H, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 56.4, 95.1, 102.4, 105.6, 108.5, 128.2, 155.0, 157.2.

2-Bromo-3-methoxyphenol (23). Compound **22** (5.94 g, 24 mmol) and 3 N HCl (50 mL) in THF (35 mL) were stirred 24 h at rt. A saturated solution of $NaHCO_3$ was then added, and the resulting solution was extracted by CH_2Cl_2 and dried over $MgSO_4$ before concentration. Purification by flash chromatography (SiO_2; petroleum ether/AcOEt, 95:5) gave 3.6 g of a tan solid (74%): mp 79−80 °C; IR (KBr) 3400 cm^{-1}; MS *m*/*z* (IS) 204 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 5.62 (s, 1H), 6.48 (d, 1H, $J = 8.3$ Hz), 6.68 (d, 1H, $J = 8.3$ Hz), 7.17 (t, 1H, $J = 8.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 56.3, 100.0, 103.6, 108.5, 128.6, 153.6, 156.5.

2-Bromo-1-methoxy-3-[(methylthio)methoxy]benzene (24). Under nitrogen, 3.6 g (17.7 mmol) of phenol **23**, NaI (2.66 g, 17.7 mmol), and chloromethyl methyl sulfide (2.0 mL, 19.5 mmol) were added successively to a suspension of NaH (60% in mineral oil, 1.42 g, 35.4 mmol) in DME (30 mL) at 0 °C. The mixture was stirred at rt for 4 h, hydrolyzed, and extracted by AcOEt. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 98:2) to give **24** as a yellow oil (3.3 g, 71%): IR (film) 1235 cm^{-1}; MS (IS) *m*/*z* 286 $(M + Na)^+$; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.88 (s, 3H), 5.22 (s, 2H), 6.59−6.64 (m, 2H), 7.21 (t, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 15.1, 56.8, 73.8, 103.4, 106.0, 108.4, 155.0, 157.7.

2-Bromo-1-(chloromethoxy)-3-methoxybenzene (3b). To a solution of **24** (2.5 g, 0.95 mmol) in CH_2Cl_2 (35 mL) at −78 °C was added dropwise SO_2Cl_2 (0.79 mL, 0.95 mmol) in 25 mL of CH_2Cl_2. After 1 h at −78 °C, CH_2Cl_2 was evaporated, and the residue was crystallized in pentane to furnish **3b** as a white solid (1.45 g, 61%): mp 57−58 °C; IR (KBr) 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 5.92 (s, 2H), 6.70 (d, 1H, $J = 8.5$ Hz), 6.88 (d, 1H, $J = 8.5$ Hz), 7.28 (t, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 56.9, 74.4, 108.0, 110.3, 111.8, 128.8, 156.7, 160.4.

(3*R*,5*S*,8a*R*)-5-[(2-Bromo-3-methoxyphenoxy)methyl]-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile (4b). Alkylation of 3.16 g (13.8 mmol) of (−)-**2** by the bromo derivative **3b** (7 g, 27.7 mmol) in the manner described for the preparation of **4a** afforded **4b** as a yellow solid in 57% yield: mp 104−105 °C; $[\alpha]^{20}_D = -116$ (*c* 1.0, $CHCl_3$); IR (KBr) 2200 cm^{-1}; MS (IS) *m*/*z* 443.5 $(M + 1, {}^{79}Br)^+$, 445.5 $(M + 1, {}^{81}Br)^+$; ^1H NMR ($CDCl_3$) δ 1.61−2.48 (m, 6H), 3.36 (d, 1H, $J = 8.9$ Hz), 3.71 (d, 1H, $J = 8.9$ Hz), 3.75−3.82 (m, 2H), 3.85 (s, 3H), 4,15 (dd, 1H, $J = 8.5$ Hz, $J' = 4.9$ Hz), 4.24 (dd, 1H, $J = 9.7$ Hz, $J' = 2.1$ Hz), 4.27 (t, 1H, $J = 8.5$ Hz), 5.59 (d, 1H, $J = 8.2$ Hz), 6.49 (d, 1H, $J = 8.2$ Hz), 6.96 (t, 1H, $J = 8.2$ Hz), 7.17−7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 28.5, 32.3, 55.4, 60.9, 61.4, 71.3, 73.5, 90.8, 100.4, 103.7, 104.2, 116.0, 126.2, 126.8, 127.0, 127.7, 141.5, 154.0, 156.1.

(2*R*)-2-[(1*S*,12*S*)-5-Methoxy-10-oxa-2,16-diazatetracyclo-[10.3.1.0^{3,12}.0^{4,9}]hexadeca-2,4(9),5,7-tetraen-16-yl]-2-phenyl-1-ethanol (5b). Imine **5b** was prepared from **4b** (3.47 g, 7.8 mmol) in 84% yield as described for **5a** to yield an amorphous white solid: mp 171−172 °C; $[\alpha]^{20}_D = -40$ (*c* 1.0, $CHCl_3$); IR (KBr) 3614−3002 cm^{-1}; MS (IS) 365.5 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.34−1.87 (m, 7H), 3.72 (dd, 1H, $J = 10.9$ Hz, $J' = 3.6$ Hz), 3.79 (dd, 1H, $J = 10.9$ Hz, $J' = 3.6$ Hz), 3.91−4.05 (m, 4H), 3.96 (s, 3H), 5.23 (t, 1H, $J = 2.1$ Hz), 6.53 (d, 1H, $J = 7.6$ Hz), 6,57 (d, 1H, $J = 7.6$ Hz), 7.25−7.4 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 16.4, 21.2, 21.6, 56.0, 61.3, 65.4, 66.5, 72.2, 83.2, 103.5, 109.5, 126.9, 127.6, 128.1, 128.4, 132.9, 140.3, 158.6, 160.0, 165.2.

(3*S*,8a*R*,14b*S*)-5-Methoxy-3-phenyl-2,3,5,6,7,8-hexahydro-14b*H*-chromeno[4,3-*b*]pyrido[2,1-*c*][1,4]oxazin-14b-ol (7b). Reduction of **5b** (0.94 g, 2.56 mmol) in the manner described for the preparation of **7a** afforded **7b** in 96% yield: amorphous white solid; mp 179−180 °C; $[\alpha]^{20}_D = +2.5$ (*c* 1.0, $CHCl_3$); IR (KBr) 3469 cm^{-1}; MS (IS) *m*/*z* 368 $(M + 1)^+$, 350 $(M - OH)^+$; ^1H NMR ($CDCl_3$) δ 1.50−1.92 (m, 6H), 2.26−2.37 (m, 1H), 2.50−2.56 (m, 1H), 3.55 (dd, 1H, $J = 11.0$ Hz, $J' = 3.8$ Hz), 3.92 (s, 3H), 3.93 (dd, 1H, $J = 11.0$ Hz, $J' = 3.8$ Hz), 4.28 (t, 1H, $J = 11.0$ Hz), 4.66 (d, 1H, $J = 10.7$ Hz), 4.79 (d, 1H, $J = 10.7$ Hz), 5.89 (s, 1H), 6.51 (d, 2H, $J = 7.9$ Hz), 7.14 (t, 1H, $J = 7.9$ Hz), 7.21−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.3, 25.4, 26.4, 44.8, 55.7, 55.9, 60.0, 60.4, 66.1, 94.6, 103.5, 110.3, 113.2, 127.3, 128.2, 129.4, 139.9, 154.3, 158.2.

(3′*S*,4′*R*)-[(1*R*)-2-Hydroxy-1-phenylethyl]-4′-hydoxy-5′-methoxy-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] (9b). Following the same procedure described for product **9a**, **9b** (1.07 g, 2.9 mmol) was reduced with a suspension of $LiAlH_4$ (0.50 mg, 13.1 mmol) in Et_2O (15 mL) at 0 °C to furnish **9b** (0.95 g) in 89% yield as an amorphous white solid: mp 70−72 °C; $[\alpha]^{20}_D = -91$ (*c* 1.0, $CHCl_3$); IR (KBr) 3588−3106 cm^{-1}; MS (IS) *m*/*z* 370 $(M + 1)^+$, 352.0 $(M - OH)^+$; ^1H NMR ($CDCl_3$) δ 1.11−1.92 (m, 7H), 2.74−2.84 (m, 1H), 2.94−3.05 (m, 1H), 3.39 (sl, 1H), 3.43 (dd, 1H, $J = 10.3$ Hz, $J' = 4.6$ Hz), 3.88 (t, 1H, $J = 10.3$ Hz), 3.89 (s, 3H), 4.09−4.20 (m, 2H), 4.51 (dd, 1H, $J = 10.3$ Hz, $J' = 4.6$ Hz), 6.49 (d, 1H, $J = 7.6$ Hz), 6.53 (d, 1H, $J = 7.6$ Hz), 7.15 (t, 1H, $J = 7.6$ Hz), 7.27−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9, 24.8, 25.6, 40.4, 55.7, 26.9, 60.4, 61.2, 62.4, 66.2, 102.8, 109.9, 113.0, 127.8, 128.6, 129.0, 129.2, 140.0, 154.6, 159.3.

(3′*S*,4′*R*)-4′-Hydoxy-5′-methoxy-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] (11b). Hydrogenolysis of compound **9b** (0.95 g, 2.6 mmol) was performed in MeOH (30 mL) in the presence of 2 drops of HCl (37%) and 10% Pd/C (100 mg) for 4 h. After filtration and concentration, the residue was dissolved in CH_2Cl_2 and washed by a saturated aq solution of K_2CO_3. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) and afforded amino alcohol **11b** (0.58 g, 91%) as a white solid: mp 181−182°C; $[\alpha]^{20}_D = -119$ (*c* 1.0, $CHCl_3$); IR (KBr) 3347, 3307−3003 cm^{-1}; MS (IS) *m*/*z* 250 $(M + 1)^+$, 232 $(M - OH)^+$; ^1H NMR ($CDCl_3$) δ 1.55−1.98 (m, 6H), 2.90−2.98 (m, 2H), 3.84 (s, 3H), 3.97 (d, 1H, $J = 11.2$ Hz), 4.18 (d, 1H, $J = 11.2$ Hz), 4.89 (br s, 1H), 6.48 (d, 1H, $J = 11.6$ Hz), 6.51 (d, 1H, $J = 11.6$ Hz), 7.16 (t, 1H, $J = 11.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 19.6, 24.9, 26.8, 41.1, 53.2, 55.7, 63.0, 66.1, 103.0, 109.9, 111.7, 129.9, 154.3, 159.4.

(3′*S*)-5′-Methoxy-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((S)-12b). Following the same procedure as described for product (*S*)-**12a**, **11b** (0.08 g, 0.3 mmol) was

reduced with a suspension of $NaBH_4$ (0.113 g, 3.1 mmol) in TFA (2 mL) and CH_2Cl_2 at 0 °C for 1.5 h to furnish (*S*)-**12b** (0.069 g, 92%) as a colorless oil: $[\alpha]^{20}_D = -46$ (*c* 0.5, $CHCl_3$); IR (film) 3740−3040 cm^{-1}; MS (IS) *m*/*z* 234 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.61−1.78 (m, 6H), 2.66 (d, 1H, $J = 17.3$ Hz), 2.92 (d, 1H, $J = 17.3$ Hz), 2.92−3.05 (m, 2H), 3.80 (s, 3H), 3.89 (d, 1H, $J = 11.0$ Hz), 4.11 (d, 1H, $J = 11.0$ Hz), 5.37 (br s, 1H), 6.44 (d, 1H, $J = 8.5$ Hz) 6.48 (d, 1H, $J = 8.5$ Hz), 7.07 (t, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.3, 26.5, 30.6, 33.3, 41.1, 48.0, 55.6, 71.7, 102.4, 109.3, 109.7, 127.1, 154.7, 158.7. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.02; H, 8.19; N, 6.07.

(3′*S*)-1-[4-(7,9-Dioxo-8-azaspiro[4.5]decanyl)butyl]-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((S)-1a). To a solution of amine (*S*)-**12a** (0.05 g, 0.12 mmol) in dry CH_3CN (3 mL) were added K_2CO_3 (0.084 g, 0.36 mmol), 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (0.077 g, 0.17 mmol), and KI (catalytic amount), and the mixture was refluxed for 18 h. After total consumption of starting material, the mixture was hydrolyzed, and the crude product was extracted with CH_2Cl_2 and dried over $MgSO_4$. After column chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5), (*S*)-**1a** was obtained as an oil (0.07 g) in 66% yield: $[\alpha]^{20}_D = +34$ (*c* 1.0, $CHCl_3$); IR (film) 1727 and 1682 cm^{-1}; MS (IS) *m*/*z* 425.5 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.39−1.77 (m, 18H), 2.32−2.49 (m, 2H), 2.57 (s, 4H), 2.59−2.74 (m, 3H), 2.95 (d, 1H, $J = 16.4$ Hz), 3.75 (t, 2H, $J = 7.3$ Hz), 3.96 (dd, 1H, $J = 10.6$ Hz, $J' = 1.8$ Hz), 4.02 (d, 1H, $J = 10.6$ Hz), 6.79 (d, 1H, $J = 8.5$ Hz), 6.86 (d, 1H, $J = 8.5$ Hz), 7.04−7.09 (m, 2H).); ^{13}C NMR ($CDCl_3$) δ 20.3, 24.3, 25.4, 25.9, 27.1, 30.4, 32.0, 37.6, 39.6, 45.0, 47.6, 49.3, 53.1, 70.8, 116.5, 120.7, 122.2, 127.1, 130.4, 154.1, 172.3. Anal. Calcd for $C_{26}H_{36}N_2O_3$: C, 73.55; H, 8.55; N, 6.60. Found: C, 73.48; H, 8.52; N, 6.67.

(3′*S*)-1-[4-(7,9-Dioxo-8-azaspiro[4.5]decanyl)butyl]-5′-methoxo-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*)-benzopyran] ((S)-1b). As described above, amine (*S*)-**12b** (0.05 g, 0.11 mmol) was alkylated by 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione to furnish, after column chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5), (S)-**1b** as an oil (0.07 g) in 64% yield: $[\alpha]^{20}_D = +24$ (*c* 1.3, $CHCl_3$); IR (film) 1725 and 1673 cm^{-1}; MS (IS) *m*/*z* 455 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.34−1.78 (m, 18H), 2.31−2.39 (m, 1H), 2.46−2.2.56 (m, 1H), 2.57 (s, 4H), 2.60−2.75 (m, 4H), 3.75 (t, 2H, $J = 7.3$ Hz), 3.82 (s, 3H), 3.88 (d, 1H, $J = 10.3$ Hz), 3.97 (d, 1H, $J = 10.3$ Hz), 6.42 (d, 1H, $J = 8.2$ Hz), 6.74 (d, 1H, $J = 8.2$ Hz), 7.04 (t, 1H, $J = 8.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.3, 24.2, 24.3, 25.5, 26.0, 27.2, 32.4, 37.6, 39.6, 45.0, 47.7, 49.4, 52.7, 55.5, 71.1, 102.1, 109.3, 111.1, 126.8, 128.7, 129.8, 154.9, 158.5, 172.3. Anal. Calcd for $C_{27}H_{38}N_2O_4$: C, 71.34; H, 8.43; N, 6.16. Found: C, 71.37; H, 8.47; N, 6.23.

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Supporting Information Available: X-ray crystal structure data and ORTEP diagram of compound **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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