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Total Synthesis of (+)-Astrophylline

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The first total synthesis of (+)-astrophylline (**2**) has been achieved, starting from readily available enantiomerically pure (+)-(1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate (**11**). A novel ruthenium-catalyzed ring-closing ring-opening ring-closing metathesis of carbocyclic 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 alkaloids[1,2] 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[1] 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*-1-(2*R*,3′*S*)-[2,3′]bipiperidinyl-1′-yl-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 piperidine 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-C_2-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 (+)-dihydrocuscohygrine, accomplished in our group.[3] Taking advantage of the powerful olefin metathesis reaction[4] as a tool for the formation of carbon−carbon bonds under mild conditions, a tandem ring rearrangement metathesis (RRM) reaction[3,5] served as the key step for the stereoselective 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**.

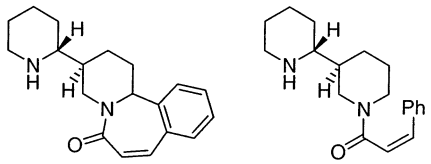

FIGURE 1.

It was envisaged that the natural product would be available from **3** after deprotection and subsequent *Z*-selective Lindlar reduction[6] (Scheme 1). Amide **3** could be derived from **4** after simple functional group interconversion operations. From previous studies in our laboratories,[3,5f,7] it was foreseen that **4** could be obtained

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(5) For further examples of tandem ring rearrangement (RCM-ROM-RCM) metathesis reactions, see: (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640. (b) Burke, S. D.; Quinn, K J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627. (c) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291−4298. (d) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829. (e) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648−2649. (f) Stapper, C.; Blechert, S. *Eur. J. Org. Chem.* **2002**, *16*, 2855−2858.
(6) (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 448. (b) Schöpf, C.; Merkel, W. *Liebigs Ann. Chem.* **1967**, *701*, 180−197.
(7) (a) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179. (b) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971−3974. (c) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584−9591. (d) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329. (e) Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *37*, 7503−7518.

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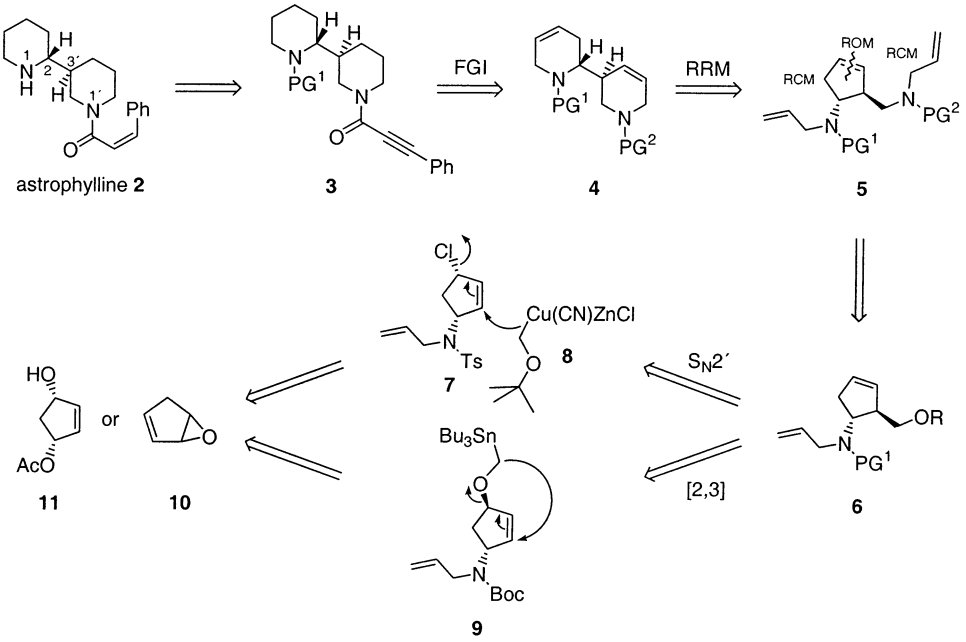
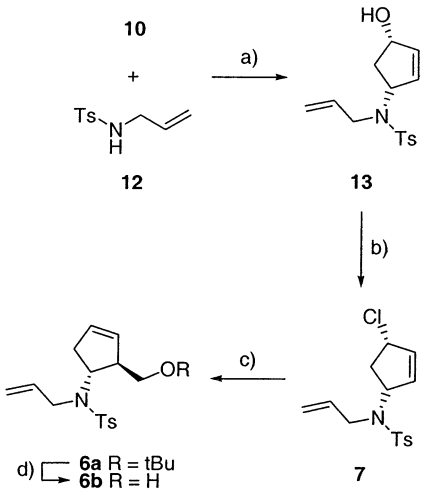
SCHEME 1. Retrosynthetic Analyses of Astrophylline 2



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**[8] or a [2,3]-Wittig−Still[9] rearrangement of stannane **9**.[10] 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 η^3-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 2. Synthesis of Alcohol 6b via S_N2' Addition[a]



[a] Reagents and conditions: (a) (i) **12**, $Pd_2(dba)_3$·$CHCl_3$ (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), *t*BuLi (4.4 equiv), −70 to −20 °C, 3 h; (ii) ZnCl (4.5 equiv), THF, −60 °C, 2 h; (iii) CuCN (1.1 equiv), LiCl (2.3 equiv), then **7**, −75 °C to room temperature, 12 h (57%). (d) (i) **6a**, TFA, CH_2Cl_2, 0 °C to room temperature, 14 h; (ii) KOH, MeOH/water, rt (79%).

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(10) For further examples of [2,3]-Wittig−Still rearrangements, see: (a) Ovaa, H.; Lastdrager, H. B.; Codee, J. D. C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, *21*, 2370−2377. (b) Riether, D.; Mulzer, J. *Org. Lett.* **2000**, *2*, 3139−3141.

(11) Gerdil, R.; Liu, H.; Bernardineli, G. *Helv. Chim. Acta* **1999**, 418−434.

(12) Shi, Y.; Trost, B. M. *J. Am. Chem. Soc.* **1993**, *115*, 9421−9438.

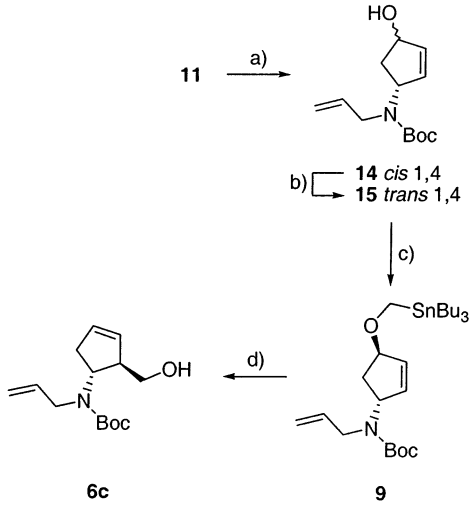
(13) Takeakin, N.; Ichiya, N.; Yoshiki, O.; Okiko, M. *Tetrahedron* **2000**, *34*, 6199−6208.

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)[8c] at low temperature followed by stirring overnight at room temperature, to give *trans*-1,2-disubstituted *tert*-butyl ether **6a** (>98% de, determined by ^{1}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[10] sigmatropic 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*-butyloxycarbonyl (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,[14] 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.[15] The Boc-protected amine **14** was obtained in good overall yield after a η^3-allyl-Pd(0) substitution with allylamine in the presence of catalytic amounts of Pd(Ph$_3$P)$_4$ followed by the addition of Boc$_2$O 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[16] 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.

SCHEME 3. Synthesis of Alcohol 6c via a [2,3]-Wittig−Still Rearrangement[a]



[a] Reagents and conditions: (a) (i) **11**, allylamine, Et$_3$N, THF, rt, 1 h; (ii) Pd(Ph$_3$P)$_4$ (5 mol %), rt, 14 h; (iii) (Boc)$_2$O, MeOH, 65 °C, 14 h (67%). (b) (i) **14**, Ph$_3$P, benzoic acid, DIAD, THF, 0 °C to room temperature, 2 h; (ii) 5% NaOH/MeOH, rt, 2 h (66%). (c) **15**, KH, dibenzo-18-crown-6, Bu$_3$SnCH$_2$I, 0 °C to room temperature, 3 h (92%). (d) **9**, *n*-BuLi (1.1 equiv), THF, −78 °C to room temperature, 12 h (69%).

We had now arrived at a point where two routes were available for the synthesis of suitably protected enantiopure **6**. Of the two, the Wittig−Still route (Scheme 3) held numerous advantages over the organocuprate methodology (Scheme 2): it is a stereoselective synthesis, affording the product as one enantiomer, it is compatible with large-scale operations (the synthesis of **8** is tedious and functions best on small scale), and it allows the desirable Boc-protection group to be used (vide supra). Thus this was the route of choice for the straightforward synthesis of **2**.

Synthesis of 3. At this stage of the synthesis our attention was focused on the necessary orthogonal protecting group strategy to provide the monoprotected target alkaloid **2**. Our initial retrosynthetic analysis (Scheme 1) identified diene **4** as a late-stage intermediate. This molecule requires two different protecting groups, as N1′ must be acylated in the presence of a protected N1 to complete the synthesis. Since PG^1 is fixed as the Boc group, it was tempting to install a benzyloxycarbonyl (Cbz) group at N1′ (i.e. as PG^2), which would be cleaved under the conditions required to hydrogenate both olefin moieties in **4**. Thus, we set about the replacement of the hydroxy moiety with a protected *N*-allylamide. Facile conversion of **6c** to the corresponding mesylate followed by substitution with sodium azide gave **16**. Subsequent Staudinger reduction[17] performed under standard conditions gave the amine in good conversion; however, due to chromatographic complications it was decided to attempt a one-pot reduction/protection procedure. The crude reaction mixture from the Staudinger reduction was cooled to room temperature and treated with a slight excess of benzyl chloroformate in the presence of K$_2$CO$_3$. After 3 h the Cbz-protected amine **17**

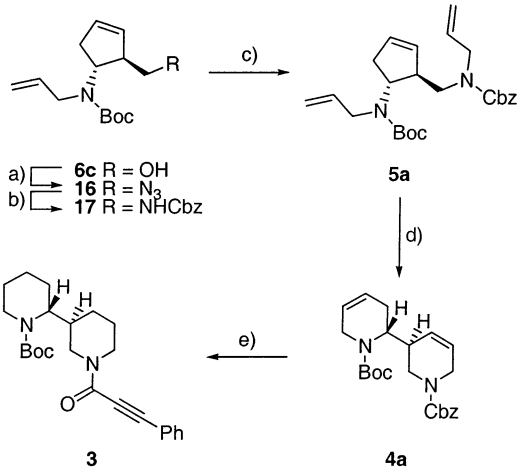
(14) As an analogue of **3**, we synthesized Boc-piperidine and mixed it with 1 equiv of 3-phenylpropinoyl-piperidine. The mixture was dissolved in methylene chloride and treated with TFA. After 1 h the Boc-group was cleaved, while the triple bond had not reacted, as indicated by TLC and a NMR analysis of the crude mixture. After subsequent hydrogenation with Lindlar catalyst in methanol 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 stereoselective formation of the *cis*-cinammoyl protected piperidine in high yield.

(15) (a) Liu, W.; Ghosh, A. K. *J. Org. Chem.* **1997**, *62*, 7908−7909. (b) Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *48*, 7287−7290.

(16) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151−166.

(17) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646.

SCHEME 4. First Generation Synthesis of Intermediate 3[a]



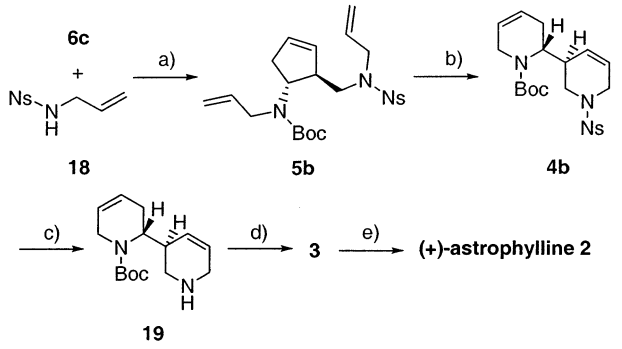
[a] Reagents and conditions: (a) (i) **6c**, methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C, 10 min; (ii) NaN_3, DMF, 60 °C, 14 h (82%). (b) (i) **16**, Ph_3P, THF, 60 °C, 13 h; (ii) benzyl chloroformate, K_2CO_3, rt, 3 h (80%). (c) **17**, NaH, allyl bromide, DMF, 0 °C to room temperature, 30 min (86%). (d) **5a**, (IHMes)$(Cy_3P)Cl_2Ru$=CHPh (1 mol %), CH_2Cl_2, 40 °C, 3 h (80%). (e) (i) **4a**, H_2, Pd/C, EtOH, rt, 14 h; (ii) phenyl-propynoyl chloride, K_2CO_3, THF, rt, 1 h (77%).

could be isolated in 80% yield (two steps). To prepare the metathesis precursor **5a**, a simple allylation with allyl bromide was carried out (Scheme 4).

The next step involved tandem metathesis of **5a** promoted by commercial available ruthenium alkylidene catalyst (IHMes)$(Cy_3P)Cl_2Ru$=CHPh[18] (1 mol %) in boiling CH_2Cl_2. After 3 h the reaction was complete (as determined by TLC) and column chromatography of the crude material gave bis-piperidine **4a** in good yield, with complete transfer of the stereochemical information from the starting material to the product (determined by ^1H NMR spectroscopy). Given the success of the one-pot reduction/acylation strategy utilized to prepare **17**, we were encouraged to attempt the synthesis of **3** from **4a** without isolating the deprotected amine. Gratifyingly, subjection of compound **4a** to hydrogenation conditions in the presence of catalytic Pd/C until TLC indicated complete consumption of the starting material, followed by removal of the heterogeneous catalyst by filtration, solvent exchange, and addition of potassium carbonate and phenyl-propynoyl chloride, gave amide **3** in 77% yield as a white solid after purification (Scheme 4).

Optimized Synthesis of 2. Although the conversion of **6c** to Cbz-protected **5a** and from there on to **3** was successful, we were dissatisfied with the overall yield (**6c** → **3**) of 35%. We postulated that direct transformation of **6c** to Ns-protected **5b** (Scheme 5) followed by cleavage of the protecting group at a later stage of the synthesis may prove more efficient in terms of yield and atom-economy. The action of diisopropyl azodicarboxylate and triphenylphosphine on diene **6c** in the presence of *N*-allyl-nosylamide (**18**)[13] afforded **5b** in high yield (95%, Scheme 5). Tandem metathesis of **5b**, 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

SCHEME 5. Improved Synthesis of Intermediate 3 and Final Steps to 2[a]



[a] Reagents and conditions: (a) **6c**, **18**, Ph_3P, DIAD, 0 °C to room temperature, 3.5 h (95%). (b) **5b**, (IHMes)$(Cy_3P)Cl_2Ru$=CHPh (1 mol %), CH_2Cl_2, 40 °C, 2 h (82%). (c) **4b**, PhSH, K_2CO_3, DMF, 70 °C, 1 h (80%). (d) (i) **19**, H_2, Pd/C, EtOH, rt, 15 h; (ii) phenyl-propynoyl chloride, K_2CO_3, THF, rt, 2h (79%). (e) (i) **3**, TFA, CH_2Cl_2, 0 °C, 1 h; (ii) Lindlar catalyst, H_2, MeOH, rt, 16 h (85%).

protecting group, which has been found to be problematic in metathesis reactions, previously[7c] 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 cleavage 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*-cinammoyl 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 acetate **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 stereocenter-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 carbocycle **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

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the natural product by using standard functional group manipulations.

Experimental Section

General. Each reaction with air- and moisture-sensitive components was performed under a N_2 atmosphere; metathesis reactions were carried out in a glovebox. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. ^{1}H NMR (500 MHz) and ^{13}C NMR spectra (125.8 MHz) were recorded in the solvent indicated. NMR chemical shifts are expressed 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 unit cell at 589 nm ([c] = g/100 mL). R_f values indicated refer to TLC on 0.2 mm analytical plates coated with silica gel. MTBE = methyl *tert*-butyl ether. Those chemicals which were purchased were used without further purification. Cyclopentadiene monoepoxide (**10**),[11] Ts- and Ns-protected allylamides (**12** and **18**),[12] and tributyl-iodmethyl-stannane[16] were prepared according to the published procedures.

***cis*-*N*-Allyl-*N*-(4-hydroxy-cyclopent-2-enyl)-4-methyl-benzenesulfonamide (13).** To a stirring solution of $Pd_2(dba)_3$·$CHCl_3$ (297 mg, 0.32 mmol, 2 mol %) in THF (10 mL, 0.03 M) was added (diphenylphosphino)ethane (510 mg, 1.28 mmol, 8 mol %). To this reaction mixture was added *N*-allyl-tosylamide **12** (3.38 g, 16.00 mmol, 1.0 equiv) in THF (16 mL, 1 M). The resulting mixture was cooled to 0 °C and treated with *N*,*O*-bis(trimethylsilyl)acetamide (4.87 g, 24.00 mmol, 1.5 equiv). The mixture was allowed to stir for 30 min, after which time cyclopentadiene monoxide **10** (3.93 g, 24.00 mmol, 1.5 equiv) was added dropwise over a period of 6 h. The temperature was kept at 0 °C for an additional hour, after which it was allowed to warm to room temperature and stirred for 14 h. The solvent was removed under reduced pressure. The remaining residue was redissolved in MTBE (50 mL) and hydrolyzed with 4 N aqueous HCl (25 mL) until complete disappearance of the initial reaction product, TMS-protected alcohol, was observed by TLC (R_f 0.9, hexane/ethyl acetate 1:2). The organic phase was separated, and the aqueous phase was extracted with MTBE (2 × 50 mL). The organic phases were combined and dried over $MgSO_4$ and the solvent was removed under reduced pressure. The free alcohol **13** (2.81 g, 60%) was isolated by flash chromatography (hexane/ethyl acetate 2:1) as a pale yellow oil. R_f 0.58 (hexane/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (dt, J = 15, 4 Hz, 1H), 1.88 (d, J = 6 Hz, 1H), 2.54 (dt, J = 15, 8 Hz, 1H), 3.72 (dddd, J = 14, 6, 6, 2 Hz, 2H), 4.64 (m, 1H), 4.84 (m, 1H), 5.13 (dd, J = 10, 1 Hz, 1H), 5.21 (dd, J = 17, 1 Hz, 1H), 5.59 (ddd, J = 6, 2, 1 Hz, 1H), 5.85 (dddd, J = 17, 10, 6, 6 Hz, 1H), 5.92 (ddd, J = 6, 2, 2 Hz, 1H), 7.29 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 21.5 (CH_3), 38.4 (CH_2), 46.7 (CH_2), 62.2 (CH), 74.7 (CH), 117.2 (CH_2), 127.2 (CH), 129.7 (CH), 133.1 (CH), 136.0 (CH), 136.9 (CH), 137.5 (C_q), 143.3 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3511, 2978, 1333, 1157, 1090; LRMS (EI) *m*/*z* (%) 293 ([M^+], 1), 276 (5), 237 (52), 210 (69), 155 (57), 138 (100), 91 (93); HRMS calcd for $C_{15}H_{19}NO_3S$ [M^+] 293.1086, found 293.1088. Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.65; H, 6.18; N 4.78.

***cis*-*N*-Allyl-*N*-(4-chloro-cyclopent-2-enyl)-4-methyl-benzenesulfonamide (7).** To a solution of alcohol **13** (1.32 g, 3.50 mmol) in CH_2Cl_2 (10 mL) was added thionyl chloride (0.57 mL, 7.20 mmol, 1.6 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. R_f 0.73 (hexane/ethyl acetate 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (dt, J = 15, 4 Hz, 1H), 2.43 (s, 3H), 2.78 (dt, J = 15, 8 Hz, 1H), 3.64 (m, 1H), 3.80 (m, 1H), 4.64 (m, 1H), 4.78 (m, 1H), 5.13 (dd, J = 10, 1 Hz, 1H), 5.23 (dd, J = 17, 1 Hz, 1H), 5.66 (m, 1H), 5.86 (dddd, J = 17, 10, 6, 6 Hz, 1H), 5.91 (m, 1H), 7.32 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 21.5 (CH_3), 38.5 (CH_2), 46.3 (CH_2), 61.0 (CH), 62.9 (CH), 117.4 (CH_2), 127.1 (CH), 129.7 (CH), 133.8 (CH), 135.0 (CH), 135.5 (CH), 137.2 (C_q), 143.5 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2924, 1336, 1158, 1091; LRMS (EI) *m*/*z* (%) 311 ([M^+], 12), 276 (100), 155 (16), 91 (37); HRMS calcd for $C_{15}H_{18}ClNO_2S$ [M^+] 311.0747, found 311.0743. Anal. Calcd for $C_{15}H_{18}ClNO_2S$: C, 57.78; H, 5.82; N, 4.47. Found: C, 57.76; H, 5.78; N 4.59.

***trans*-*N*-Allyl-*N*-(2-*tert*-butoxymethyl-cyclopent-3-enyl)-4-methyl-benzenesulfonamide (6a).** To a suspension of KO*t*Bu (256 mg, 2.28 mmol, 4.0 equiv) in MTBE (2.9 mL) was added *t*BuLi (1.7 M/pentane, 1.46 mL, 2.51 mmol, 4.4 equiv) dropwise at −70 °C. The resulting mixture was stirred for several minutes at −70 °C until its color changed to yellow. The reaction was allowed to warm to −20 °C (3 h). Subsequently the solution was cooled to −60 °C and treated with a 0.5 M solution of $ZnCl_2$ in THF (347 mg of $ZnCl_2$/5.1 mL of THF, 2.52 mmol, 4.5 equiv). After being stirred at −60 °C for 2 h, a solution of CuCN (56 mg, 0.62 mmol, 1.1 equiv) and LiCl (60 mg, 1.43 mmol, 2.3 equiv) in THF (2.0 mL) was introduced. Then the mixture was cooled to −75 °C and treated with a solution of chloride **7** (175 mg, 0.56 mmol, 1.0 equiv) in THF (0.5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Saturated aq NH_4Cl (10 mL) was then added, and the resulting mixture was extracted with MTBE (2 × 20 mL). The combined organic phases were dried over $NaSO_4$ and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography (hexane/ethyl acetate 8:1) gave compound **6a** (116 mg, 57%) as a colorless oil. R_f 0.87 (hexane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) 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 (ddd, J = 9, 5, 5 Hz, 1H), 5.07 (br d, J = 10 Hz, 1H), 5.18 (br d, J = 17 Hz), 5.65 (m, 2H), 5.89 (dddd, J = 17, 10, 6, 6 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 21.4 (CH_3), 27.4 (CH_3), 36.6 (CH_2), 46.7 (CH_2), 50.8 (CH), 59.4 (CH), 63.5 (CH_2), 72.7 (C_q), 116.7 (CH_2), 127.4 (CH), 129.5 (CH), 129.8 (CH), 131.8 (CH), 135.8 (CH), 138.0 (C_q), 143.0 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 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 $C_{20}H_{29}NO_3S$ [M^+] 363.1868, found 363.1868.

***trans*-*N*-Allyl-*N*-(2-hydroxymethyl-cyclopent-3-enyl)-4-methyl-benzenesulfonamide (6b).** To a solution of ether **6a** (200 mg, 0.55 mmol) in CH_2Cl_2 (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, then concentrated to dryness; the residue was redissolved in a mixture of MeOH and water (1 mL/2 mL) and treated with KOH (40 mg, 0.95 mmol, 1.7 equiv); and the solution was stirred at room temperature until complete disappearance of the initial reaction product (trifluoroacetic acid ester) was observed by TLC (R_f 0.74, hexane/ethyl acetate 3:1). The reaction mixture was diluted with saturated aqueous NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, and the solvents were removed under reduced pressure. The alcohol **6b** (268 mg, 79%) was obtained by flash chromatography (hexane/ethyl acetate 3:1) as a colorless oil. R_f 0.26 (hexane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (m, 1H), 2.39−2.47 (m, 4H), 3.13 (m, 1H), 3.64 (m, 1H), 3.89 (m, 1H), 4.14 (dd, J = 11, 6 Hz, 1H), 4.39 (ddd, J = 9, 5, 5 Hz, 1H), 4.45 (dd, J = 11, 5 Hz, 1H), 5.12 (br d, J = 10 Hz, 1H), 5.19 (br d, J = 17 Hz), 5.56 (m, 1H), 5.76 (m, 1H), 5.89 (dddd, J = 17, 10, 6, 6 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 21.5 (CH_3), 35.7 (CH_2), 46.7 (CH_2), 49.2 (CH), 59.1 (CH), 68.3 (CH_2), 117.2 (CH_2), 127.2 (CH), 128.8 (CH), 129.7 (CH), 132.0 (CH), 135.5 (CH), 137.5 (C_q), 143.5 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3528, 2924, 1334, 1155, 1091; LRMS (EI) *m*/*z* (%) 307 ([M^+],

<1), 276 (90), 222 (29), 152 (94), 91 (100), 68 (34); HRMS calcd for $C_{16}H_{21}NO_3S$ [M^+] 307.1242, found 307.1247.

Allyl-((1*R*,4*S*)-4-hydroxy-cyclopent-2-enyl)-carbamic Acid *tert*-Butyl Ester (14). To a mixture of acetate **11** (10.00 g, 70.3 mmol) and allylamine (13.20 mL, 175.8 mmol, 2.5 equiv) in THF (280 mL, 0.25 M) was added triethylamine (29.40 mL, 210.9 mmol, 3.0 equiv), and the solution was stirred for 1 h at room temperature. Then $Pd(Ph_3P)_4$ (4.05 g, 3.5 mmol, 5 mol %) was introduced in eight portions over 80 min, and the mixture was stirred for 13 h at room temperature. The solution was concentrated in vacuo, dissolved in methanol (175 mL), and filtered through a small pad of silica. The filtrate was treated with di-*tert*-butyl dicarbonate (16.94 g, 77.4 mmol, 1.1 equiv) and stirred for 14 h at 65 °C. The solvent was removed under reduced pressure, and the alcohol **14** (11.27 g, 67%) was obtained by flash chromatography (hexane/ethyl acetate 2:1) as a colorless oil. R_f 0.57 (hexane/ethyl acetate 1:1). $[\alpha]^{20}_D$ +247° (*c* 0.83, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.63 (m, 1H), 2.48 (br s, 1H), 2.68 (dt, J = 15, 8 Hz, 1H), 3.77 (m, 2H), 4.65 (m, 1H), 5.09−5.15 (m, 2H), 5.43 (m, 1H), 5.77−5.86 (m, 2H), 5.97 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 28.3 (CH_3), 39.0 (CH_2), 48.2 (CH_2), 60.9 (CH), 74.8 (CH), 79.8 (C_q), 115.4 (CH_2), 133.3 (CH), 135.4 (CH), 136.1 (CH), 155.1 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3424, 2976, 1690, 1668, 1404, 1168, 1142; LRMS (EI) *m*/*z* (%) 239 ([M^+], <1), 183 (38), 165 (54), 120 (27), 57 (100); HRMS calcd for $C_{13}H_{21}NO_3$ [M^+] 239.1521, found 239.1522. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 64.89; H, 8.83; N 5.84.

Allyl-((1*R*,4*R*)-4-hydroxy-cyclopent-2-enyl)-carbamic Acid *tert*-Butyl Ester (15). To a solution of alcohol **14** (8.52 g, 35.6 mmol) in THF (225 mL, 0.16 M) was added triphenylphosphine (18.70 g, 71.2 mmol, 2.0 equiv) and benzoic acid (6.53 g, 53.4 mmol, 1.5 equiv). The mixture was cooled to 0 °C and diisopropyl azodicarboxylate (12.8 mL, 60.5 mmol, 1.7 equiv) was introduced dropwise over 1 h. After being stirred for 2 h at room temperature, the solvent was removed in vacuo, and the residue dissolved in ethyl acetate (50 mL). Then the mixture was filtered over a small pad of silica, the filtrate was concentrated under reduced pressure, and the crude benzoate was then hydrolyzed by addition of 40 mL of 5% NaOH/methanol. The reaction mixture was stirred for 2 h at room temperature, then the solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate 2:1−1:1) to give the alcohol **15** (5.62 g, 66%) as a colorless oil. R_f 0.25 (hexane/ethyl acetate 2:1). $[\alpha]^{20}_D$ +157° (*c* 0.84, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 1.45 (s, 9H), 2.06 (m, 2H), 3.56 (m, 2H), 4.95 (m, 1H), 5.03−5.09 (m, 2H), 5.43 (m, 1H), 5.78 (m, 1H), 5.86 (m, 1H), 5.98 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 28.3 (CH_3), 39.0 (CH_2), 45.6 (CH_2), 61.1 (CH), 75.8 (CH), 79.8 (C_q), 115.3 (CH_2), 128.2 (CH), 129.8 (CH), 135.6 (CH), 155.4 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3416, 2976, 1690, 1669, 1403, 1170, 1141; LRMS (EI) *m*/*z* (%) 239 ([M^+], <1), 183 (22), 165 (6), 120 (11), 57 (100); HRMS calcd for $C_{13}H_{21}NO_3$ [M^+] 239.1521, found 239.1520. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.10; H, 8.87; N 5.72.

Allyl-((1*R*,4*R*)-4-tributylstannanylmethoxy-cyclopent-2-enyl)-carbamic Acid *tert*-Butyl Ester (9). To a solution of alcohol **15** (5.0 g, 20.9 mmol) in THF (60 mL, 0.35 M) was added KH (1.94 g, 45.9 mmol, 2.2 equiv) and dibenzo-18-crown-6 (71 mg, 0.2 mmol, 0.5 mol %) at 0 °C. Bu_3SnCH_2I (10.81 g, 25.07 mmol, 1.2 equiv) was added, then the solution was allowed to warm to room temperature and stirred for 3 h. After addition of saturated aqueous NH_4Cl (40 mL) the mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 40:1) provided stannane **9** (10.42 g, 92%) as a colorless oil. R_f 0.62 (hexane/ethyl acetate 4:1). $[\alpha]^{20}_D$ +125° (*c* 0.85, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 0.89 (m, 15H), 1.29 (tq, J = 7, 7 Hz, 6H), 1.45 (s, 9H), 1.49 (m, 6H), 1.85 (m, 1H), 2.13 (m, 1H), 3.48−3.60 (m, 2H), 3.62 (d, J = 10 Hz, 1H), 3.68 (d, J = 10 Hz, 1H), 4.44 (m, 1H), 5.06 (m, 2H), 5.34 (m, 1H), 5.77 (m, 1H), 5.85 (m, 1H), 6.01 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 7.5 (CH_2), 13.6 (CH_3), 27.1 (CH_2), 28.3 (CH_3), 29.0 (CH_2), 35.1 (CH_2), 45.6 (CH_2), 58.7 (CH_2), 61.2 (CH), 79.5 (C_q), 87.0 (CH), 115.1 (CH_2), 134.3 (CH), 135.8 (CH), 155.3 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2926, 1695, 1401, 1172, 1141, 1049; LRMS (EI) *m*/*z* (%) 487 ([$M^+ - C_4H_8$], 21), 291 (71), 177 (44), 57 (100); HRMS calcd for $C_{22}H_{41}NO_3Sn$ [$M^+ - C_4H_8$] 487.2108, found 487.2110. Anal. Calcd for $C_{26}H_{49}NO_3Sn$: C, 57.58; H, 9.11; N, 2.58. Found: C, 57.52; H, 9.04; N 2.50.

Allyl-((1*R*,2*R*)-2-hydroxymethyl-cyclopent-3-enyl)-carbamic Acid *tert*-Butyl Ester (6c). Stannane **9** (10.0 g, 18.40 mmol) was dissolved in THF (260 mL, 0.07 M) and the solution was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 12.65 mL, 20.24 mmol, 1.1 equiv) was added dropwise via the cold wall of the flask. The solution was allowed to warm to room temperature and was stirred for 12 h. The solution was poured onto saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 4:1−2:1) provided alcohol **6c** (3.20 g, 69%) as a colorless oil. R_f 0.53 (hexane/ethyl acetate 1:1). $[\alpha]^{20}_D$ −76° (*c* 0.50, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 1.46 (s, 9H), 2.48 (m, 1H), 2.62 (m, 1H), 2.86 (m, 1H), 3.31 (br s, 1H), 3.45 (m, 1H), 3.53−3.71 (m, 2H), 3.82 (ddt, J = 16, 5, 1 Hz, 1H), 4.52 (m, 1H), 5.07 (br d, J = 10 Hz, 1H), 5.18 (br d, J = 17 Hz, 1H), 5.59 (m, 1H), 5.75 (m, 1H), 5.85 (dddd, J = 17, 10, 6, 6 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 28.4 (CH_3), 35.8 (CH_2), 46.2 (CH_2), 54.7 (CH), 58.4 (CH), 65.0 (CH_2), 80.3 (C_q), 115.4 (CH_2), 130.3 (CH), 130.5 (CH), 135.4 (CH), 155.2 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3438, 2976, 1690, 1669, 1366, 1166, 1140; LRMS (EI) *m*/*z* (%) 197 ([$M^+ - C_4H_8$], 41), 179 (37), 122 (50), 57 (100); HRMS calcd for $C_{10}H_{15}NO_3$ [$M^+ - C_4H_8$] 197.1052, found 197.1055. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.02; H, 9.10; N 5.57.

Allyl-((1*R*,2*S*)-2-azidomethyl-cyclopent-3-enyl)-carbamic Acid *tert*-Butyl Ester (28). To a solution of alcohol **6c** (280 mg, 1.11 mmol) and triethylamine (0.45 mL, 6.60 mmol, 6 equiv) in CH_2Cl_2 (10 mL, 0.1 M) at 0 °C was slowly added methanesulfonyl chloride (0.16 mL, 2.20 mmol, 2 equiv). After being stirred for 10 min, the mixture was diluted with water (5 mL) and the layers were separated. The organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude mesylate (368 mg, 100%). The product was used in the next step without further purification. To a solution of the mesylate in DMF (4 mL, 0.3 M) was added, in one portion, NaN_3 (430 mg, 6.6 mmol, 6 equiv). The resulting mixture was stirred at 60 °C for 14 h and then diluted with water (4 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 10 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 6:1) gave azide **16** (253 mg, 82%) as a colorless oil. R_f 0.84 (hexane/ethyl acetate 3:1). $[\alpha]^{20}_D$ −104° (*c* 0.74, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 1.45 (s, 9H), 2.45 (m, 1H), 2.61 (m, 1H), 2.96 (m, 1H), 3.30 (m, 1H), 3.42 (m, 1H), 3.68−3.87 (m, 2H), 4.09−4.46 (m, 1H), 5.05−5.14 (m, 2H), 5.61 (m, 1H), 5.74−5.87 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 28.3 (CH_3), 36.3 (CH_2), 47.5 (CH_2), 49.7 (CH), 54.4 (CH_2), 59.0 (CH), 79.8 (C_q), 115.6 (CH_2), 130.4 (CH), 131.2 (CH), 135.3 (CH), 155.2 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2977, 2097, 1690, 1691, 1366, 1165; LRMS (EI) *m*/*z* (%) 278 ([M^+], < 1), 179 (35), 136 (73), 57 (100); HRMS calcd for $C_{14}H_{22}N_4O_2$ [M^+] 278.1743, found 278.1752. Anal. Calcd for $C_{14}H_{22}N_4O_2$: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.15; H, 7.89; N, 20.20.

Allyl-[(1*R*,2*S*)-2-(benzyloxycarbonylamino-methyl)-cyclopent-3-enyl]-carbamic Acid *tert*-Butyl Ester (17). To a solution of azide **16** (160 mg, 0.57 mmol) in THF (8 mL, 0.07

M) was added triphenylphosphine (181 mg, 0.68 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 K_2CO_3 (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 Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 7:1) gave dicarbamate **17** (176 mg, 80%) as a colorless oil. R_f 0.53 (hexane/ethyl acetate 3:1). $[\alpha]^{20}_D$ −63° (*c* 0.51, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 1.43 (s, 9H), 2.42 (m, 1H), 2.57 (m, 1H), 2.73−2.98 (m, 2H), 3.47−3.79 (m, 3H), 4.55 (m, 1H), 5.03−5.15 (m, 4H), 5.57 (m, 1H), 5.71−5.83 (m, 2H), 7.27−7.39 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 28.2 (CH_3), 35.8 (CH_2), 44.0 (CH_2), 46.2 (CH_2), 49.9 (CH), 58.9 (CH), 66.2 (CH_2), 80.0 (C_q), 115.3 (CH_2), 127.8 (CH), 128.2 (CH), 128.3 (CH), 130.5 (CH), 130.9 (CH), 135.3 (CH), 136.7 (C_q), 155.9 (C_q), 156.5 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3336, 2976, 2129, 1723, 1691, 1366, 1249, 1165; LRMS (EI) *m*/*z* (%) 368 ([M$^+$], < 1), 229 (22), 122 (64), 91 (100), 57 (62); HRMS calcd for $C_{22}H_{30}N_2O_4$ [M$^+$] 386.2206, found 386.2210. Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.87; N 7.24.

Allyl-{(1*R*,2*S*)-2-[allyl-(benzyloxycarbonylamino)-methyl]-cyclopent-3-enyl}-carbamic Acid *tert*-Butyl 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 H_2 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 × 10 mL), and the combined extracts were washed with brine (5 mL) and dried over Na_2SO_4. Removal of the solvents left an oil that was purified by flash chromatography (hexane/ethyl acetate 6:1), affording triene **5a** (92 mg, 86%) as a colorless oil. R_f 0.80 (hexane/ethyl acetate 3:1). $[\alpha]^{20}_D$ −55° (*c* 0.85, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 1.43 (s, 9H), 2.36 (m, 1H), 2.58 (m, 1H), 3.00−3.40 (m, 3H), 3.53−4.04 (m, 4H), 4.42 (m, 1H), 4.98−5.18 (m, 6H), 5.60 (m, 1H), 5.65−5.86 (m, 3H), 7.25−7.37 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 28.2 (CH_3), 36.5 (CH_2), 48.7 (CH), 50.1 (CH_2), 50.3 (CH_2), 50.6 (CH_2), 59.3 (CH), 67.1 (CH_2), 79.7 (C_q), 115.2 (CH_2), 116.5 (CH_2), [127.7, 127.8] (CH), 128.3 (CH), 129.9 (CH), 131.4 (CH), 133.3 (CH), 133.6 (CH), 135.4 (CH), 136.6 (C_q), 155.2 (C_q), 156.0 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2976, 1692, 1365, 1238, 1165, 916; LRMS (EI) *m*/*z* (%) 426 ([M$^+$], < 1), 269 (25), 160 (37), 122 (54), 91 (100), 57 (53); HRMS calcd for $C_{25}H_{34}N_2O_4$ [M$^+$] 426.2519, found 426.2521. Anal. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.27; H, 7.96; N 6.45.

(2*R*,3′*S*)-3,6,3′,6′-Tetrahydro-2*H*,2′*H*-[2,3′]bipyridinyl-1,1′-dicarboxylic Acid 1′-Benzyl Ester 1-*tert*-Butyl Ester (4a). Triene **5a** (167 mg, 0.39 mmol) and (IHMes)(Cy_3P)Cl_2-Ru=CHPh (4 mg, 1 mol %) were heated at reflux temperature in dry CH_2Cl_2 (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 bipiperidine **4a** (124 mg, 80%) as a colorless semisolid. R_f 0.62 (hexane/ethyl acetate 3:1). $[\alpha]^{20}_D$ +56° (*c* 0.63, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture) δ 1.44 (s, 9H), 2.18 (m, 1H), 2.34 (m, 1H), 2.55 (m, 1H), 2.85−3.53 (m, 2H), 3.52−4.42 (m, 5H), 5.03−5.30 (m, 2H), 5.55−5.84 (m, 4H), 7.27−7.37 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 25.6 (CH_2), 28.4 (CH_3), 35.4 (CH), 39.6 (CH_2), 43.6 (CH_2), 43.9 (CH_2), 49.2 (CH), 67.0 (CH_2), 79.8 (C_q), 122.5 (CH), 124.0 (CH), 125.0 (CH), 125.7 (CH), 126.9 (CH), [127.8, 127.9] (CH), 128.4 (CH), 136.7 (C_q), 154.8 (C_q), 155.4 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2957, 1691, 1410, 1232, 1168, 1111; LRMS (EI) *m*/*z* (%) 398 ([M$^+$], < 1), 298 (1), 182 (34), 126 (100), 91 (83), 57 (39); HRMS calcd for $C_{23}H_{30}N_2O_4$ [M$^+$] 398.2207, found 398.2216. Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.18; H, 7.47; N 7.30.

(2*R*,3′*S*)-1′-(3-Phenyl-prop-2-ynoyl)-[2,3′]bipiperidinyl-1-carboxylic Acid *tert*-Butyl Ester (3). A solution of bipiperidine **4a** (55 mg, 0.138 mmol) in ethanol (1.4 mL, 0.1 M) containing palladium on charcoal (14 mg, 10 mol %) was hydrogenated at room temperature for 14 h. The catalyst was removed by filtration over Celite and the solution concentrated in vacuo to give the crude amine as a colorless oil. This was redissolved in THF (0.7 mL, 0.2 M) and treated with potassium carbonate (57 mg, 0.414 mmol, 3.0 equiv) and phenyl-propynoyl chloride (27 mg, 0.166 mmol, 1.2 equiv), and the solution was stirred for 1 h at room temperature. Then the mixture was diluted with water (1 mL) and allowed to stir for 1 h. Ethyl acetate (5 mL) was added, the layers were separated and the organic layer was washed with saturated aqueous potassium carbonate (3 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 3:1) gave **3** (41 mg, 77%) as a white solid. R_f 0.37 (hexane/ethyl acetate 3:1). Mp 50−51 °C; $[\alpha]^{20}_D$ +124° (*c* 0.79, EtOH); ^{1}H NMR (500 MHz, $(CD_3)_2$-SO, 100 °C, not fully coalesced) δ 1.19−1.60 (m, 16H), 1.71−2.07 (m, 4H), 2.52−2.91 (m, 3H), 3.91 (m, 2H), 4.26 (m, 2H), 7.37−7.57 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 19.0 (CH_2), 19.1 (CH_2), 25.2 (CH_2), 28.4 (CH_3), 28.7 (CH_2), 29.0 (CH_2), 34.0 (CH), 35.5 (CH), 42.0 (CH_2), 47.8 (CH_2), 50.3 (CH_2), 79.5 (C_q), 81.5 (C_q), 90.1 (C_q), 120.7 (C_q), [128.4/128.5] (CH), [129.8/130.0] (CH), 132.3 (CH), 152.8 (C_q), 155.0 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2933, 2212, 1684, 1630, 1416, 1168; LRMS (EI) *m*/*z* (%) 396 ([M$^+$], < 1), 295 (15), 212 (100), 129 (52), 84 (80), 57 (26); HRMS calcd for $C_{24}H_{32}N_2O_3$ [M$^+$] 396.2413, found 396.2411. Anal. Calcd for $C_{24}H_{32}N_2O_3$: C, 72.70; H, 8.13; N, 7.06. Found: C, 72.62; H, 8.23; N 7.15.

Allyl-((1*R*,2*S*)-2-{[allyl-(4-nitro-benzenesulfonyl)-amino]-methyl}-cyclopent-3-enyl)-carbamic Acid *tert*-Butyl Ester (5b). To a solution of alcohol **6c** (3.00 g, 11.8 mmol) in THF (80 mL, 0.15 M) was added triphenylphosphine (7.77 g, 29.6 mmol, 2.5 equiv) and *N*-allyl-*p*-nosylamide **18** (3.72 g, 15.4 mmol, 1.3 equiv). The mixture was cooled to 0 °C and diisopropyl azodicarboxylate (4.80 mL, 23.7 mmol, 2.0 equiv) was introduced dropwise over 30 min. After the solution was stirred for 3 h at room temperature, the solvent was removed in vacuo, and the residue was purified by flash chromatography (hexane/ethyl acetate 6:1) to provide triene **5b** (5.37 g, 95%) as a colorless oil. R_f 0.67 (hexane/ethyl acetate 3:1). $[\alpha]^{20}_D$ −99° (*c* 0.53, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.43 (br dd, *J* = 17, 5 Hz, 1H), 2.62 (m, 1H), 3.07−3.26 (m, 3H), 3.66−3.95 (m, 4H), 4.30 (m, 1H), 5.07−5.18 (m, 4H), 5.50 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.65 (m, 1H), 5.75 (m, 1H), 5.82 (dddd, *J* = 17, 11, 6 Hz, 6 Hz, 1H), 7.98 (d, *J* = 8 Hz, 2H), 8.35 (d, *J* = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 28.3 (CH_3), 36.3 (CH_2), 47.7 (CH_2), 48.4 (CH), 50.3 (CH_2), 59.4 (CH), 79.8 (C_q), 115.7 (CH_2), 119.9 (CH_2), 124.3 (CH), 128.4 (CH), 130.8 (CH), 131.8 (CH), 135.3 (CH), 145.7 (C_q), 149.9 (C_q), 155.2 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 2977, 1686, 1531, 1350, 1164, 931, 774; LRMS (EI) *m*/*z* (%) 376 ([M − $C_5H_9O_2$]$^+$, 5), 268 (4), 182 (16), 126 (100), 82 (85), 57 (80); HRMS calcd for $C_{18}H_{22}N_3O_4S$ [M − $C_5H_9O_2$]$^+$ 376.1331, found 376.1337. Anal. Calcd for $C_{23}H_{31}N_3O_6S$: C, 57.84; H, 6.54; N, 8.80. Found: C, 57.69; H, 6.52; N 8.86.

(2*R*,3′*S*)-1′-(4-Nitro-benzenesulfonyl)-3,6,1′,2′,3′,6′-hexahydro-2*H*-[2,3′]bipyridinyl-1-carboxylic Acid *tert*-Butyl Ester (4b). Triene **5b** (5.00 g, 10.47 mmol) and (IHMes)-(Cy_3P)Cl_2Ru=CHPh (89 mg, 1 mol %) were heated at reflux temperature in dry CH_2Cl_2 (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 bipiperidine **4b** (3.86 g, 82%) as a white solid. R_f 0.47 (hexane/ethyl acetate 3:1). Mp 158−159 °C; $[\alpha]^{20}_D$ +67° (*c* 0.18, EtOH); ^{1}H NMR (500 MHz, $(CD_3)_2$SO, 100 °C, not fully coalesced) δ 1.44 (s, 9H), 2.18 (m, 1H), 2.27 (m, 1H), 2.49 (m,

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 (dddd, J = 17, 2, 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); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C [25.6/25.8] (CH_2), 28.3 (CH_3), [35.1/35.8] (CH), [39.6/40.8] (CH_2), 44.8 (CH_2), 45.4 (CH_2), [49.1/50.6] (CH), 80.0 (C_q), 122.4 (CH), 123.4 (CH), 124.2 (CH), 127.0 (CH), 128.7 (CH), 142.4 (C_q), 150.1 (C_q), 154.8 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 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 $C_{21}H_{27}N_3O_6S$ [M$^+$] 449.1621, found 449.1616. Anal. Calcd for $C_{21}H_{27}N_3O_6S$: C, 56.11; H, 6.05; N, 9.35. Found: C, 55.92; H, 6.12; N 9.30.

(2*R*,3′*S*)-3,6,1′,2′,3′,6′-Hexahydro-2*H*-[2,3′]bipyridinyl-1-carboxylic Acid *tert*-Butyl Ester (19). Bipiperidine **4b** (1.50 g, 3.34 mmol) and K_2CO_3 (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 $NaSO_4$, and concentrated in vacuo. Purification of the residue by filtration over silica (CH_2Cl_2/methanol 1:0−1:1) furnished amine **19** (703 mg, 80%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C 25.6 (CH_2), 28.3 (CH_3), 33.6 (CH), [39.7/40.7] (CH_2), [44.1/44.2] (CH_2), 44.6 (CH_2), [49.4/50.9] (CH), 79.9 (C_q), [122.4/122.7] (CH), [123.2/123.9] (CH), 127.1 (CH), [127.8/128.3] (CH), 155.5 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3335, 2974, 1689, 1409, 1172, 1110; LRMS (EI) m/z (%) 264 ([M$^+$], 3), 126 (59), 82 (100), 57 (69); HRMS calcd for $C_{15}H_{24}N_2O_2$ [M$^+$] 264.1838, found 264.1833.

(2*R*,3′*S*)-1′-(3-Phenyl-prop-2-ynoyl)-[2,3′]bipiperidinyl-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 phenylpropynoyl 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 Na_2SO_4, 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-(2*R*,3′*S*)-[2,3′]Bipiperidinyl-1′-yl-3-phenyl-propenone [(+)-Astrophylline] (2).** Compound **3** (150 mg, 0.39 mmol) was dissolved in CH_2Cl_2 (1.5 mL, 0.26 M), the solution was cooled to 0 °C, and trifluoroacetic acid (0.6 mL, 4 mL/g) 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/$BaSO_4$ (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 CH_2Cl_2 (3 mL) and treated with aq potassium hydroxide solution (10%, 3 mL) for 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were concentrated in vacuo and the residue was purified by flash chromatography (MTBE/5% Et_2N) yielding astrophylline **2** (99 mg, 85%) as a viscous oil. R_f 0.59 (MTBE/5% Et_2N). $[\alpha]^{20}_D$ +27° (*c* 0.35, EtOH) (lit. $[\alpha]^{20}_D$ +23° (*c* unspecified, EtOH)); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 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); ^{13}C NMR (125.8 MHz, $CDCl_3$, rotameric mixture) δ_C [24.6/24.9] (CH_2), 26.4 (CH_2), [26.9/27.1] (CH_2), 27.7 (CH_2), [29.7/30.1] (CH_2), [40.9/42.2] (CH), [42.0/44.1] (CH_2), 47.3 (CH_2), 49.8 (CH_2), [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] (C_q), 167.4 (C_q); IR (neat, cm^{-1}) $\tilde{\nu}$ 3315, 2928, 1634, 1614, 1557, 1439, 1260; LRMS (EI) m/z (%) 298 ([M$^+$], 12), 214 (9), 131 (21), 103 (15), 84 (100); HRMS calcd for $C_{19}H_{26}N_2O$ [M$^+$] 298.2045, found 298.2043. Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.55; H, 8.87; N 9.42.

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