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Application of the photocyclization reaction of 1,2-cyclopenta-fused pyridinium perchlorate to formal total syntheses of (−)-cephalotaxine

Zhiming Zhao and Patrick S. Mariano*

Department of Chemistry, University of New Mexico, Albuquerque, NM 87131, USA

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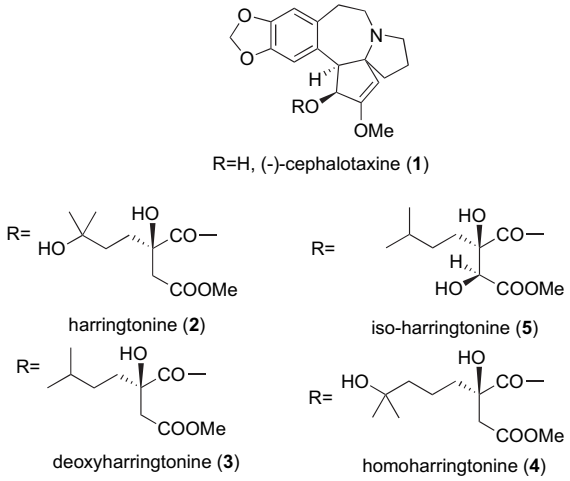
Abstract—Two strategies for the formal total synthesis of (−)-cephalotaxine, based on pyridinium salt photochemistry, are described. The routes begin with photocyclization reaction of 1,2-cyclopenta-fused pyridinium perchlorate. This process efficiently and regioselectively produces a tricyclic aziridine, which undergoes sequential aziridine ring opening and enzymatic desymmetrization to generate enantio-enriched intermediates that contain the spirocyclic D,E-ring system found in cephalotaxine. These substances serve as precursors to late stage key intermediates used by Mori, Tietze, and Yoshida in earlier syntheses of (−)-cephalotaxine.

1. Introduction

(−)-Cephalotaxine is the parent member of the harringtonine alkaloid family. These natural products occur in about eight known species of the genus *Cephalotaxus*, evergreen plum yews that are indigenous to Southeast Asia.[1] (−)-Cephalotaxine was isolated from yew plants by Paudler and his co-workers in 1963[2] and its structure was determined in 1969.[3] This natural product has become an interesting synthetic target,[4a–q] not only because of its unique pentacyclic ring skeleton, containing a 1-azaspiro[4.4]-nonane moiety fused to a benzazepine system, but also as a result of the observed antileukemic and antitumor activities of several of its C-3 2-alkylhydroxysuccinate derivatives, including harringtonine **2**, deoxyharringtonine **3**, homoharringtonine **4**, and isoharringtonine **5** (Scheme 1).[5] The cancer chemotherapeutic effectiveness of homoharringtonine **4** has been evaluated in phase II–III clinical trials,[6] and this substance has been investigated in the treatment of chloroquine-resistant malaria.[7]

Extensive studies have been carried out in our laboratory to both develop and demonstrate the preparative utility of pyridinium salt photochemistry in sequences targeted at a variety of biomedically interesting natural and nonnatural products.[8] Recently, we reported the results of an exploratory study of the photochemistry of a 1,2-cyclopenta-fused pyridinium perchlorate **6** (Scheme 2).[9] Specifically, we observed that irradiation of a basic aqueous solution of this substance promotes a remarkably regioselective photocyclization reaction that results in efficient formation of a single tricyclic-allylic alcohol **8**. The degree of structural, functional, and stereochemical complexity introduced in this 'green' chemical process is remarkable. Moreover, transformation of **8** to the corresponding spirocyclic amido diester **9** by acid promoted, regiocontrolled aziridine ring opening followed by enzymatic desymmetrization was used to produce the enantiomerically pure monoalcohol **10**



Scheme 1.

Keywords: Pyridinium salt photochemistry; (−)-Cephalotaxine formal synthesis.
* Corresponding author. Tel.: +1 505 277 6390; fax: +1 505 277 6202; e-mail: mariano@unm.edu

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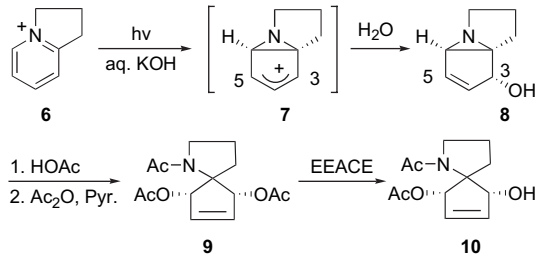
(Scheme 2) that contains a structurally interesting [4.4]-spirocyclic framework.



Scheme 2.

The unique structural and stereochemical features of spirocyclic amide **10** along with the efficiency of its construction should make this substance and its relatives ideal synthons in routes for the preparation of a number of natural product targets. The aim of the effort described below was to demonstrate how the photochemistry of 1,2-cyclopenta-fused pyridinium perchlorate **6** can be readily adapted to routes that rapidly generate two key intermediates in the syntheses of (−)-cephalotaxine.

2. Results and discussion

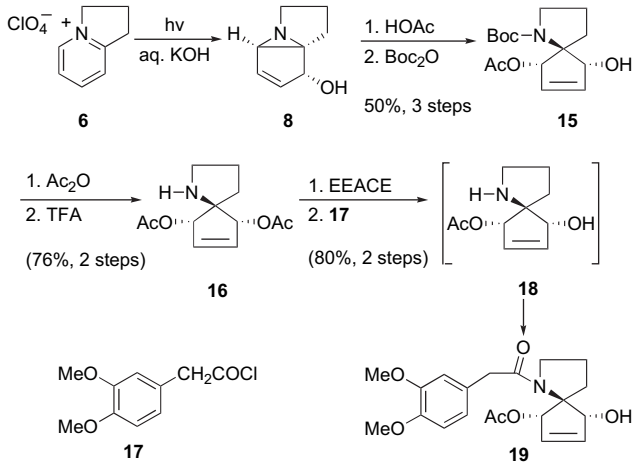
2.1. Retrosynthetic analyses

Two retrosynthetic plans for formal total syntheses of (−)-cephalotaxine, designed on the basis of pyridinium salt photochemistry, are outlined in Scheme 3. A key intermediate in both sequences is pentacyclic alkene **11**, a substance used by Mori and Isono in the first nonracemic total synthesis of this natural product.[4i] We envisaged that in one approach **11** would be derive from the known spirocyclic amido-allylic alcohol **12**, which has already been converted to **11** in the seminal synthesis of (−)-cephalotaxine reported by Mori and Isono.[4i] We assumed that **12** would be easily prepared from an aminomonoalcohol **14**, formed by an enzymatic hydrolytic desymmetrization process[10] on a *meso*-diester derived by application of the pyridinium salt photocyclization/aziridine ring opening sequence (Scheme 2).

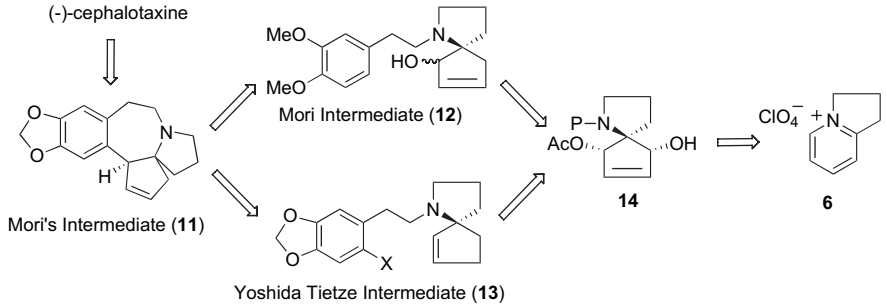
In more recent approaches to the synthesis (−)-cephalotaxine, Tietze[4j] and Yoshida[4l] have utilized Heck coupling reactions of haloarylethyl tethered spirocyclic intermediates **13** to form the late stage intermediate **11** in Mori's synthesis of (−)-cephalotaxine. We visualized that these synthons would arise by appropriate manipulation of the monoalcohol **14**.

2.2. One formal total synthesis of (−)-cephalotaxine

The sequence developed for formal total synthesis of (−)-cephalotaxine that targets construction of the Mori spirocyclic allylic alcohol **12** is initiated by the known photocyclization reaction of the the cyclopenta-fused pyridinium salt **6** (Scheme 4). Irradiation of an aqueous basic solution of this substance gives tricyclic aziridine **8**, which is directly transformed to *N*-Boc-protected spirocyclic monoalcohol **15** by treatment with acetic acid, to promote regioselective aziridine ring opening, followed by protection of the liberated secondary amine through the action of Boc_2O and Et_3N. This three-step sequence serves as an exceptionally convenient method to access the racemic structurally and functionally complex intermediate **15** in a 50% overall yield. Acetylation of **15** with Ac_2O and pyridine followed by deprotection of the Boc group with TFA yields the *meso* aminodiester **16** (81%, two steps). Importantly, this diester serves as an active substrate for EEACE[9] catalyzed hydrolysis (pH=6.9, 0.5 M NaH_2PO_4) that affords a modestly unstable aminomonoalcohol intermediate **18**, which without purification is reacted with (3,4-dimethoxyphenyl)acetyl chloride (**17**) to furnish amidomonoalcohol **19** in a 80% two-step yield. The enantiomeric purity of **18** is determined by its conversion to an *N*-Boc derivative followed by reaction



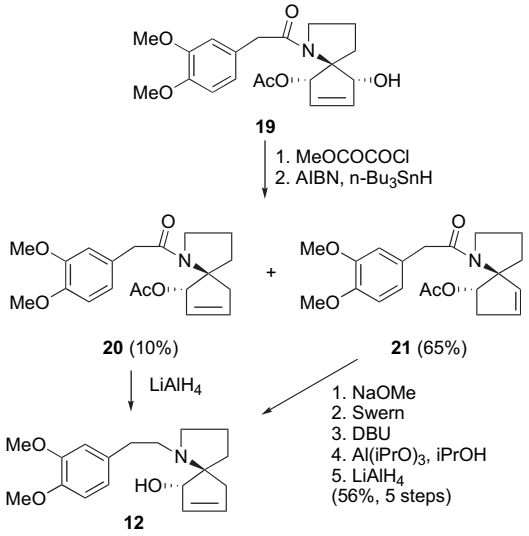
Scheme 4.



Scheme 3.

with both (*R*)- and (*S*)-Mosher acetyl chloride and ^{1}H NMR analysis of the derived esters.[11] The % ee determined in this manner are in the range of 80–90% ee depending on the time/percent conversion of the enzymatic reaction.

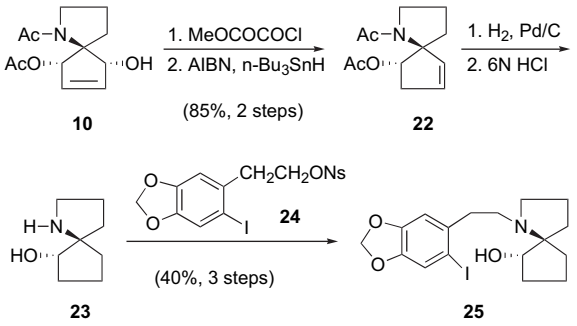
The transformation of spirocyclic monoalcohol **19** to the Mori intermediate **11**, on first thought seemed simple since all that is required is reductive removal of the unblocked hydroxyl group. Among a number of radical reduction approaches explored for this purpose (e.g., *O*-phenoxythiocarbonate reduction), Barton[12] type oxalate reduction was superior. Accordingly, treatment of **19** with methyl(chlorocarbonyl)formate followed by free radical reduction of the intermediate mixed oxalate ester by using AIBN/*n*-Bu_3SnH in refluxing toluene leads to the generation of the desired dehydroxylated product **20** in a 10% yield along with the rearranged homoallylic alcohol **21** as the major product (65%). As expected, treatment of **20** with lithium aluminum hydride gives **12** (95%) (Scheme 5), which has physical and spectroscopic properties that match those reported by Mori and Isono.[4i] In addition, **21** is also transformed to Mori intermediate through a fivestep sequence (55% overall yield) involving alcohol liberation and oxidation, α,β-unsaturated enone formation, and reduction, and amide reduction (Scheme 5).



Scheme 5.

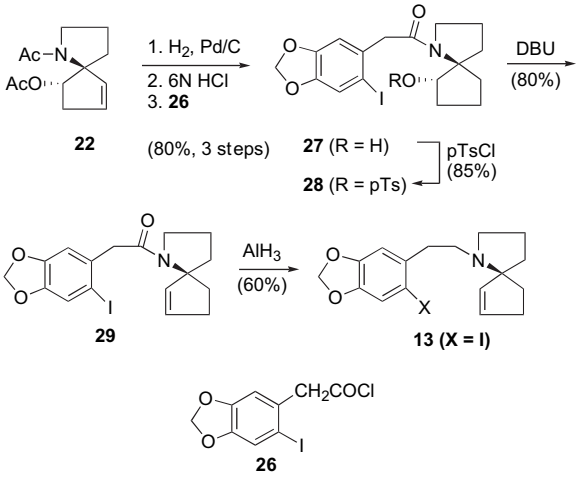
2.3. Another formal total synthesis of (−)-cephalotaxine

The second approach developed for the synthesis of (−)-cephalotaxine links with the iodoarylethyl spirocyclic alkene **13**, which served as a key intermediate in Yoshida and his co-workers' synthesis of this target. The sequence begins with monoalcohol **10**[9] (Scheme 6), a substance we prepared earlier in nonracemic form by using a sequential-photocyclization/aziridine ring opening/enzymatic desymmetrization sequence (Scheme 2). Free radical reduction (AIBN, *n*-Bu_3SnH, toluene, reflux) of the mixed oxalate arising by treatment of **10** with methyl(chlorocarbonyl)formate gives the homoallylic ester **22** (90%). Hydrogenation of **22** with 10% Pd/C in ethanol generates the saturated amide, which upon reaction in refluxing 6 N HCl affords the HCl salt of spirocyclic aminoalcohol **23**. Without purification, this substance is reacted with the iodoarylethyl 4-nitrobenzenesulfonate **24**[4i] to generate the spirocyclic aminoalcohol **25**. A brief exploration for optimal conditions resulted in an optimized 40% yield for the three-step sequence. In order to complete the synthesis of Yoshida spirocyclic alkene **13** all that is needed was dehydration of aminoalcohol **25**. However, we found that this was a difficult task when we observed that several typical time-tested methods ($POCl_3$/Py, Burgess salts, CS_2/MeI, and MeOCOCOCl/Pyr) failed to give satisfactory results.



Scheme 6.

As a result of low yields of the N-alkylation reaction of spirocyclic amine **23** and dehydration reaction of alcohol **25**, the synthetic plan was modified by employing the amidoalcohol **27** as an intermediate (Scheme 7). As anticipated, **23** derived by successive hydrogenation of **22** and amide hydrolysis, reacts with iodoarylacetyl chloride **26** to give spirocyclic amidoalcohol **27** in a dramatically improved 80% three-step yield. Formation of the tosylate derivative **28** by reaction of **27** with *p*-TsCl and pyridine (85%) is followed by smooth DBU[13] catalyzed elimination to afford the unsaturated amide **29** in an 80% yield. Finally, low temperature (−40 °C) aluminum hydride reduction[14] of **29** (60%) gives **13**, the late stage intermediate in Yoshida's formal synthesis of (−)-cephalotaxine along with about 20% of a product (**13**, X=H) missing the iodide group. Importantly, the physical and spectroscopic properties of **13**, prepared by the current methodology, match those reported by Yoshida and his co-workers.[4l]



Scheme 7.

3. Conclusions

The results described above add further to the growing body of observations that suggest that pyridinium salt photochemistry can serve as an important methodology in synthetic organic chemistry. Despite the well recognized limitations (e.g., scale up) of photochemical reactions, the ability to construct structurally, stereochemically, and functionally complex substances by irradiation of pyridinium salts stands as a unique feature of this chemistry that is unmatched by any ground state processes. As with all interesting excited state reactions of organic compounds, this environmentally friendly process will become an important component of the synthetic arsenal, especially if/when the cost of photon production becomes low.

4. Experimental

4.1. General

All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification. All compounds were isolated as oils and shown to be >90% pure by ^{1}H NMR/or ^{13}C NMR, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on $CDCl_3$ solution unless otherwise specified and chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ at 7.24 ppm (for ^{1}H NMR at 250 or 500 MHz) and 77.0 ppm (for ^{13}C NMR at 62.9 MHz). ^{13}C NMR resonance assignments were aided by the use of DEPT technique to determine the number of attached hydrogens.

4.1.1. *N*-Boc-1-acetoxy-6-azaspiro[4.4]non-2-en-4-ol (15). A solution of fused pyridinium salt **6** (2.14 g, 0.01 mol) in water (500 mL) containing KOH (0.60 g, 0.01 mol) was irradiated in a circular reactor with light emitted from 2537 Å lamps for 24 h (70% conversion). Concentration of the photolysate in vacuo provided a residue, which was triturated with chloroform. Concentration of the triturate in vacuo to yield the known[9] bicyclic alcohol **8**, which was used without purification in the next step.

A solution of **8** in CH_2Cl_2 (100 mL) and HOAc (5 mL) was stirred at room temperature for 12 h. Triethylamine (7 mL) and di-*tert*-butyl dicarbonate (3.4 g, 15.6 mmol) were then added and then the mixture was stirred for 12 h at room temperature, diluted sequentially with 5% aq $KHSO_4$ (10 mL) and $CHCl_3$ (200 mL), washed sequentially with 5% aq $KHSO_4$ and satd aq $NaHCO_3$, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, 30% acetone/hexane) to provide **15** (1.04 g, 50%, three steps). ^{1}H NMR (1:1 mixture of two rotamers) 1.45 (s, 9H), 1.46 (s, 9H), 1.60–1.65 (m, 2H), 1.75–1.83 (m, 3H), 1.95–2.05 (m, 1H), 2.17 (s, 6H), 2.21–2.36 (m, 2H), 3.30–3.54 (m, 5H), 3.71 (br s, 1H), 5.11 (s, 1H), 5.35 (s, 1H), 5.76 (s, 2H), 5.91 (d, J=5.6 Hz, 2H), 6.13 (s, 1H), 6.32 (s, 1H); ^{13}C NMR (1:1 mixture of two rotamers) 20.2 (2), 21.9, 22.3, 26.0, 27.3, 27.6 (2), 46.9, 47.0, 75.5, 76.0, 77.6, 77.7, 77.8, 77.9, 78.9, 79.0, 129.7 (2), 135.3, 135.2, 152.7, 153.0, 169.9 (2); HRMS (ES) *m/z* 320.1452 (M+Na), calcd for $C_{15}H_{23}NO_5Na$ 320.1474.

4.1.2. 1,4-Diacetoxy-6-azaspiro[4.4]non-2-ene (16). A solution of Boc-protected amidomonoalcohol **15** (3.0 g, 0.01 mol) in CH_2Cl_2 (100 mL), DMAP (300 mg), Ac_2O (5 mL), and pyridine (10 mL) was stirred at room temperature for 12 h, poured into satd $NaHCO_3$ solution, and extracted with $CHCl_3$. The chloroform extracts were dried and concentrated in vacuo to provide the crude diacetate, which was subjected to column chromatography (silica gel, 30% acetone/hexane) to give pure diacetate (3.1 g, 90%). ^{1}H NMR (1:0.8 mixture of rotamers) 1.48 (s, 16.2H), 1.65–1.74 (m, 3.6H), 2.00 (t, J=7.0 Hz, 2H), 2.10 (s, 10.8H), 2.14 (t, J=7.0 Hz, 1.6H), 3.31 (t, J=7.0 Hz, 2H), 3.40 (t, J=7.0 Hz, 1.6H), 5.89 (s, 1.6H), 5.90 (s, 2H), 6.14 (s, 1.6H), 6.34 (s, 2H); ^{13}C NMR (1:0.8 mixture of rotamers) 20.9 (4), 22.5, 23.1, 27.7, 28.4 (2), 29.1, 47.2, 47.6, 75.3, 76.2, 78.6 (2), 79.2 (2), 79.6, 80.6, 132.3 (2), 132.4 (2), 153.0, 153.6, 170.0 (4) ; HRMS (ES) *m/z* 362.1535 (M+Na), calcd for $C_{17}H_{25}NO_6Na$ 362.1580.

A solution of the diacetate (1.5 g, 4.4 mmol) in CH_2Cl_2 (10 mL) and TFA (3.5 mL) was stirred overnight at room temperature, diluted with satd aq $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to provide a residue, which was subjected to column chromatography (silica gel, 10% MeOH/ethyl acetate) to yield **16** (0.9 g, 85%). ^{1}H NMR 1.71–1.80 (m, 4H), 2.10 (s, 6H), 2.98 (t, J=6.8 Hz, 2H), 5.37 (s, 2H), 6.07 (s, 2H); ^{13}C NMR 20.8 (2), 24.8, 26.8, 45.9, 74.6, 82.1 (2), 134.0 (2), 170.2 (2); HRMS (ES) *m/z* 240.1233 (M+1), calcd for $C_{12}H_{18}NO_4$ 240.1236.

4.1.3. (1*S*,4*R*,5*S*)-*N*-(3,4-Dimethoxyphenylacetyl)-1-acetoxy-6-azaspiro[4.4]non-2-en-4-ol (19). A solution of 50 mg of sodium azide, 500 units of lypholized electric eel acetyl cholinesterase (EEACE) and amine-diacetate **16** (4.0 g, 16.7 mmol) in 100 mL of 0.58 M sodium dihydrogen phosphate buffer (pH=6.9) at room temperature was gently stirred for 0.5–1 h and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to yield the recovered **16** (3.0 g). The aqueous layer was concentrated in vacuo to provide a residue, which was dissolved in methanol and filtered. The filtrate was concentrated in vacuo to yield the monoalcohol **18**, which was used without further purification in the next step. ^{1}H NMR (D_2O) 1.96–2.06 (m, 3H), 2.26 (s, 3H), 2.18–2.21 (m, 1H), 3.32 (t, J=6.5 Hz, 2H), 4.58 (s, 1H), 5.56 (s, 1H), 6.13 (d, J=6.0 Hz, 1H), 6.28 (d, J=5.5 Hz, 1H); ^{13}C NMR (D_2O) 20.1, 21.9, 25.1, 45.0, 76.5, 77.5, 78.9, 130.9, 136.9, 173.1; HRMS (ES) *m/z* 198.1127 (M+1), calcd for $C_{10}H_{16}NO_3$ 198.1130. The % ee of the monoalcohol (80–90%, depending on reaction time) was determined by conversion to the *N*-Boc derivative, followed by reaction with (*R*)- and (*S*)-Mosher acetyl chloride.

To a solution of the crude monoalcohol in CH_3CN (30 mL) at −40 °C were added sequentially Et_3N (2 mL) and a solution of 3,4-dimethoxyphenylacetyl chloride (**17**) (0.7 g, 3.24 mmol) in CH_3CN (10 mL). The mixture was stirred at −40 °C for 70 min, diluted with water, and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to yield a residue, which was subjected to column chromatography (silica gel, 33% acetone/hexane) to provide **19** (0.94 g, 80%); $[\alpha]_D^{23}$ +7.4 (*c* 0.41, $CHCl_3$). ^{1}H NMR 1.70–1.81 (m, 1H), 1.85–1.92 (m, 2H), 2.07 (s, 3H), 2.17–2.22

(m, 1H), 3.40–3.44 (m, 1H), 3.47–3.52 (m, 1H), 3.56 and 3.61 (abq, J=15.0 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 5.48 (d, J=1.0 Hz, 1H), 5.79 (d, J=6.0 Hz, 1H), 5.91 (dd, J=2.0, 6.3 Hz, 1H), 6.42 (d, J=1.5 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.82 (s, 1H); ^{13}C NMR 20.9, 23.7, 26.5, 42.7, 48.5, 55.8 (2), 76.2, 78.5, 79.2, 111.1, 112.2, 121.1, 127.1, 130.6, 136.2, 147.7, 148.9, 170.3 (2); HRMS (ES) *m/z* 376.1757 (M+1), calcd for $C_{20}H_{26}NO_6$ 376.1760.

4.1.4. (1*S*,5*S*)-*N*-(3,4-Dimethoxyphenylacetyl)-1-acetoxy-6-azaspiro[4.4]non-2-ene (20) and (4*S*,5*S*)-*N*-(3,4-dimethoxyphenylacetyl)-5-acetoxy-6-azaspiro[4.4]non-1-ene (21). To a solution of monoalcohol **19** (1.1 g, 2.9 mmol) in CH_2Cl_2 (30 mL) containing DMAP (1.1 g, 9.0 mmol) at 0 °C, was added methyl chlorooxoacetate (0.7 mL). The mixture was stirred at room temperature for 4 h, diluted with $CHCl_3$ and water, and separated. The $CHCl_3$ layer was washed with aq NH_4Cl, dried, and concentrated in vacuo to afford the mixed oxalate ester, which was used without further purification in the next step. ^{1}H NMR 1.74–1.86 (m, 2H), 2.05 (t, J=6.8 Hz, 2H), 2.09 (s, 3H), 3.42 (dd, J=2.0, 6.5 Hz, 2H), 3.63 (s, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 5.96 (dd, J=6.0, 12.3 Hz, 2H), 6.45 (s, 1H), 6.58 (s, 1H), 6.78 (d, J=8.0 Hz, 1H), 6.81 (s, 1H), 6.82 (d, J=8.0 Hz, 1H); ^{13}C NMR 20.8, 23.7, 27.4, 42.5, 47.8, 53.5, 55.7 (2), 77.4, 78.0, 81.5, 111.1, 112.1, 121.2, 126.9, 130.8, 133.8, 147.7, 148.9, 156.9, 157.9, 169.9, 170.5; HRMS (ES) *m/z* 462.1765 (M+1), calcd for $C_{23}H_{28}NO_9$ 462.1764.

To a solution of the crude oxalate in toluene (10 mL) were added AIBN (0.3 g, 1.8 mmol) and *n*-Bu_3SnH (3 mL, 11.3 mmol). The mixture was stirred at 100 °C for 2 h, cooled to room temperature, diluted with $CHCl_3$, washed with satd aq $NaHCO_3$, dried, and concentrated in vacuum to afford a residue, which was subjected to column chromatography (silica gel, 30% acetone/hexane) to afford **20** (0.11 g, 10%), **21** (0.68 g, 65%), and recovered starting material **19** (0.3 g).

Compound **20**: $[\alpha]_D^{23}$ +90.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR 1.62 (dt, J=6.0, 13.0 Hz, 1H), 1.78 (dt, J=7.0, 13.0 Hz, 2H), 2.20 (s, 3H), 2.22 (ddd, J=7.5, 5.5, 4.5 Hz, 2H), 3.27 (dd, J=1.5, 16.3 Hz, 1H), 3.42 (abq, J=7.5 Hz, 1H), 3.51 (abq, J=6.0 Hz, 1H), 3.59 (abq, J=15.0 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 5.66 (dd, J=1.5, 6.0 Hz, 1H), 5.95 (dd, J=2.0, 6.5 Hz, 1H), 6.49 (s, 1H), 6.77 (d, J=9.5 Hz, 1H), 6.80 (s, 1H), 6.82 (d, J=9.5 Hz, 1H); ^{13}C NMR 21.1, 23.7, 35.2, 42.8, 44.0, 48.3, 55.8, 72.7, 81.9, 111.1, 111.9, 121.1, 127.3, 129.2, 133.2, 147.7, 148.9, 169.6, 170.5; HRMS (ES) *m/z* 360.1823 (M+1), calcd for $C_{20}H_{26}NO_5$ 360.1811.

Compound **21**: $[\alpha]_D^{23}$ +94.9 (*c* 0.28, $CHCl_3$); ^{1}H NMR 1.61–1.65 (m, 1H), 1.81 (abq, J=7.5 Hz, 2H), 2.06 (s, 3H), 2.21–2.27 (m, 2H), 3.10 (dd, J=8.0, 17.0 Hz, 1H), 3.44–3.47 (m, 1H), 3.50–3.57 (m, 1H), 3.57 (abq, J=15.0 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 5.52 (d, J=4.0 Hz, 1H), 5.75–5.77 (m, 1H), 5.88–5.90 (m, 1H), 6.76 (d, J=8.5 Hz, 1H), 6.80 (s, 1H), 6.81 (d, J=8.5 Hz, 1H); ^{13}C NMR 21.1, 23.7, 32.8, 38.1, 42.9, 48.1, 55.8, 76.7, 77.6, 111.1, 111.9, 121.1, 127.3, 128.1, 134.1, 147.7, 148.9, 169.6, 170.4; HRMS (ES) *m/z* (M+1), 360.1810 calcd for $C_{20}H_{26}NO_5$ 360.1811.

4.1.5. (1*S*,5*S*)-*N*-[2-(3,4-Dimethoxyphenylethyl)]-6-azaspiro[4.4]non-2-en-1-ol (12) from 20. To a solution of **20** (0.10 g, 0.3 mmol) in THF (10 mL) was added $LiAlH_4$ (1 mL, 1 M solution, 1 mmol). The mixture was stirred at reflux for 3 h, cooled, sequentially diluted by addition of a solution of 0.5 mL water in 10 mL THF followed by 0.6 mL 10% aq NaOH, and filtered. The filtrate was concentrated in vacuo to afford a residue, which was subjected to column chromatography (silica gel, 10% $CHCl_3$/MeOH) to afford **12** (0.09 g, 95%), $[\alpha]_D^{23}$ +44.4 (*c* 0.03, $CHCl_3$) [lit.[4i] 86.4 (*c* 1.02, $CHCl_3$)] whose spectroscopic properties matched with those previously reported.[4i] ^{1}H NMR 1.56–1.61 (m, 1H), 1.80–1.86 (m, 2H), 2.02 (d, J=17.0 Hz, 1H), 2.23 (ddd, J=8.0, 12.0, 12.0 Hz, 1H), 2.39 (d, J=17.0 Hz, 1H), 2.40–2.45 (m, 1H), 2.64–2.74 (m, 4H), 3.11 (dd, J=3.5, 9.0 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 4.63 (s, 1H), 5.70 (dd, J=2.0, 6.0 Hz, 1H), 5.82 (d, J=5.5 Hz, 1H), 6.70 (s, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H); ^{13}C NMR 20.7, 32.4, 35.4, 36.5, 51.4, 51.8, 55.8, 55.8, 75.3, 78.0, 111.1, 112.0, 120.4, 132.2, 132.9, 133.0, 147.3, 148.7; HRMS (ES) *m/z* 304.1906 (M+1), calcd for $C_{18}H_{26}NO_3$ 304.1913.

4.1.6. Spirocyclic cyclopentenol 12 from 21. A solution of **21** (0.36 g, 1.0 mmol) and NaOMe (0.10 g, 19 mmol) in MeOH (10 mL) was stirred at room temperature for 2 h, diluted with water and extracted with $CHCl_3$, The extracts were washed with satd aq NaCl, dried and concentrated in vacuo to yield the crude homoallylic alcohol (0.32 g). $[\alpha]_D^{23}$ +99.4 (*c* 0.264, $CHCl_3$); ^{1}H NMR 1.68–1.72 (m, 1H), 1.78–1.81 (m, 1H), 1.91–2.17 (m, 2H), 2.53 (dd, J=2.0, 19.3 Hz, 1H), 2.73 (dd, J=5.5, 20.5 Hz, 1H), 3.53 (abq, J=7.5 Hz, 1H), 3.64 (abq, J=18.0 Hz, 2H), 3.86 (s, 6H), 3.96–3.99 (m, 1H), 4.4 (d, J=11.5 Hz, 1H), 5.60 (d, J=6.0 Hz, 1H), 5.82 (d, J=5.5 Hz, 1H), 6.78 (d, J=8.5 Hz, 1H), 6.81 (s, 1H), 6.81 (d, J=8.0 Hz, 1H); ^{13}C NMR 23.0, 36.6, 41.8, 42.4, 49.0, 55.7 (2), 77.8, 79.3, 111.1, 111.8, 121.0, 126.7, 128.0, 133.2, 147.8, 148.9, 173.1; HRMS (ES) *m/z* 318.1702 (M+1), calcd for $C_{18}H_{24}NO_4$ 318.1705.

To a solution of oxalyl chloride (1 mL, 2 M solution, 2 mmol) and DMSO (0.31 g, 4 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added a solution of the crude homoallylic alcohol (0.32 g, 1 mmol) in CH_2Cl_2 (20 mL) slowly. The mixture was stirred at −78 °C for 2 h, and diluted with Et_3N (5 mL). After stirring for 1 h, the mixture was diluted with satd aq NH_4Cl, and extracted with $CHCl_3$. The extracts were washed with satd aq NaCl, dried, and concentrated in vacuo to afford the crude unsaturated enone, which was used without purification in the next step. ^{1}H NMR 1.75–1.78 (m, 1H), 1.95–2.05 (m, 3H), 2.74 and 3.28 (abq, J=23.0 Hz, 2H), 3.51–3.52 (m, 2H), 3.53 (abq, J=7.0 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 5.85 (dt, J=2.0, 7.0 Hz, 1H), 6.23 (dt, J=2.0, 7.0 Hz, 1H), 6.68 (d, J=7.5 Hz, 1H), 6.69 (s, 1H), 6.76 (d, J=7.5 Hz, 1H); ^{13}C NMR 24.6, 35.7, 41.0, 41.4, 48.1, 55.8 (2), 71.8, 111.2, 111.6, 120.9, 126.6, 129.8, 132.5, 147.8, 149.0, 168.9, 213.6; HRMS (ES) *m/z* 316.1553 (M+1), calcd for $C_{18}H_{22}NO_4$ 316.1549.

A solution of the crude nonconjugated enone and DBU (2.5 mL) in CH_3CN (10 mL) was stirred at room temperature for 12 h, diluted with satd aq $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried and concentrated

in vacuo to yield a residue, which was subjected to column chromatography (silica gel, 1:1 acetone/hexane) to give the crude conjugated enone as a colorless oil (0.19 g, 60%, three steps). $[\alpha]_D^{23}$ −27.4 (*c* 0.13, $CHCl_3$); ^1H NMR 1.74–1.76 (m, 1H), 1.97–2.00 (m, 2H), 2.08–2.17 (m, 1H), 2.54 and 3.13 (abq, *J*=23.0 Hz, 2H), 3.50–3.53 (m, 1H), 3.55 (abq, *J*=9.0 Hz, 2H), 3.59–3.65 (m, 1H), 3.85 (s, 3H), 3.90 (s, 3H), 6.27 (dt, *J*=2.0, 6.0 Hz, 1H), 6.75 (d, *J*=8.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 6.82 (s, 1H), 7.72 (m, 1H); ^{13}C NMR 24.5, 38.0, 41.4, 42.1, 48.4, 55.7, 55.8, 68.4, 111.1, 111.7, 120.9, 126.7, 132.3, 147.7, 148.9, 159.2, 168.8, 206.9; HRMS (ES) *m/z* 316.1551 (M+1), calcd for $C_{18}H_{22}NO_4$ 316.1549.

To a solution of the conjugated enone (0.15 g, 0.48 mmol) in ^{i}PrOH (5 mL) was added Al(^{i}PrO)$_3$ (4.7 g, 18.3 mmol). The solvent was removed by distillation at 80 °C and the residue was stirred at 130 °C for 2 h, cooled, and poured into 100 mL of dilute HCl at 0 °C. The mixture was stirred for 30 min and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to yield the crude allylic alcohol, which was used without purification in the next step. ^1H NMR 1.49–1.58 (m, 1H), 1.70–1.83 (m, 1H), 1.93 (dt, *J*=6.0, 12.5 Hz, 1H), 2.04 (d, *J*=6.5 Hz, 1H), 2.12 (dd, *J*=2.0, 16.0 Hz, 1H), 2.46–2.51 (m, 1H), 3.23 (dd, *J*=2.0, 16.0 Hz, 1H), 3.50 (t, *J*=6.8 Hz, 2H), 3.57 (abq, *J*=18.0 Hz, 2H), 3.86 (s, 3H), 3.86 (s, 3H), 5.56 (br s, 1H), 5.67 (d, *J*=6.0 Hz, 1H), 5.85 (d, *J*=5.5 Hz, 1H), 6.76 (d, *J*=8.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 6.82 (s, 1H); ^{13}C NMR 23.7, 34.1, 43.0, 43.1, 48.9, 55.8 (2), 74.4, 78.9, 111.1, 111.9, 121.0, 127.3, 131.6, 133.0, 147.7, 148.9, 169.5; HRMS (ES) *m/z* 318.1707 (M+1), calcd for $C_{18}H_{24}NO_4$ 318.1705.

To a solution of the crude allylic alcohol (0.1 g, 0.28 mmol) in anhydrous THF (5 mL) was added $LiAlH_4$ (1 mL, 1 mmol). The mixture was stirred at reflux for 1 h, cooled, diluted with ether, and then slowly diluted with a solution of 0.5 mL water in 10 mL THF followed by 0.6 mL 10% aq NaOH, and filtered. The filtrate was concentrated in vacuo to afford a residue, which was subjected to column chromatography (silica gel, 10% $CHCl_3$/MeOH) to afford **12** (0.09 g, 92%).

4.1.7. (4*S*,5*S*)-*N*-Acetyl-4-acetoxy-6-azaspiro[4.4]non-1-ene (22). To a solution of the known[9] alcohol **10** (2.4 g, 10 mmol, 80% ee) in CH_2Cl_2 (50 mL) containing DMAP (2.5 g, 20 mmol) was added methyl chlorooxoacetate (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h, diluted with chloroform and water, and separated. The combined organic layers were washed with satd aq NH_4Cl, dried, and concentrated in vacuo giving the oxalate ester, which was used without further purification.

A solution of the crude oxalate, AIBN (0.6 g, 3.6 mmol), and *n*-Bu_3SnH (12 mL, 45 mmol) in 20 mL toluene was stirred at 100 °C for 1 h, cooled, diluted with chloroform, and washed with satd aq $NaHCO_3$. The organic layer was dried and concentrated in vacuo to afford the residue, which was subjected to silica gel column chromatography (30% acetone/hexane) to afford the unsaturated amido-ester **22** [1.34 g, 85% based on recovered 0.64 g (25%) starting material]. $[\alpha]_D^{22}$ +111.6 (*c* 0.7, $CHCl_3$); ^1H NMR (4:1 mixture of two rotamers) major rotamer 1.66 (dt, *J*=8.5, 13.0 Hz, 1H), 1.88 (dd, *J*=7.5, 8.0 Hz, 1H), 2.04 (s, 3H), 2.06 (s, 3H), 2.21–2.30 (m, 3H), 3.05–3.09 (m, 1H), 3.47–3.53 (m, 2H), 5.55 (dt, *J*=6.0, 2.0 Hz, 1H), 5.75 (dt, *J*=6.0, 2.5 Hz, 1H), 5.83 (dd, *J*=5.5, 8.0 Hz, 1H); ^{13}C NMR (major rotamer) 20.9, 23.4, 23.9, 32.7, 37.7, 48.7, 76.0, 77.6, 127.5, 134.2, 168.9, 170.2; HRMS (ES) *m/z* 246.1106 (M+Na), calcd for $C_{12}H_{17}NO_3Na$ 246.1105.

4.1.8. 2-Iodo-4,5-methylenedioxyphenylacetyl chloride (26). To a solution of CrO_3 (6 g, 0.06 mol) and concd H_2SO_4 (4 mL) in 20 mL water was added 2-(3,4-methylenedioxy-6-iodophenyl)ethanol[4c] (6.0 g, 0.021 mol) in 80 mL acetone and the mixture was stirred at room temperature for 5 h. Then 10 mL ^{i}PrOH was added and the solution was stirred for an additional 1 h and filtered through Celite. The filtrate was concentrated in vacuo, diluted with 50 mL 3 N NaOH, washed with chloroform, and acidified to pH 1–2 by the addition of concd HCl. The formed solid was filtered and dried to give 3.9 g (60%) of 2-(3,4-methylenedioxy-6-iodophenyl)acetic acid. ^1H NMR (CD_3COCD_3) 3.75 (s, 2H), 6.04 (s, 2H), 6.97 (s, 1H), 7.29 (s, 1H); ^{13}C NMR 46.0, 89.4, 102.9, 111.7, 118.9, 132.8, 148.6, 149.5, 171.8.

A solution of (3,4-methylenedioxy-6-iodophenyl)acetic acid (1.37 g, 0.0045 mol) in 10 mL $SOCl_2$ containing two drops of DMF was stirred at room temperature for 4 h and concentrated in vacuo to give the crude 2-(3,4-methylenedioxy-6-iodophenyl)acetyl chloride (**26**) (1.46, 100%).

4.1.9. (1*S*,5*R*)-*N*-(2-Iodo-4,5-methylenedioxyphenylacetyl)-6-azaspiro[4.4]nonan-1-ol (27). A solution of **22** (2.23 g, 10 mmol) in EtOH (30 mL) containing 10% Pd/C (2.0 g) and H_2 (1 atm) was stirred under an atmosphere of hydrogen at 25 °C for 12 h, and filtered through a Celite pad. The filtrate was concentrated in vacuo to yield a crude amido-ester (2.24 g, ca. 100%, >95% purity), which was used without purification. $[\alpha]_D^{22}$ +48.4 (*c* 0.79, $CHCl_3$). ^1H NMR 1.45–1.55 (m, 2H), 1.62–1.66 (m, 2H), 1.76–1.94 (m, 3H), 2.03 (s, 6H), 2.22–2.31 (m, 2H), 2.59–2.64 (m, 1H), 3.43 (dd, *J*=16.0, 7.0 Hz, 2H), 5.88 (t, *J*=7.5 Hz, 1H); ^{13}C NMR 20.1, 21.1, 23.2, 24.5, 30.0, 34.4, 34.9, 49.2, 71.8, 76.5, 168.9, 170.3; HRMS (ES) *m/z* 248.1255 (M+Na), calcd for $C_{12}H_{19}NO_3Na$ 248.1263.

A solution of amido-ester (2.24 g, 10 mmol) in 6 N HCl (20 mL) was stirred at 100 °C for 3 h, cooled, and concentrated in vacuo to afford the spirocyclic aminoalcohol **23** as its HCl salt (1.69 g, 95%, >95% purity), which was used without purification. ^1H NMR (D_2O) 1.53–1.69 (m, 2H), 1.75–1.95 (m, 4H), 1.97–2.10 (m, 4H), 3.32 (m, 2H), 4.04 (2d, *J*=5.0 Hz, 1H); ^{13}C NMR (D_2O) 22.3, 26.0, 34.5, 36.0, 36.5, 48.0, 78.0, 78.3.

To a solution of aminoalcohol **23** (0.89 g, 5 mmol) and Et_3N (10 mL) in CH_3CN (30 mL) at −40 °C was slowly added a solution of 2-(3,4-methylenedioxy-6-iodophenyl)acetyl chloride (**26**) (1.46 g, 4.5 mmol) in CH_3CN (10 mL). The mixture was stirred at −40 °C for 70 min, diluted with water, and extracted with chloroform. The combined extracts were dried and concentrated in vacuo to give a residue, which was subjected to silica gel column chromatography (33%

acetone/hexane) to provide arylacetamide **27** (1.54 g, 80% based on **26**). $[\alpha]_D^{22}$ +14.2 (*c* 0.65, $CHCl_3$). ^1H NMR 1.45–1.51 (m, 2H), 1.77–1.80 (m, 1H), 1.89–1.94 (m, 6H), 2.69–2.76 (m, 1H), 3.63–3.64 (m, 1H), 3.70 (abq, *J*=16.5 Hz, 2H), 3.77 (dt, *J*=10.0, 5.0 Hz, 1H), 4.44 (dd, *J*=3.5, 10.5 Hz, 1H), 5.94 (d, *J*=1.5 Hz, 2H), 6.80 (s, 1H), 7.23 (s, 1H); ^{13}C NMR 21.2, 23.1, 34.5, 35.3, 41.2, 47.5, 49.4, 74.2, 81.7, 89.0, 101.5, 110.3, 118.3, 131.5, 147.3, 148.4, 171.4; HRMS (ES) 430.0507 (M+1), calcd for $C_{17}H_{21}NO_4I$ 430.0515.

4.1.10. (1*S*,5*R*)-*N*-(2-Iodo-4,5-methylenedioxyphenylacetyl)-6-azaspiro[4.4]nonan-1-yl-*p*-toluenesulfonate (28). To a solution of amidoalcohol **27** (0.75 g, 1.75 mmol) and pyridine (1 mL) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.67 g, 3.5 mmol). The mixture was stirred at 0 °C for 4 h and at 25 °C for 12 h, diluted with 15% aq NaOH, and extracted with chloroform. The extracts were washed with satd aq NaCl, dried, and concentrated in vacuo to yield a residue, which was subjected to silica gel column chromatography (30% acetone/hexane) to give the tosylate **28** (0.71 g, 85% based on recovered 0.11 g starting material). $[\alpha]_D^{22}$ +16.4 (*c* 0.37, $CHCl_3$). ^1H NMR 1.29–1.39 (m, 1H), 1.46–1.50 (m, 1H), 1.63–1.65 (m, 1H), 1.86–2.06 (m, 4H), 2.12–2.21 (m, 2H), 2.43 (s, 3H), 2.87–2.90 (m, 1H), 3.59–3.65 (m, 2H), 3.68 (abq, *J*=16.5 Hz, 2H), 4.52 (t, *J*=7.0 Hz, 1H), 5.93 (d, *J*=8.0 Hz, 2H), 6.83 (s, 1H), 7.22 (s, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.76 (d, *J*=8.5 Hz, 2H); ^{13}C NMR 21.5, 21.7, 22.7, 32.5, 34.4, 41.6, 47.8, 49.2, 71.2, 88.0, 89.0, 101.5, 110.7, 118.1, 127.5 (2), 129.6 (2), 132.3, 134.5, 144.3, 147.2, 148.4, 168.7; HRMS (ES) 584.0592 (M+1), calcd for $C_{24}H_{27}NO_6I$ 584.0604.

4.1.11. (5*S*)-*N*-(2-Iodo-4,5-methylenedioxyphenylacetyl)-6-azaspiro[4.4]non-1-ene (29). A solution of tosylate **28** (0.59 g, 1 mmol) and DBU (5 mL) in DMF (10 mL) was stirred at 120 °C for 12 h, cooled, diluted with EtOAc, washed with satd aq NaCl, and concentrated in vacuo, giving a residue, which was subjected to silica gel column chromatography (20% acetone/hexane) to give amidoalkene **29** (0.25 g, 80% based on recovered 0.15 g starting material). $[\alpha]_D^{22}$ −57.6 (*c* 0.18, $CHCl_3$). ^1H NMR (2.5:1 mixture of two rotamers) major rotamer 1.75–1.79 (m, 1H), 1.83–1.95 (m, 4H), 2.25–2.32 (m, 1H), 2.39–2.45 (m, 1H), 2.60–2.69 (m, 1H), 3.51–3.65 (m, 4H), 5.54 (t, *J*=3.0 Hz, 1H), 5.81 (t, *J*=3.0 Hz, 1H), 5.92 (d, *J*=5.5 Hz, 2H), 6.77 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (major rotamer) 23.6, 31.7, 34.5, 39.7, 47.6, 48.4, 76.0, 88.9, 101.5, 110.6, 118.2, 131.5, 132.3, 133.7, 147.2, 148.4, 167.8; HRMS (ES) 412.0404 (M+1), calcd for $C_{17}H_{19}NO_3I$ 412.0410.

4.1.12. (5*S*)-*N*-[2-(2-Iodo-4,5-methylenedioxyphenylethyl)]-6-azaspiro[4.4]non-1-ene (13). To a solution of amidoalkene **29** (0.041 g, 0.1 mmol) in THF (3 mL) at −40 °C was added a solution of AlH_3 in THF (0.2 mL, 0.67 M, 0.134 mmol). The solution was stirred at −40 °C for 15 min, diluted with satd aq Na_2SO_4, and filtered. The filtrate was dried and concentrated in vacuo, giving a residue, which was subjected to silica gel column chromatography (EtOAc then 10:1 EtOAc/MeOH containing 1% Et_3N) to yield aminoalkene **13** (24 mg, 60%) whose spectroscopic properties (except for its optical rotation, which was not reported in Ref. 41) matched with those reported earlier.[41] $[\alpha]_D^{22}$ −32.0 (*c* 0.08, $CHCl_3$). ^1H NMR 1.49–1.66 (m, 1H), 1.75–1.96 (m, 5H), 2.30 (m, 2H), 2.38–2.49 (m, 2H), 2.78–2.84 (m, 3H), 2.97–3.01 (m, 1H), 5.56–5.57 (m, *J*=1 Hz, 1H), 5.80–5.81 (m, 1H), 5.93 (s, 2H), 6.74 (s, 1H), 7.20 (s, 1H); ^{13}C NMR 21.4, 29.7, 31.5, 38.2, 40.9, 50.0, 51.3, 77.7, 87.8, 101.4, 109.6, 118.5, 132.1, 134.7, 136.8, 146.7, 148.4; HRMS (ES) 398.0610 (M+1), calcd for $C_{17}H_{21}NO_2I$ 398.0617.

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Supplementary data

Within this section are (1) the general experimental section, and (2) ^1H and ^{13}C NMR spectra of **12**, **13**, **15**, **16**, **18**–**23**, **27**–**29**, (*S*)-Mosher ester derivative of *N*-Boc-**13**, and (*R*)-Mosher ester derivative of *N*-Boc-**13**. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tet.2006.05.045.

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