Total Synthesis of (+)-Astrophylline

Marco Schautd and Siegfried Blechert*
Institut für Chemie, Technische Universität Berlin, Strasse des 17, Juni 135, D-10623 Berlin, Germany
blechert@chem.tu-berlin.de

Received December 4, 2002

The first total synthesis of (+)-astrophylline (2) has been achieved, starting from readily available enantiomerically pure (+)-(1R,4S)-4-hydroxycyclopent-2-ethyl acetate (11). A novel ruthenium-catalyzed ring-closing ring-opening ring-closing metathesis of carboxyclic olefins of general type 5 was the key step, providing the stereochemically well-defined bis-piperidyl skeleton of the target molecule. A [2,3]-Wittig–Still rearrangement of 9 was also employed as the critical transformation in the stereocontrolled generation of the 1,2-trans configuration of the cyclopentene intermediate 6c. Our early synthetic efforts toward 1,2-trans cyclopentene derivatives of type 6, as well as the synthetic pathway to an optimized 13-step total synthesis of 2 (12% overall yield), are reported.

Introduction

Several new alkaloids1,2 were isolated in the end of the sixties from Astrocasia phyllanthoides, a shrub belonging to the Euphorbiaceae family and native to Central America. Structure 1 was proposed for the predominant alkaloid, astrocasine, based largely on spectral data (IR, UV, NMR, MS) and partial degradation studies. Later,2 the isolation of 2 by Lloyd in 1965 from the same plant and its characterization as cis-(2R,3S)-[2,3]bi(2-piperidinyl)-3-phenyl-propenone provided strong support for structure 1. Astrophylline 2 was also the first natural cis-cinnamoyl alkaloid reported in the literature.

The key structural features of 2 include a cinnamoyl-protected amine in the presence of a second piperidine substructure, which makes the use of a carefully conceived orthogonal protecting group strategy essential. The unusual carbon skeleton of 2 represents a synthetic challenge, due to the presence of unsymmetrically bridged piperidyl heterocycles, and a well-defined absolute configuration of the two neighboring stereogenic centers. At the start of this work, there were no general synthetic methods known for the preparation of non-C2-symmetric bridged bicyclic piperidines such as 2. Herein we report the first total synthesis of 2, including our initial endeavors toward key precursors of type 6.

Results and Discussion

Retrosynthetic Analysis. Our approach was based on previous work on the total synthesis of (+)-dihydrocuscuhoygrine, accomplished in our group.3 Taking advantage of the powerful olefin metathesis reaction4 as a tool for the formation of carbon–carbon bonds under mild conditions, a tandem ring rearrangement metathesis (RRM) reaction5 served as the key step for the stereo-

FIGURE 1.

selective synthesis of the bis-pyrrolidine alkaloid. We envisaged that this type of transformation would also be feasible for the stereocontrolled construction of the heterocyclic skeleton of 2.

It was envisaged that the natural product would be available from 3 after deprotection and subsequent Z-selective Lindlar reduction6 (Scheme 1). Amide 3 could be derived from 4 after simple functional group interconversion operations. From previous studies in our laboratories,1,7 it was foreseen that 4 could be obtained

after a ring-rearrangement metathesis reaction of key intermediate 5, which involves the formation of two new carbon–carbon bonds in one step. Since it was expected that the stereochemical information associated with 5 would be transferred to 4 and thus to the natural product, the synthetic challenge is reduced to the preparation of enantiopure 5 from simple starting materials. Thus, amide 6 \((R = H)\) could give 5 after displacement of the hydroxy functionality with a suitably protected allylamine. It was postulated that trans-1,2-disubstituted 6 could be prepared from 7 or 9 via either an \(S_N2'\)-anti addition of zinc cyanocuprate 8 to cis-1,4-disubstituted chloride 7 or a [2,3]-Wittig–Still rearrangement of stannane 9. This is highly desirable, as both 7 and 9 can be obtained from either epoxide 10 or enantiopure acetate 11, both of which are trivial to prepare in multigram quantities.

**Synthesis of 6.** Monoepoxide 10,11 which could be prepared easily from cyclopentadiene, was considered to be a suitable racemic starting material to examine the nucleophilic attack of the \(O\)-protected hydroxymethylcuprate 8 on cyclopentene derivatives of type 7. The efficiency of \(\delta\)-allyl-Pd(0) substitutions with \(N\)-allyl sulfonamides to open epoxide 10 has been demonstrated.5a,12 The tosyl group was chosen to protect the amine nitrogen, as other standard protecting groups (Ns, Cbz, Boc) were found to be problematic later in the synthesis. Thus Ts-protected allylamine 12 was prepared by using the literature procedure.13 Pd(0)-catalyzed allylic amination of 10 with 12 proceeded smoothly to provide alcohol 13 in reasonable yield (Scheme 2). Subsequent chlorination of the hydroxy functionality with thionyl chloride afforded 7 in a 5:1 diastereomeric mixture. The minor trans-chloride was separated by column chromatography. The halogen-leaving group is essential, as the corresponding triflates and mesylates were too unstable to be conveniently handled, whereas acetate was found to be unre-

**SCHEME 1.** Retrosynthetic Analyses of Astrophylline 2

![Diagram](image1)

**SCHEME 2.** Synthesis of Alcohol 6b via \(S_N2'\) Additiona

![Diagram](image2)

---

*aeda* Reagents and conditions: (a) (i) 12, \(\text{Pd}_2(\text{dba})_3\), CHCl\(_3\) (2 mol %), dppe (8 mol %), BSA, THF, 0 °C, 30 min; (ii) 10, 0 °C to room temperature, 21 h (60%). (b) 13, SOCl\(_2\), 0 °C, 5 min (87%). (c) (i) MTBE, KO\(_t\)Bu (4.0 equiv), tBuLi (4.4 equiv), −70 to −20 °C, 3 h; (ii) ZnCl (4.5 equiv), THF, −60 °C, 2 h; (iii) CuCN (1.1 equiv), LICI (2.3 equiv), then 7, −75 °C to room temperature, 12 h (57%). (d) (i) 6a, TFA, CH\(_2\)Cl\(_2\), 0 °C to room temperature, 14 h; (ii) KOH, MeOH/water, rt (79%).

---


active in the organometallic addition step. We were now in a position to examine the feasibility of the S_N2 reaction. After considerable experimentation, optimized conditions involved treatment of 7 with 8 (prepared in situ from MTBE) at low temperature followed by stirring overnight at room temperature, to give trans,1,2-disubstituted tert-butyl ether 6a (>98% de, determined by H NMR spectroscopy), which was subsequently hydrolyzed (via the TFA-ester) to give the required alcohol 6b in 45% yield over two steps (Scheme 2). In this transformation, the use of the tosyl moiety is critical, as both nosyl and carbamate-based protecting groups underwent reaction with 8.

The possible benefits of the use of a [2,3]-Wittig–Still rearrangement for the synthesis of 6 were considered. The advantage of this reaction is that it can offer greater protecting group flexibility compared with the S_N2 process outlined previously. For example, carbamate-protecting groups (which were incompatible with the S_N2 reaction), such as the tert-butylcarbonyl (Boc) group should be inert under the basic rearrangement conditions. The Boc-moiety would be the ideal choice for the protection group PG_1 (see Scheme 1), as preliminary experiments indicated that it was compatible in terms of cleavage conditions with the functionality present in the latter stages of the synthesis, and in this regard was expected to be superior to the tosyl group.

Although the synthetic route to 9 could conceivably start from 10, due to concerns about the practicality of performing asymmetric Pd(0) allylic substitution reactions on large scale, it was decided to evaluate the feasibility of acetate 11 as a starting material, which could be prepared easily on a 50-g scale from cyclopentadiene. The Boc-protected amine 14 was obtained in good overall yield after a n^3-allyl-Pd(0) substitution with allylamine in the presence of catalytic amounts of Pd(Ph_3P)_4 followed by the addition of BocO to the filtered reaction mixture (Scheme 3). To provide the correct absolute product stereochemistry the configuration at C4 in 14 had to be inverted. Thus, a Mitsunobu reaction with benzoic acid was successful, affording the desired trans,1,4-disubstituted alcohol 15 in 66% yield over these two steps after hydrolysis of the intermediate ester. Next, attention was focused on the installation of the hydroxymethyl substituent via the [2,3]-Wittig–Still rearrangement. Reaction of 15 with tributyl-iodomethylstannane yielded the precursor 9 in excellent yield. Our first attempts to transmetalate 9 with n-BuLi at -78 °C resulted in a [2,3]-sigmatropic rearrangement in unsatisfactory yield. Further experimentation led to an optimized multigram scale protocol (see Experimental Section), which furnished the key building block 6c in good yield.

(14) As an analogue of 3, we synthesized Boc-piperidine and mixed it with 1 equiv of 3-phenylpropionyl-piperidine. The mixture was dissolved in methylene chloride and treated with TFA. After 1 h the Boc-group was cleaved, while the triple bond had not reacted, as indicated by TLC and a NMR analysis of the crude mixture. After subsequent hydrogenation with Lindlar catalyst in methanad for 12 h at room temperature and conventional workup, the NMR spectra of the reaction residue showed the unchanged TFA salt of piperidine, together with stereoelectronic formation of the cis-cinnamyl protected piperidine in high yield.


SCHEME 4. First Generation Synthesis of Intermediate 3

![](image)

| Reagents and conditions: (a) (i) 6c, methanesulfonyl chloride, Et3N, CH2Cl2, 0°C, 10 min; (ii) NaN3, DMF, 60°C, 14 h (82%). (b) (i) 16, Ph3P, THF, 60°C, 13 h; (ii) benzyl chloroformate, K2CO3, rt, 3 h (80%). (c) 17, NaH, allyl bromide, DMF, 0°C to room temperature, 30 min (86%). (d) 5a, (IHMe)(Cy3P)Cl2Ru=CHPh (1 mol %), CH2Cl2, 40°C, 3 h (80%). (e) 4a, H2, Pd/C, EtOH, rt, 14 h; (ii) phenyl-propynoyl chloride, K2CO3, THF, rt, 1 h (77%). |

were encouraged to attempt the synthesis of 3 using the reduction/acylation strategy utilized to prepare 4. Given the success of the one-pot approach without isolating the deprotected amine. Gratifyingly, the action of diisopropyl azodicarboxylate and triphenylphosphine on diene 3f to Ns-protected 6c afforded 5a in high yield (95%, Scheme 5). Tandem metathesis of 5a, under identical conditions to those used to convert 5a, provided the bicyclic 4b in good yield (82%). It is interesting to note that the nosyl protecting group, which has been found to be problematic in metathesis reactions, previously gave no difficulties in this metathesis rearrangement. Deprotection of the Ns-group with thiophenol led to the amine 19, and a subsequent hydrogenation—acylation sequence provided intermediate 3 in good yield. Again it is noteworthy that this order of reaction is critical, as attempted hydrogenation of the olefins with the nosyl moiety still bound results in efficient reduction of the nitro functionality to give a less easily removable aniline derivative. Overall, this route to 3 from 6c is three steps shorter than the original synthetic pathway, and affords the product in improved yield (49%).

The final steps of the total synthesis entailed the deavage of the Boc-group and subsequent cis-selective Lindlar hydrogenation of the triple bond with catalyst (85% yield over two steps) afforded the natural product 2 after purification. Spectral and analytical data for 2 were comparable with those reported in the literature (see ref 2). It is remarkable that the cis-cinnamoyl group could only be prepared from the TFA salt of 3 (after deprotection). If after deprotection of 3 the free-piperidine is isolated and hydrogenated, complete reduction of the triple bond to the corresponding saturated derivative is observed.

Conclusion

We have accomplished a highly efficient stereoselective synthesis of cis-cinnamoyl alkaloid (+)-astrophylline 2 in 13 steps and 12% overall yield. Starting from the common enantiomeric pure carbonyl 11, two powerful key rearrangements have been used to construct the bis-piperidine skeleton of the natural product. Access to the trans,1,2-disubstituted chiral cyclopentene intermediate 6c could be obtained by taking advantage of a selective sterocenter-forming [2,3]-Wittig—Still rearrangement. The preparation of the target skeleton could be achieved by tandem olefin metathesis, where the chiral information from the readily prepared carbonyl 5b is completely transferred to both product heterocycles in a facile and highly efficient carbon—carbon bond-forming transformation, furnishing a product, which can be transformed into...
Experimental Section

**General.** Each reaction with air- and moisture-sensitive components was performed under a N2 atmosphere; metathesis reactions were carried out in a glovebox. Tetrahydrofuran was distilled from sodium benzenophenone, and dichloromethane was distilled from calcium hydride. 1H NMR (500 MHz) and 13C NMR spectra (125.8 MHz) were recorded in the solvent indicated. NMR chemical shifts are reported in ppm upfield, relative to the internal solvent peak. Mass spectra were obtained at an ionizing potential of 70 eV. IR spectra were measured by attenuated total reflectance (ATR). Optical rotations were determined on a polarimeter as solutions in a 10 cm cell at 589 nm (c = 1 g/100 mL). Rf values indicated refer to TLC on 0.2 mm analytical plates coated with silica gel. MTBE = methyl tert-butyl ether. Those chemicals that were purchased were used without further purification. Cyclopentadiene monoxide (10), T3- and N3-protected allylamides (12 and 18), and tributyl-iodomethyl-stannane were prepared according to the published procedures.

cis-N-Allyl-(4-hydroxy-cyclopent-2-enyl)-4-methyl-benzensulfonamide (13). To a stirring solution of Pd(dba)2 (297 mg, 0.32 mmol, 2 mol %) in THF (10 mL, 0.03 M) was added (diphenylphosphino)ethane (510 mg, 1.28 mmol, 8 equiv). Then the mixture was cooled to 0 °C and treated with (2-tert-butoxymethyl-cyclopent-3-enyl)-208 (71), 155 (62), 91 (100), 57 (77); HRMS calcd for C20H29-NO3S [M]+ 363.1868, found 363.1868.

trans-N-Allyl-(2-hydroxy-cyclopent-3-enyl)-4-methyl-benzensulfonamide (6b). To a solution of ether (200 mg, 0.55 mmol) in CH2Cl2 (2 mL, 0.3 M) was added trifluoroacetic acid (0.4 mL) dropwise at 0 °C. The solution was stirred for 14 h at room temperature and was treated with a solution of chloroform (175 mg, 0.56 mmol, 1.1 equiv) in THF (0.5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Saturated aq NaHCO3 (10 mL) was added, and the resulting mixture was extracted with MTBE (2 × 20 mL). The combined organic phases were dried over Na2SO4 and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography (hexane/ethyl acetate 8:2) gave compound 6a (116 mg, 57%) as a colorless oil. Rf 0.87 (hexane/ethyl acetate 3:1). 1H NMR (500 MHz, CDCl3) δ 1.14 (s, 9H), 2.14 (m, 1H), 2.42 (s, 3H), 2.41–2.50 (m, 1H). 2.78 (m, 1H), 3.11 (dd, J = 8, 8 Hz, 1H), 3.22 (dd, J = 8, 6 Hz, 1H), 3.63 (m, 1H), 3.81 (m, 1H), 4.34 (dd, J = 5, 5.5 Hz, 1H), 5.07 (br d, J = 10, 10 Hz), 5.18 (d, J = 10, 10 Hz). 5.64 (dd, J = 10, 6 Hz, 1H). 7.27 (dd, J = 8, 2 Hz), 7.76 (d, J = 8, 2 Hz); 13C NMR (125.8 MHz, CDCl3) δ 21.4 (CH2), 27.4 (CH2), 36.6 (CH2), 46.7 (CH2), 50.8 (CH2), 63.4 (CH2), 72.7 (Cq), 116.7 (Cq), 127.4 (CH), 129.8 (CH2), 131.8 (CH), 135.8 (Cq), 138.0 (Cq), 143.0 (Cq); IR (neat, cm−1) ν 2973, 1340, 1158, 1091; LRMS (EI) m/z (%) 363 (M+−1), 289 (40), 276 (75), 208 (71), 155 (62), 91 (100), 57 (77); HRMS calcd for C20H29-NO3S [M]+ 363.1868, found 363.1868.

cis-N-Allyl-(2-chloro-cyclopent-2-enyl)-4-methyl-benzensulfonamide (7). To a solution of alcohol 13 (1.32 g, 3.50 mmol) in CH2Cl2 (10 mL) was added thionyl chloride (0.57 mL, 7.20 mmol, 1.16 equiv) dropwise at 0 °C. After 5 min of stirring the mixture was concentrated in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate 4:1) to yield chloride 7 (1.22 g, 87%) as a colorless oil. Rf 0.73 (hexane/ethyl acetate 2:1). 1H NMR (500 MHz, CDCl3) δ 1.74 (dt, J = 15, 4 Hz, 1H), 2.43 (s, 3H), 2.78 (dt, J = 15, 8 Hz, 2H), 2.86 (m, 1H), 3.80 (m, 1H), 4.65 (m, 1H), 4.78 (m, 1H), 5.13 (dd, J = 10, 10 Hz, 1H), 5.23 (dd, J = 17, 1 H, 1H), 5.66 (m, 1H), 5.86 (dd, J = 17, 10, 6, 6 Hz, 1H), 5.91 (m, 1H), 7.32 (d, J = 8, 8 Hz, 2H), 7.72 (d, J = 8, 8 Hz, 2H); 13C NMR (125.8 MHz, CDCl3) δ 21.5 (CH3), 38.5 (CH3), 46.3 (CH3), 61.0 (CH2), 72.7 (CH2), 117.4 (CH2), 127.1 (CH), 129.7 (CH), 133.8 (CH), 135.0 (CH), 135.5 (Cq), 137.2 (Cq), 143.5 (Cq); IR (neat, cm−1) ν 2924, 1334, 1158, 1091; LRMS (EI) m/z (%) 311 (M+1), 276 (100), 155 (16), 91 (37); HRMS calcd for C15H13CINO3S [M]+ 311.0747, found 311.0743. Anal. Calc. for C15H13CINO3S: C, 57.78; H, 5.82; N, 4.47. Found: C, 57.76; H, 5.78; N 4.59.

The natural product by using standard functional group manipulations.
Allyl-(1R,4S)-4-hydroxy-cyclopent-2-enyl-carbamic Acid tert-Butyl Ester (14). To a solution of alcohol 13 (8.52 g, 35.6 mmol) in THF (225 mL, 0.16 M) was added triphenylphosphine (18.7 g, 71.2 mmol, 2.0 equiv) and benzoic acid (29.7 g, 204 mmol, 1.5 equiv). The mixture was cooled to 0 °C and diisopropyl azodicarboxylate (12.8 mL, 60.5 mmol, 1.7 equiv) was added. The mixture was allowed to warm to room temperature and stirred for 1 h at room temperature, then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature. Then Pd(Ph3P)4 (4.05 g, 3.5 mmol, 5 mol %) was introduced. The reaction mixture was stirred for 1 h at room temperature.
M) was added triphenylphosphine (181 mg, 0.66 mmol, 1.2 equiv) and the mixture was stirred for 13 h at 60 °C. Then the reaction mixture was cooled to room temperature and treated with K₂CO₃ (236 mg, 1.71 mmol, 3.0 equiv) and benzyl chloroformate (0.1 mL, 0.69 mmol, 1.2 equiv). After being stirred for 3 h, the resulting mixture was diluted with water (10 mL) and stirred for 1 h at room temperature. Ethyl acetate (15 mL) was added, the solution was washed with saturated aqueous potassium carbonate (10 mL) and brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 7:1) gave dicarboxamido carbamate 17 (176 mg, 80% as a colorless oil. Rₚ 0.53 (hexane/ethyl acetate 3:1). [α]D²⁵ 63° (c 0.51, EtOH); [α]D³⁰ 100 °C, not fully coalesced) > 2976, 2212, 1684, 1630, 1416, 1168; LRMS (EI) m/z (%) 368 (M+, < 1), 293 (22), 129 (64), 91 (100), 57 (62); HRMS calcd for C₁₁₂H₁₈N₂O₄ [M+] 386.2220, found 386.2220. Anal. Calcd for C₁₁₂H₁₈N₂O₄: C, 68.37; H, 7.82; N, 7.35. Found: C, 68.35; H, 7.87; N 7.24.

Allyl(1R,2S)-2-[allyl-benzyloxy carbonylamino]methyl-cyclopent-3- enyl-carmic Acid tert-Buyl Ester(5a). To a stirred solution of 17 (95 mg, 0.25 mmol) in DMF (2.5 mL, 0.1 M) at 0 °C was added NaH (60%, 59 mg, 1.5 mmol; 6 equiv). After the evolution of H₂ had ceased, allyl bromide (0.08 mL, 0.74 mmol, 3 equiv) was added. After being stirred for 30 min at room temperature, the mixture was quenched with water (3 mL). The aqueous layer was extracted with MTBE (2 x 10 mL), and the combined extracts were washed with brine (5 mL) and dried over Na₂SO₄. Removal of the solvents left an oil that was purified by flash chromatography (hexane/ethyl acetate 1:1), affording triene 5a (92 mg, 86%) as a colorless oil. Rₚ 0.80 (hexane/ethyl acetate 3:1). [α]D²⁵ 55° (c 0.85, EtOH); [α]D³⁰ 100 °C, not fully coalesced) > 2976, 2212, 1684, 1630, 1416, 1168; LRMS (EI) m/z (%) 368 (M+, < 1), 293 (22), 129 (64), 91 (100), 57 (62); HRMS calcd for C₁₁₂H₁₈N₂O₄ [M+] 386.2220, found 386.2220. Anal. Calcd for C₁₁₂H₁₈N₂O₄: C, 68.37; H, 7.82; N, 7.35. Found: C, 68.35; H, 7.87; N 7.24.

[(2R,3S)-3,6-Diethyl-2H,3H-1,2,3-bispyrindinyl-1,1-dicarboxylic Acid 1-Benzyl Ester 1-tert-Butyl Ester (4a). Triene 5a (167 mg, 0.39 mmol) and (IHMes)Cy²P[Cl (-)-Ru=CHPh (4 mg, 1 mol%) were heated at reflux temperature in dry CH₂Cl₂ (4 mL, 0.1 M) for 3 h. The solution was then concentrated in vacuo, and the residue was purified by flash chromatography (hexane/ethyl acetate 6:1), affording bispyridine 4a (124 mg, 80%) as a colorless semisolids. Rₚ 0.62 (hexane/ethyl acetate 3:1). [α]D²⁵ 55° (c 0.63, EtOH). [α]D³⁰ 100 °C, not fully coalesced) > 2976, 2212, 1684, 1630, 1416, 1168; LRMS (EI) m/z (%) 368 (M+, < 1), 293 (22), 129 (64), 91 (100), 57 (55); HRMS calcd for C₁₇₂H₂₁₇N₂O₄ [M+] 426.2519, found 426.2521. Anal. Calcd for C₁₇₂H₂₁₇N₂O₄: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.27; H, 7.96; N 6.45.

[(2R,3S)-3,6-Diethyl-2H,3H-1,2,3-bispyrindinyl-1,1-dicarboxylic Acid 1-Benzyl Ester 1-tert-Butyl Ester (4b). Triene 5b (5.00 g, 10.47 mmol) and (IHMes)Cy²P[Cl (-)-Ru=CHPh (89 mg, 1 mol%) were heated at reflux temperature in dry CH₂Cl₂ (100 mL, 0.1 M) for 2 h. The solution was then concentrated in vacuo, and the residue was purified by flash chromatography (hexane/ethyl acetate 6:1), affording bispyridine 4b (3.86 g, 82%) as a white solid. Rₚ 0.47 (hexane/ethyl acetate 1:1). [α]D²⁵ 56° (c 0.18, EtOH). [α]D³⁰ 100 °C, not fully coalesced) > 2976, 2212, 1684, 1630, 1416, 1168; LRMS (EI) m/z (%) 368 (M+, < 1), 293 (22), 129 (64), 91 (100), 57 (55); HRMS calcd for C₁₇₂H₂₁₇N₂O₄ [M+] 426.2519, found 426.2521. Anal. Calcd for C₁₇₂H₂₁₇N₂O₄: C, 70.27; H, 8.03; N, 6.57. Found: C, 70.27; H, 7.96; N 6.45.

[(2R,3S)-3,6-Diethyl-2H,3H-1,2,3-bispyrindinyl-1,1-dicarboxylic Acid 1-Benzyl Ester 1-tert-Butyl Ester (4b). Triene 5b (5.00 g, 10.47 mmol) and (IHMes)Cy²P[Cl (-)-Ru=CHPh (89 mg, 1 mol%) were heated at reflux temperature in dry CH₂Cl₂ (100 mL, 0.1 M) for 2 h. The solution was then concentrated in vacuo, and the residue was purified by flash chromatography (hexane/ethyl acetate 6:1), affording bispyridine 4b (3.86 g, 82%) as a white solid. Rₚ 0.47 (hexane/ethyl acetate 1:1). [α]D²⁵ 56° (c 0.18, EtOH). [α]D³⁰ 100 °C, not fully coalesced) > 2976, 2212, 1684, 1630, 1416, 1168; LRMS (EI) m/z (%) 368 (M+, < 1), 293 (22), 129 (64), 91 (100), 57 (55); HRMS calcd for C₁₇₂H₂₁₇N₂O₄ [M+] 426.2519, found 426.2521. Anal. Calcd for C₁₇₂H₂₁₇N₂O₄: C, 70.27; H, 8.03; N, 6.57. Found: C, 70.27; H, 7.96; N 6.45.
1H), 2.99 (dd, J = 12, 8 Hz, 1H), 3.34 (dd, J = 12, 5 Hz, 1H), 3.47 (m, 1H), 3.50 (m, 1H), 3.63 (ddd, J = 17, 2, 2 Hz, 1H), 3.76 (m, 1H), 4.08 (m, 1H), 4.23 (m, 1H), 5.68–5.81 (m, 4H), 8.0 (d, J = 8 Hz, 2H), 8.35 (d, J = 8 Hz, 2H); 13C NMR (125.8 MHz, CDCl₃, rotameric mixture) δ [25.6/25.8] (CH₃), 28.3 (CH₃), [35.3/35.8] (CH₂), [39.6/40.8] (CH₂), 44.8 (CH₂), 45.4 (CH₂), [49.1/50.6] (CH), 80.0 (C₆), 122.4 (CH), 123.4 (CH), 124.2 (CH), 127.0 (CH), 128.7 (CH), 142.4 (C₂), 150.1 (C₁), 154.8 (C₀); IR (neat, cm⁻¹) ν 2965, 1686, 1530, 1350, 1168, 1109; LRMS (EI) m/z (%) 449 ([M⁺] - 1), 376 (5), 182 (16), 126 (98), 82 (98), 57 (100); HRMS calcd for C₆H₇N₂O₅S [M⁺] 449.1621, found 449.1616. Anal. Calc. for C₆H₇N₂O₅S: C, 56.11; H, 6.05; N, 9.35. Found: C, 55.92; H, 6.12; N 9.30.

(2R,3S)-3,6-Diethylcarboxylic Acid tert-Butyl Ester (19). Biperidine 4b (1.50 g, 3.34 mmol) and K₂CO₃ (1.85 g, 13.36 mmol, 4 equiv) were suspended in DMF (30 mL, 0.12 M). PhSH (0.41 mL, 4.00 mmol, 1.2 equiv) was added and the suspension was stirred at 70 °C for 1 h. The mixture was poured onto water (15 mL) and extracted with MTBE (15 mL). The aqueous phase was saturated with NaCl and further extracted with MTBE (2 × 15 mL). The combined organic phases were washed with brine (15 mL), dried over Na₂SO₄, and concentrated in vacuo. Purification of the residue by filtration over silica (CH₂Cl₂/methanol 1:1) furnished amine 19 (703 mg, 80%) as a pale yellow oil. H NMR (500 MHz, CDCl₃) δ 1.41 (s, 9H), 2.17 (br dd, J = 17.4 Hz, 1H), 2.29 (m, 2H), 2.68 (br dd, J = 13, 4, 1H), 2.84 (m, 1H), 3.27–3.46 (m, 3H), 3.90 (br s, 1H), 4.13 (m, 1H), 4.27 (m, 1H), 5.48–5.81 (m, 4H); 13C NMR (125.8 MHz, CDCl₃, rotameric mixture) δ 25.6 (CH₃), 28.3 (CH₃), 33.6 (CH₂), [39.7/40.7] (CH₂), [44.4/44.2] (CH₂), [44.9/50.9] (CH), 79.9 (C₆), [122.4/122.7] (CH), [123.2/123.9] (CH), 127.1 (CH), [127.8/128.3] (CH), 155.5 (C₀); IR (neat, cm⁻¹) ν 3335, 2974, 1689, 1409, 1172, 1110; LRMS (EI) m/z (%) 264 ([M⁺] - 1), 126 (59), 82 (100), 57 (69); HRMS calcd for C₅H₉N₂O₂: [M⁺] 264.1838, found 264.1833.

(2R,3S)-1-(3-Phenyl-prop-2-ynyl)-2,3]Biperidinyl-1-carboxylic Acid tert-Butyl Ester (3). A solution of amine 19 (700 mg, 2.65 mmol) in ethanol (25 mL, 0.1 M) containing palladium on charcoal (270 mg, 10 mol %) was hydrogenated at room temperature for 15 h. The catalyst was removed by filtration over Celite, and the solution concentrated in vacuo to give the crude product (710 mg, 100%) as a colorless oil. This was redissolved in THF (13 mL, 0.2 M) and treated with potassium carbonate (1.13 g, 7.95 mmol, 3.0 equiv) and phenylpropynyl chloride (522 mg, 3.18 mmol, 1.2 equiv), and the solution was stirred for 2 h at room temperature. Then the mixture was diluted with water (10 mL) and allowed to stir for 1 h. Ethyl acetate (20 mL) was added, the layers were separated, and the organic layer was washed with saturated aqueous potassium carbonate (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 3:1) gave 3 (801 mg, 79%) as a white solid. The spectroscopic data were identical with those obtained starting from 4a (Scheme 4).

cis-1-(2R,3S)-[2,3]Bipiperidinyl-1-yl-3-phenyl-propene-1-one [(+)-Astrophyllone] (2). Compound 3 (150 mg, 0.39 mmol) was dissolved in CH₂Cl₂ (1.5 mL, 0.26 M), the solution was cooled to 0 °C, and trifluoroacetic acid (0.6 mL, 4 M/L) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and concentrated to dryness in vacuo. The crude TFA salt was dissolved in methanol (1 mL) containing Pd(BaSO₄) (80 mg, 20 mol %) and chinoline, and the salt was hydrogenated at room temperature for 16 h. The catalyst was removed by filtration over Celite and the solution was concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (3 mL) and treated withaq potassium hydroxide solution (10%, 3 mL) for 15 min. The layers were separated and the aqueous layer was extracted with aq potassium hydrogenate solution (10%, 3 mL) for 15 min. The combined organic layers were concentrated in vacuo and the residue was purified by flash chromatography (MTBE/5% Et₂N) yielding astrophyllone 2 (99 mg, 85%) as a viscous oil. R₁ 0.59 (MTBE/5% Et₂N). [α]⁺₂₅ +27° (c 0.35, EtOH) (lit. [α]⁺₂₅ +23° (c unspecified, EtOH)); 1H NMR (500 MHz, CD₂Cl₂) SO, 100 °C, not fully coalesced) δ 1.11–1.38 (m, 6H), 1.43–1.64 (m, 3H), 1.67–1.79 (m, 2H), 2.24 (m, 1H), 2.44–2.53 (m, 1H), 2.64–2.85 (m, 3H), 3.88–4.22 (m, 2H), 6.09 (d, J = 12 Hz, 1H), 6.60 (d, J = 12 Hz, 1H), 7.23–7.44 (m, 5H); 13C NMR (125.8 MHz, CDCl₃, rotameric mixture) δ [24.6/24.9] (CH₃), 26.4 (CH₃), [26.9/27.1] (CH₂), 27.7 (CH₂), [29.7/30.1] (CH₃), [40.9/42.2] (CH₂), [42.0/44.1] (CH₃), 47.3 (CH₂), 49.8 (CH₂), [58.5/58.9] (CH), [123.5/123.9] (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), [132.7/133.2] (CH), [135.7/135.9] (C₁), 167.4 (C₀); IR (neat, cm⁻¹) ν 3315, 2928, 1634, 1614, 1547, 1439, 1260; LRMS (EI) m/z (%) 298 (M⁺), 12, 214 (9), 131 (21), 103 (15), 84 (100); HRMS calcd for C₁₉H₂₈N₂O [M⁺] 298.2045, found 298.2043. Anal. Calcd for C₁₉H₂₈N₂O: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.55; H, 8.87; N 9.42.

J O026803H