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A Diastereoselective Intramolecular Pauson-Khand Approach to the Construction of the BC Ring System in Tuberostemoninol

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Abstract

Herein we describe an asymmetric approach to the synthesis of a BC-ring synthon in tuberostemoninol *via* an intramolecular Pauson-Khand reaction stereocontrolled by a commercially available chiral glycinate.

Keywords

Stemona alkaloids; chiral glycinate; intramolecular Pauson-Khand reaction

1. Introduction

Stemona alkaloids represent a unique class of natural products detected to date only from the monocotyledonous family *Stemonaceae*.¹ Their intricate polycyclic structures and a broad range of biological activities have been inspiring extensive phytochemical and biological studies² as well as synthetic studies³ during the past two decades. Some representative examples of *stemona* alkaloids include stenine (**1**), tuberostemonine (**2**), croomine (**3**), stemoamide (**4**), and stemofoline (**5**) (Figure 1), characterized as having a [1,2-*a*]azepine nucleus. Tuberostemoninol (**6**), lacking this [1,2-*a*]azepine nucleus, but possessing a azabicyclo[4.3.1]decan-10-one nucleus instead, was first isolated from a Chinese medicinal herb *S. tubersa* Lour as a minor component in 1994 by Lin and coworkers.⁴ It is thought that tuberostemoninol is biogenetically related to tuberostemonine (**2**),^{3e} a major component isolated from *S. tuberosa* Lour. The other two *Stemona* alkaloids structurally close to tuberostemoninol are neotuberostemoninol (**7**), isolated from *S. tuberosa* Lour in 2002,⁵ and maireistemoninol (**8**), isolated from species *S. mairei* in 2007.⁶

Published synthetic strategies and methodologies for *Stemona* alkaloids like stenine and tuberostemonine, have included an early stage construction of the highly functionalized cyclohexane ring, the bicyclic hydroindole ring, or the tricyclic core via stereoselective Diels-Alder reactions in Hart's,^{3a} Morimoto's^{3b} and Padwa's^{3c} syntheses of stenine, a tandem Diels-Alder/Azido-Schmit reaction in Aube's synthesis of stenine,^{3d} and a diastereoselective spirocyclization of a L-tyrosine derivative in Wipf's synthesis of tuberostemonine.^{3e} Herein, we would like to present a new approach to the construction of the functionalized cyclopenta [*c*]pyridine bicycle (BC ring) as part of our studies toward the total synthesis of tuberostemoninol (**6**).

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2. Results and discussion

Our synthetic strategy is outlined in Scheme 1 where, tricycle **10** or amino acid derivative **9** could serve as a scaffold for the construction of the tricyclic core. This flexible strategy allows for introduction of the stereogenic centers in the target natural product **6** as well as embracing neotuberostemoninol (**7**) and maireistemoninol (**8**) (Figure 1). We envisioned an intramolecular Pauson-Khand reaction (IMPK)⁷ of a chiral glycinate derivative, the 1,7-enyne **12** to construct the tricycle **10** with the illustrated *trans* stereochemical outcome between R₂ and H group, presumably through the more stable chair-like transition state of the coordinated complex **11** (Scheme 1). The chiral glycine template can be readily cleaved by hydrogenolysis.⁸

2.1. Preparation of IMPK precursors and studies of IMPK reactions

Preparation of the IMPK precursors **12** started with the commercially available optically pure glycinate **13**. Enolate monoalkylation of **13** in tetrahydrofuran (THF) with propargyl bromide (80% wt/v in toluene) in the presence of sodium bis(trimethylsilyl) amide (NaHMDS) (1.0 M solution in THF)⁹ gave compound **14**. Deprotection of the *tert*-butyl carbonate group with hydrochloric acid (4.0 M solution in dioxane) in dichloromethane followed by basic workup gave the free secondary amine **15** in 65% yield. Alkylation of amine **15** delivered 1,7-enyne **12** (Scheme 2).

A screening of *N*-alkylation reactions with various allylic side chains was conducted (Table 1). It was found that the highly reactive methyl 2-(bromomethyl)acrylate (entry 5), acryloyl chloride (entry 6) and allylic acetate (entry 1)¹⁰ gave the best results under the illustrated conditions. However, allylic bromides in entries 2, 3 and 4 gave very poor yields (10–16% as the best results) with mostly starting material recovered under concentrated conditions (1M) in *N,N*-dimethylformamide (DMF) or acetonitrile in the presence of alkali metal (Na, K, Cs) carbonates. We also found that raising the reaction temperature to 60–65°C and addition of tetrabutylammonium iodide (TBAI) catalyst did not improve the yields for entries 2, 3 and 4 but instead, we recovered mostly starting material with apparent epimerization at the α -position.

Treatment of precursors **12a–d** with dicobaltoctacarbonyl (Co₂(CO)₈) in dichloromethane followed by addition of *N*-methyl morpholine *N*-oxide (NMO) to initiate the cyclization at 0°C to room temperature (condition A) provided the corresponding cyclopentenone products **10a–d** in 65% to fair yields. The newly generated stereochemistry as proposed was supported by nOe analysis of one of the IMPK cycloadduct **10a**.¹³ Surprisingly, substrate **12f** provided the desired product **10f** under thermal condition B (Co₂(CO)₈, MeCN, reflux).¹⁴ However, either thermal (condition B) or Lewis base (NMO (condition A), DMSO (condition C), *n*BuSMe (condition D), Me₂S (condition E)) at a temperature range of 35–75°C in acetonitrile or toluene failed to convert **12e** to the desired cycloadduct **10e**. With the exception of the cobalt-alkyne complex formed during the first stage of the reaction (as monitored by TLC), there was no evidence for other discreet intermediates formed in the reaction.¹⁵ Considering the successful (with a significant low yield though) reactions of the electron-deficient species **12f** as well as the precursors with relatively hindered geminal alkenes **12b–d**, it could be that the more electron-deficient nature of **12e** adversely affected conversion to **10e**.

2.2. Modification of IMPK reactions

Modification of the electronic properties of compound **12e** was easily achieved by diisobutylaluminum hydride (DIBAL-H) reduction of the ester group followed by acetylation of the resulting lactol alcohol **16** providing diacetate compound **17**. To our delight, when precursor **17** was subjected to IMPK conditions, a single diastereomer **18** was obtained in 45–

50% yield under the *N*-methyl morpholine *N*-oxide promoted conditions, and the yield was improved to above 80% under dimethyl sulfoxide (toluene, reflux, 3–5 h) or *n*-butyl methyl sulfide (1,2-dichloroethane, 82°C, 2–3 h) promoted thermal conditions (Scheme 3). In a similar manner, cyclopentenone **20** was also obtained from precursor **19** prepared by respective protection of diol **16** with thiopyridyl (SPy)¹⁶ and *tert*-butyl dimethyl silyl (TBS) groups. The proposed stereochemistry of the IMPK products **18** and **20** shown in Scheme 3, was confirmed by single crystal X-ray diffraction of diacetate cyclopentenone **18** (Figure 2).¹⁷

3. Conclusion

In conclusion, a diastereoselective intramolecular Pauson-Khand reaction was developed using a commercially available glycinate as the stereochemical-determining element for an efficient construction of the BC ring system containing a quaternary carbon center present in tuberostemoninol. The IMPK methodology deployed herein, should be quite useful in the preparation of cyclopenta[*c*]pyridine containing amino acid derivatives and natural products. In our laboratory, elaboration of these intermediates toward an asymmetric total synthesis of tuberostemoninol is currently under way and will be reported on in due course.

4. Experimental

4.1. General

All chemicals from commercial sources were used without further purification. Both glycinate **13** (2*R*, 3*S*)-*tert*-butyl 6-oxo-2,3-diphenylmorpholine-4-carboxylate and its enantiomer were used in reactions. All dry reactions were carried out using standard syringe-septum technique. Analytical and preparation TLC used Merck silica gel 60 F254 plates, and flash chromatography was performed on Merck silica gel Kiesegel 60 (230–400 mesh). Nuclear magnetic resonance spectra ¹HNMR (300 MHz and 400 MHz), ¹³CNMR (75 MHz and 100 MHz) were recorded on Varian Inova spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ¹H) or the central line (77.23 ppm) of CDCl₃ (for ¹³C). High-resolution mass spectra were recorded on a Fisons VG Autospec or Finnigan LCQ-DUO with HP1100 Series HPLC. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 series. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter.

4.1.1. (3*R*,5*R*,6*S*)-*tert*-butyl 2-oxo-5,6-diphenyl-3-(prop-2-ynyl) morpholine-4-carboxylate (14**)**—To –78°C cooled solution of the oxazinone **13** (10.0 g, 28.30 mmol) in THF (180 ml) was added sodium bis(trimethylsilyl) amide (31.12 ml, 1.0 M solution in THF) dropwise via syringe during a period of 15 min. The resulting mixture was stirred for an additional 1 h at –78°C. Propargyl bromide (4.1 ml, 36.78 mmol, 80% w/v in toluene) was added dropwise via syringe to the above mixture, stirred for 2.5 h under –78°C. The reaction was then carefully quenched with ammonium chloride saturated aqueous solution and diluted with ethyl acetate. Remove cold and let it warm up to above 0°C. The reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate for 3 times, the combined organic layer was washed with ammonium chloride saturated aqueous and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was subjected to flash column chromatography (Hexanes/EtOAc, 8:1) to afford 9.2 g (83%) of compound **14** as white powder. $[\alpha]_D^{25} = -30.9$ (*c*1, CH₂Cl₂). IR (NaCl thin film): 3492.85 cm⁻¹, 3281.11 cm⁻¹, 2255.68 cm⁻¹, 1747.67 cm⁻¹, 1700.51 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ 7.25–6.56 (m, 10H), 6.47 (d, *J*=2.8Hz, 1H), 5.16 (t, *J*=4.8Hz, 1H), 5.05 (d, *J*=3.2Hz, 1H), 3.32 (ddd, *J*=2.4Hz, 5.2Hz, 17.2Hz, 1H), 3.07 (td, *J*=3.2Hz, 17.2Hz, 1H), 2.22 (t, *J*=2.4Hz, 1H), 1.13 (s, 9H). ¹³CNMR (CDCl₃, 100 MHz): δ 168.90, 153.95, 136.53, 134.57, 128.61, 128.19, 127.87, 127.75, 127.56, 126.54, 81.69, 79.97, 79.41, 72.69, 60.73, 55.80, 27.91, 23.80. FAB-HRMS: calcd for C₂₄H₂₅NO₄ [MH⁺] 392.1863, found 392.1825.

4.1.2. (3R,5R,6S)-5,6-diphenyl-3-(prop-2-ynyl) morpholine-2-one (15)—To an ice cooled solution of compound **14** (9.7 g, 24.78 mmol) in dichloromethane (62 ml) was added hydrochloric acid (75.4 ml, 4.0 M solution in dioxane) during a 10 min period. Remove cooling bath, the reaction was stirred for 3 to 5 h or until the disappearance of starting material monitored by TLC. Solvent was removed under reduced pressure. Diethyl ether was added to precipitate the hydrochloride salt, poured out the solvent. The white solid was rinsed with diethyl ether and dried to provide 6.0 g white milky powder, which was redissolved in dichloromethane (70 ml). Saturated sodium bicarbonate (0.95 ml) was added followed by slowly addition of solid sodium bicarbonate (1.54 g). The resulting suspension was stirred at room temperature for 3 h. Anhydrous magnesium sulfate was added and stirred for an additional 1 h, filtered and concentrated. Flash chromatography (hexanes/EtOAc, 3:1 to 2:1 to 1:1) provided 4.71 g (65%) of compound **15** as light white solid. $[\alpha]_D^{25} = -117.3$ (c1, CH₂Cl₂). IR (NaCl thin film): 3326.53 cm⁻¹, 3287.77 cm⁻¹, 1732.27 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ 7.27–7.17 (m, 6H), 7.03–7.01 (m, 2H), 6.95 (d, J=8.0Hz, 2H), 5.73 (d, J=3.6Hz, 1H), 4.82 (d, J=3.6Hz, 1H), 4.21 (d, J=3.6Hz, 1H), 3.04 (dddd, J=0.8Hz, 2.4Hz, 8.8Hz, 16.8Hz, 1H), 2.91 (dddd, J=1.2Hz, 2.8Hz, 3.6Hz, 16.8Hz, 1H), 2.37 (br s, 1H), 2.11 (ddd, J=1.2Hz, 2.8Hz, 3.6Hz, 1H). ¹³CNMR (CDCl₃, 100 MHz): δ 169.49, 136.89, 134.93, 128.57, 128.32, 128.27, 127.86, 127.83, 127.21, 85.49, 80.12, 72.15, 57.09, 55.38, 24.03. FAB-HRMS: calcd for C₁₉H₁₇NO₂ [MH⁺] 292.1338, found 292.1337.

4.1.3. (3S,5S,6R)-4-allyl-5,6-diphenyl-3-(prop-2-ynyl) morpholine-2-one (12a)—A mixture of Pd₂(dba)₃ (8 mg), PPh₃ (27 mg), K₂CO₃ (28 mg) in anhydrous THF (2 ml) was stirred under argon, secondary amine **15** (30 mg, 0.103 mmol) was added followed by allyl acetate (13.3 μl, 0.1236 mmol), the resulting mixture was stirred at room temperature for 1 day during which more allyl acetate was added. The reaction was filtered through a pad of celite, concentrated. The residue was subjected to flash chromatography (3:1 Hexane/EtOAc) to give the desired product **12a** in decent yield. ¹HNMR (CDCl₃, 300 MHz): δ 7.20–7.12 (m, 6H), 7.05–7.02 (m, 2H), 6.79–6.76 (m, 2H), 6.21–6.20 (d, J=3.0Hz, 1H), 5.90–5.76 (ddd, J=4.8Hz, 7.8Hz, 10.2Hz, 1H), 5.18–5.17 and 5.09–5.07 (app d, J=27.6Hz, 1H), 5.14 (br., 1H), 4.30–4.29 (d, J=3.0Hz, 1H), 4.06–4.03 (t, J=4.2Hz, 1H), 3.30–3.23 (dddd, J=14.4Hz, 1.8Hz, 1.8Hz, 5.1Hz, 1H), 3.17–3.10 (app dd, J=14.4Hz, 7.8Hz, 1H), 3.03–2.95 (ddd, J=16.8Hz, 2.7Hz, 3.6Hz, 1H), 2.85–2.77 (dd, J=16.8Hz, 2.4Hz, 4.5Hz, 1H), 2.16–2.15 (t, J=2.55Hz, 1H). FAB-MS: calcd for C₂₂H₂₁NO₂ [MH⁺] 331.2, found 332.2 (low resolution MS).

4.1.4. General procedure for 12b, 12c, 12d, 12e preparation—To 0°C cooled solution of the amine **15** in DMF (1M) was added potassium carbonate (1.2 equiv) as solid followed by dropwise addition of allylic bromide (1.5 or more equiv). The resulting mixture was stirred at room temperature for 12 h to 2 days. Reaction mixture was filtered out the solid, the filtrate was partitioned between ammonium chloride saturated aqueous and ethyl acetate, separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over MgSO₄, filtered and concentrated. Flash chromatography gave products **12b**, **12c**, **12d**, and **12e** respectively.

4.1.4.1. (3S,5S,6R)-4-(2-methylallyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (12b): ¹HNMR (CDCl₃, 300 MHz): δ 7.20–7.10 (m, 6H), 7.05–7.00 (m, 2H), 6.78–6.74 (m, 2H), 6.20 (d, J=3.0Hz, 1H), 4.90 (br s, 1H), 4.81 (br s, 1H), 4.16 (d, J=3.0Hz, 1H), 3.79–3.78 (d, J=4.2Hz, 1H), 3.08–3.05 (d, J=17.2Hz, 1H), 2.96–2.90 (dd, J=4.8Hz, 18.0Hz, 1H), 2.78–2.70 (ddd, J=4.4Hz, 9.6Hz, 18.4Hz, 1H), 2.51–2.44 (d, J=24.8Hz, 1H), 2.42–2.34 (app t, J=14.8Hz, 1H), 1.93–1.86 (d, J=24.8Hz, 1H), 1.83–1.79 (d, J=17.2Hz, 1H), 1.01 (s, 9H), 0.29–0.21 (d, J=29.2Hz, 6H).

4.1.4.2. (3S,5S,6R)-4-(2-((*tert*-butyldimethylsilyloxy)methyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (12c): ¹HNMR (CDCl₃, 300 MHz): δ 7.20–7.12 (m, 6H), 7.02–6.99 (m, 2H), 6.78–6.74 (m, 2H), 6.18–6.17 (d, J=3.0Hz, 1H), 5.21 (br, 1H), 4.91 (br, 1H), 4.20–4.19 (d, J=3.0Hz, 1H), 4.03 (app t, J=3.9Hz, 1H), 3.04 (s, 2H), 3.02–2.95 (m, 1H), 2.84–2.75 (ddd, J=2.7Hz, 4.5Hz, 16.8Hz, 1H), 2.13 (t, J=2.7Hz, 1H). 1.85 (s, 3H).

4.1.4.3. (3R,5R,6S)-4-(6-(*tert*-butyldimethylsilyloxy)-2-methylenehexyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (12d): ¹HNMR (CDCl₃, 300 MHz): δ 7.25–7.21 (m, 6H), 7.12–7.08 (m, 4H), 5.03 (d, J=1.8Hz, 1H), 4.86–4.83 (t, J=2.3Hz, 1H), 4.78–4.77 (d, J=1.5Hz, 1H), 4.05–3.97 (comp m, 4H), 3.40–3.36 (t, J=3.9Hz, 1H), 3.20–3.19 (d, J=4.2Hz, 1H), 2.57–2.52 (ddd, J=2.7Hz, 5.4Hz, 11.1Hz, 1H), 2.01–1.96 (m, 2H), 1.61–1.52 (m, 4H), 1.48–1.40 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). FAB-HRMS: calcd for C₃₂H₄₃NO₃ [MH]⁺ 518.3012, found 518.3103.

4.1.4.4. methyl 2-(((3R,5R,6S)-2-oxo-5,6-diphenyl-3-(prop-2-ynyl)morpholino)methyl)acrylate (12e): To 0°C cooled solution of the amine **15** (6.735 g, 23.12 mmol) in DMF (23 ml) was added potassium carbonate solid (4.7 g, 34.68 mmol) followed by dropwise addition of methyl 2-(bromomethyl)acrylate (4.48 g, 24.27 mmol). The resulting mixture was stirred at room temperature for 24 h. Reaction was filtered out the solid, the filtrate was portioned between ammonium chloride saturated and ethyl acetate, separated. The aqueous layer was extracted with ethyl acetate for 3 times. The combined organic layer was washed with water for 3 times, then washed with brine, dried over Magnesium sulfate anhydrous, filtered and concentrated. Flash chromatography (Hexanes/EtOAc, 8:1) gave 8.82 g (98%) product **12e** as light yellow sticky solid. [α]_D²⁵ = –41.3 (c1, CH₂Cl₂). IR (NaCl thin film): 3293.66 cm^{–1}, 3061.76 cm^{–1}, 3031.07 cm^{–1}, 2950.84 cm^{–1}, 2922.65 cm^{–1}, 2849.68 cm^{–1}, 1742.83 cm^{–1}, 1635.77 cm^{–1}, 1603.27 cm^{–1}. ¹HNMR (CDCl₃, 400 MHz): δ 7.23–7.14 (m, 6H), 7.01–6.99 (m, 2H), 6.73–6.71 (m, 2H), 6.27 (d, J=1.4Hz, 1H), 6.20 (d, J=3.0Hz, 1H), 5.70 (d, J=1.4Hz, 1H), 4.19 (d, J=3.0Hz, 1H), 4.16 (t, J=4.0Hz, 1H), 3.82 (s, 3H), 3.41 (d, J=4.0Hz, 1H), 3.82 (s, 3H), 3.41 (d, J=4.4Hz, 2H), 3.02 (ddd, J=2.8Hz, 3.6Hz, 16.8Hz, 1H), 2.91 (ddd, J=2.4Hz, 4.4Hz, 16.8Hz, 1H), 2.12 (t, J=2.4Hz, 1H). ¹³CNMR (CDCl₃, 100 MHz): δ 170.80, 167.22, 137.29, 135.87, 134.48, 129.51, 128.50, 128.22, 127.39, 126.38, 82.38, 80.77, 71.20, 63.16, 62.61, 52.37, 52.30, 24.71. FAB-HRMS: calcd for C₂₄H₂₃NO₄ [MH]⁺ 390.1706, found 390.1700.

4.1.5. (3S,5S,6R)-4-acryloyl-5,6-diphenyl-3-(prop-2-ynyl) morpholine-2-one 12f —To an ice cooled solution of the secondary amine **15** (117 mg) in dichloromethane (4 ml) was added triethyl amine (72 μl) followed by acryloyl chloride (42.5 μl). The reaction mixture was continued to stir at 0°C for 2 h or until the disappearance of the starting material spot on TLC. Solvent was removed and the residue was subjected to flash chromatography (3:1 Hexane/EtOAc) to give product **12f** 85 mg (61%) as colorless crystals. ¹HNMR (CDCl₃, 300 MHz): δ 7.32–7.20 (m, 4H), 7.15–7.10 (m, 2H), 7.01–6.98 (m, 2H), 6.63–6.62 (d, J=3.0Hz, 1H), 6.54–6.52 (app d, J=7.2Hz, 2H), 6.31–6.27 (d, J=13.8Hz, 1H), 6.31–6.30 (d, J=1.8Hz, 1H), 5.59–5.55 (dd, J=3.0Hz, 9.3Hz, 1H), 5.44–5.41 (dd, J=3.9Hz, 5.7Hz, 1H), 5.18–5.17 (d, J=3.0Hz, 1H), 3.52–3.49 (ddd, J=17.3Hz, 3.0Hz, 6.0Hz, 1H), 3.17–3.09 (ddd, J=17.3Hz, 2.7Hz, 3.9Hz, 1H), 2.25–2.23 (t, J=2.7Hz, 1H). FAB-HRMS: calcd for C₂₂H₁₉NO₃ [MH]⁺ 346.1365, found 346.1445.

4.1.6. (2S,3R,5R,6S)-4-(2-(hydroxymethyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl) morpholin-2-ol (16)—To –78°C cooled solution of compound **12e** (4.0 g, 10.27 mmol) was added DIBAL (41.1 ml, 1.0 M solution in dichloromethane) dropwise during a period of 20 min. The reaction was stirred for an additional 20 min and cold-bath was removed. After stirring for another 20 min, the reaction was quenched slowly with sodium potassium tartrate saturated

aqueous solution, diluted with ethyl acetate, and then stirred at room temperature for 2 h, the mixture was transferred to a separatory funnel and separated. The aqueous layer was extracted with ethyl acetate for 3 times. The combined organic layers were washed with brine, dried over sodium sulfate anhydrous, filtered and concentrated. Flash chromatography (Hexanes/EtOAc, 3:1 to 1:1) gave 2.95 g (79.3%) product **16** as white foam. $[\alpha]_D^{25} = +60.0$ (c1, CH₂Cl₂). IR (NaCl thin film): 3293.83 cm⁻¹, 2921.85 cm⁻¹, 2850.80 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ 7.34–7.31 (m, 2H), 7.17–7.04 (m, 8H), 5.25–5.21 (m, 2H), 5.19–5.18 (d, J=4.0Hz, 1H), 4.88 (s, 1H), 4.44–4.31 (app q, J=17.6Hz, 1H), 4.08–4.07 (d, J=4.0Hz, 1H), 3.77–3.76 (d, J=5.6Hz, 1H), 3.58–3.53 (d, J=17.6Hz, 1H), 3.11–3.06 (m, 1H), 2.91–2.84 (dt, J=24Hz, 3.2Hz, 1H), 2.81–2.69 (comp m, 2H), 2.21–2.19 (t, J=3.6Hz, 1H). ¹³CNMR (CDCl₃, 100 MHz): δ 144.19, 138.18, 134.48, 131.95, 127.89, 127.74, 127.59, 127.19, 127.17, 116.92, 96.72, 79.91, 78.58, 72.16, 67.32, 63.91, 56.88, 52.96, 18.84. HRMS-TOF: calcd for C₂₂H₂₅NO₃ [MH⁺] 364.1834, found 364.1893.

4.1.7. 2-(((2R,3R,5R,6S)-2-acetoxy-5,6-diphenyl-3-(prop-2-ynyl)morpholino)methyl)allyl acetate (17)—To an ice cooled solution of diol **16** (12.73 g, 35.03 mmol) in tetrahydrofuran (146 ml) was added pyridine (14.64 ml, 175.15 mmol), acetic anhydride (13.64 ml, 140.10 mmol) followed by DMAP (860 mg, 20%). After removing the cold, the reaction was stirred for 5 to 9 h or until the disappearance of starting material monitored by TLC. Excess solvent was removed under reduced pressure. The residue was subjected to flash chromatography (Hexanes/EtOAc, 5:1) and gave 13.38 g (85%) product **17** as light yellow solid. $[\alpha]_D^{25} = +57.3$ (c1, CH₂Cl₂). IR (NaCl thin film): 3290.97 cm⁻¹, 2929.45 cm⁻¹, 2849.92 cm⁻¹, 1740.27 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ 7.28–7.26 (m, 2H), 7.16–6.97 (m, 8H), 6.07 (d, J=8.4Hz, 1H), 5.31 (d, J=3.2Hz, 1H), 5.23 (s, 1H), 5.11 (s, 1H), 4.90 (d, J=13.8Hz, 1H), 4.73 (d, J=13.8Hz, 1H), 4.00 (d, J=3.2Hz, 1H), 3.44 (d, J=14.0Hz, 1H), 3.27 (ddd, J=3.6Hz, 3.6Hz, 7.6Hz, 1H), 2.83 (d, J=14.0Hz, 1H), 2.58 (ddd, J=2.8Hz, 4.4Hz, 18.0Hz, 1H), 2.47 (dt, J=18.0Hz, 3.2Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 2.07 (t, J=2.6Hz, 1H). ¹³CNMR (CDCl₃, 100 MHz): δ 170.74, 169.16, 141.27, 137.94, 134.78, 131.52, 127.68, 127.64, 127.35, 126.89, 115.36, 94.50, 79.66, 78.90, 77.22, 71.62, 65.29, 63.09, 54.88, 51.37, 21.29, 21.16, 18.96. HRMS-TOF: calcd for C₂₇H₂₉NO₅ [MH⁺] 448.2125, found 448.2128.

4.1.8. IMPK precursor (19)—To an 0°C cooled solution of the diol **16** (55 mg, 0.1513 mmol) and 1,2-di(pyridin-2-yl)disulfane (35.7 mg, 0.1589 mmol) in dichloromethane (0.8 ml) was added Bu₃P (39 μ l, 0.1513 mmol). The reaction mixture was warmed up to room temperature and stirred for 12 h. Solvent removed, the residue was subjected to column (5:1 to 3:1 Hexane/EtOAc) provided 53 mg (77%) product.

To a solution of the above product (53 mg, 0.1161 mmol) in DMF (0.2 ml) was added imidazole (39.6 mg, 0.5805 mmol), TBSCl (34.9 mg, 0.2322 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 36 h, filtered out the solid and concentrated. Flash chromatography (5:1 Hexane/EtOAc) gave product **19** 54 mg (81%). ¹HNMR (CDCl₃, 300 MHz): δ 8.47–8.44 (m, 1H), 7.53–7.47 (m, 1H), 7.34–6.97 (m, 12H), 5.36 (s, 1H), 5.28–5.27 (d, J=4.2Hz, 1H), 5.14–5.12 (d, J=10.0Hz, 1H), 5.05 (s, 1H), 4.30–4.25 (d, J=19.0Hz, 1H), 4.12–4.07 (d, J=19.0Hz, 1H), 4.05–4.04 (d, J=4.2Hz, 1H), 3.50–3.45 (d, J=18.8Hz, 1H), 3.07–3.02 (ddd, J=4.8Hz, 4.8Hz, 10.0Hz, 1H), 2.86–2.81 (d, J=18.8Hz, 1H), 2.67 (t, J=3.2Hz, 1H).

4.1.9.1. Cyclopentenone (18): Procedure A: To a solution of acetate **17** (2.56 g, 5.720 mmol) in dichloromethane (57.2 ml) was added dicobalt octacarbonyl solid (2.162 g, 6.292 mmol), the resulting dark purple suspension was stirred at room temperature for 2 h or until the disappearance of starting material monitored by TLC. The reaction solution was diluted to 114.4 ml and cooled to 0°C, first batch of N-methyl morpholine N-oxide (3.02 g, 25.74 mmol) was added as solid slowly to the reaction, stirred for 30 min before removing the cold bath.

After 2 h, reaction was cooled down to 0°C, a second batch of N-methyl morpholine N-oxide was added and stirred for 30 min and then an additional 21 h at room temperature. The purple reaction mixture was filtered through celite and concentrated. The residue was subjected to flash chromatography (Hexanes/EtOAc, 2:1 to 1:1) to provide compound **18** as light yellow solid 1.24 g (45.6%). $[\alpha]_D^{25} = +24.8$ (C1, CH₂Cl₂). IR (NaCl thin film): 2905.52 cm⁻¹, 2832.32 cm⁻¹, 1742.45 cm⁻¹, 1714.11 cm⁻¹, 1630.75 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ 7.29–7.03 (m, 10H), 5.93 (d, J=8.6Hz, 1H), 5.92 (d, J=1.6Hz, 1H), 5.41 (d, J=3.2Hz, 1H), 4.68 (d, J=11.0Hz, 1H), 4.36 (d, J=11.0Hz, 1H), 3.89 (d, J=3.2Hz, 1H), 3.00 (d, J=11.6Hz, 1H), 2.99 (ddd, J=3.6Hz, 8.6Hz, 11.6Hz, 1H), 2.83 (dd, J=3.6Hz, 14.0Hz, 1H), 2.45–2.41 (m, 1H), 2.43 (d, J=18.4Hz, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 1.91 (d, J=18.4Hz, 1H), 1.85 (d, J=11.6Hz, 1H). ¹³CNMR (CDCl₃, 100 MHz): δ 205.85, 176.89, 171.00, 169.28, 137.34, 134.15, 130.81, 129.95, 128.03, 128.00, 127.97, 127.91, 127.86, 127.20, 125.91, 96.31, 79.13, 67.92, 66.58, 60.30, 56.20, 47.35, 44.14, 30.04, 21.27, 20.96. HRMS (TOF-ESI): calcd for C₂₈H₂₉NO₆ [MH]⁺ 476.1995, found 476.20495. Enantiomer: $[\alpha]_D^{25} = -24.9$ (C1, CH₂Cl₂).

Procedure C: To a solution of acetate **17** (3.682 g, 8.228 mmol) in toluene (164 ml) was added dicobaltoctacarbonyl solid (3.113 g, 9.050 mmol), the resulting dark red solution was stirred at room temperature for 1 h. DMSO (6.06 ml, 82.28 mmol) was introduced and the resulting mixture was then heated to 110°C for 2–3 h or until the disappearance of the complex spot monitored by TLC. The reaction was cooled down to room temperature, solvent removed under reduced pressure. The residue was subjected to flash chromatography (Hexanes/EtOAc: 3:1 to 2:1 to 1:1) providing compound **18** as light yellow solid 3.21 g (82%).

4.1.9.2. Cyclopentenone 10a: ¹HNMR (CDCl₃, 400 MHz): δ 7.24–7.16 (m, 7H), 7.12–7.09 (m, 2H), 7.03–7.00 (m, 2H), 6.14–6.14 (d, J=3.6Hz, 1H), 5.89 (s, 1H), 4.28–4.27 (d, J=3.6Hz, 1H), 3.49–3.44 (dd, J=3.2Hz, 13.6Hz, 1H), 3.31–3.27 (dd, J=6.0Hz, 10.8Hz, 1H), 3.01 (br, 1H), 2.71–2.64 (t, J=12.4Hz, 1H), 2.50–2.44 (dd, J=6.4Hz, 18.4Hz, 1H), 1.88–1.83 (dd, J=2.4Hz, 21.2Hz, 1H), 1.74–1.69 (t, J=22.0Hz, 1H). FAB-HRMS: calcd for C₂₃H₂₁NO₃ [MH⁺] 360.1521, found 374.1398.

4.1.9.3. Cyclopentenone 10b: $[\alpha]_D^{25} = +135.3$ (c1, CH₂Cl₂). ¹HNMR (CDCl₃, 300 MHz): δ 7.32–7.02 (m, 10H), 6.24 (d, J=3.6Hz, 1H), 5.86 (d, J=1.5Hz, 1H), 4.25 (d, J=3.6Hz, 1H), 3.42–3.36 (dd, J=3.6Hz, 13.5Hz, 1H), 3.26–3.21 (dd, J=3.3Hz, 12.3Hz, 1H), 3.02 (d, J=10.8Hz, 1H), 2.87–2.78 (m, 1H), 2.30 (d, J=18.5Hz, 1H), 2.14 (d, J=18.5Hz, 1H), 1.95 (d, J=10.8Hz, 1H), 1.51 (s, 3H). ¹³CNMR (CDCl₃, 100 MHz): δ 206.661, 181.55, 169.03, 135.73, 129.88, 128.65, 128.57, 128.45, 128.04, 128.01, 125.65, 83.36, 66.84, 64.02, 58.63, 48.30, 43.50, 30.95, 24.67. HRMS-TOF: calcd for C₂₄H₂₃NO₃ [MH⁺] 374.1676, found 374.1748.

4.1.9.4. Cyclopentenone 20: ¹HNMR (CDCl₃, 300 MHz): δ 8.47–8.45 (m, 1H), 7.54–7.48 (m, 1H), 7.27–7.02 (m, 12H), 5.90–5.89 (d, J=2.0Hz, 1H), 5.31–5.30 (d, J=4.2Hz, 1H), 4.94–4.91 (d, J=10.0Hz, 1H), 3.92 (s, 2H), 3.79–3.78 (d, J=4.2Hz, 1H), 3.08–3.05 (d, J=17.2Hz, 1H), 2.96–2.90 (dd, J=4.8Hz, 18.0Hz, 1H), 2.78–2.70 (ddd, J=4.4Hz, 9.6Hz, 18.4Hz, 1H), 2.51–2.44 (d, J=24.8Hz, 1H), 2.42–2.34 (app t, J= 14.8Hz, 1H). 1.93–1.86 (d, J=24.8Hz, 1H), 1.83–1.79 (d, J=17.2Hz, 1H), 1.01 (s, 9H), 0.29–0.21 (d, J=29.2Hz, 6H).

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Figure 1.
Examples of several *Stemona* alkaloids.

Figure 2.
ORTEP diagram of compound **18**¹⁷

Scheme 1.
Planned IMPK and stereochemistry generation.

Scheme 2.

IMPK precursor preparation, reagents and conditions: a. NaHMDS, propargyl bromide, THF, -78°C , CH_2Cl_2 ; 90%; b. HCl, dioxane/ CH_2Cl_2 , then $\text{NaHCO}_3/\text{H}_2\text{O}$; 65%

Scheme 3.

Modified IMPK Reactions, reagents and conditions: a. DIBAL, CH_2Cl_2 , -78°C , 79%; b. Ac_2O , pyr., THF, 85%; c. $\text{Co}_2(\text{CO})_8$, NMO, CH_2Cl_2 , 45–50%; d. $\text{Co}_2(\text{CO})_8$, DMSO, Toluene, 110°C , 82%; e. PySSPy, Bu_3P , CH_2Cl_2 , 74%; f. TBSCl, imidazole, DMAP, CH_2Cl_2 , 86%

Table 1Preparation of IMPK precursors **12**

Entry	Allylic side chains	Conditions	Products (yields)
1	$\text{CH}_2=\text{CH}-\text{CH}_2\text{OAc}$	$\text{Pd}_2(\text{dba})_3$, PPh_3 , K_2CO_3 , THF, r.t., nd	12a , 70–90 %
2	$\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}_2\text{Br}$	K_2CO_3 , TBAI, DMF, r.t., 2d	12b , 16%, and rec S.M.
3 ^a	$\text{CH}_2=\text{C}(\text{CH}_2\text{OTBS})-\text{CH}_2\text{Br}$	K_2CO_3 , TBAI, DMF, r.t., 3d	12c , 5–10%, and rec S.M.
4 ^b	$\text{CH}_2=\text{C}(\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS})-\text{CH}_2\text{Br}$	NaHCO_3 , DMF, r.t., 36h	12d , 5–10%, and rec S.M.
5	$\text{CH}_2=\text{C}(\text{COOCH}_3)-\text{CH}_2\text{Br}$	KHCO_3 , DMF, r.t., 12–24h	12e , 98%
6	$\text{CH}_2=\text{CH}-\text{COCl}$	Et_3N , CH_2Cl_2 , 0°C–r.t., 2h	12f , 61%

^a see reference ¹¹ for preparation of the allylic bromide.^b see reference ¹² for preparation of allylic bromide.

Table 2

IMPK reactions

Precursors 12	Conditions	Products, yields
12a	A	10a , 65%
12b	A	10b , <50%
12c	A	10c , <50%
12d	A	10d , <50%
12e	A–E	10e , 0%
12f	B	10f , 16%