Tetrahedron: *Asymmetry* 19 (2008) 2901–2906

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A diastereoselective intramolecular Pauson–Khand approach to the construction of the BC-ring system in tuberostemoninol

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ARTICLE INFO

Article history:
Received 23 October 2008
Accepted 27 November 2008
Available online 10 January 2009

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.

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 led to extensive phytochemical and biological studies[2] as well as synthetic studies[3] over the past two decades. Some representative examples of stemona alkaloids include stenine **1**, tuberostemonine **2**, croomine **3**, stemoamide **4**, and stemofoline **5** (Fig. 1), which are characterized as having a [1,2-a]azepine nucleus. Tuberostemoninol **6**, which lacks this [1,2-a]azepine nucleus, but possesses an azabicyclo[4.3.1]decan-10-one nucleus instead, was first isolated from the Chinese medicinal herb *Stemona tuberosa* Lour as a minor component in 1994 by Lin et al.[4] It is thought that tuberostemoninol is biogenetically related to tuberostemonine **2**,[3e] which is 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, such as stenine and tuberostemonine, included an early stage construction of the highly functionalized cyclohexane rings, 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 report 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**.

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 the introduction of the stereogenic centers in the target natural product **6** as well as embracing neotuberostemoninol **7** and maireistemoninol **8** (Fig. 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 the R_2 and H groups, presumably via 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

The 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 work-up, gave the free secondary amine **15** in 65% yield. Alkylation of amine **15** gave 1,7-enyne **12** (Scheme 2).

A screening of N-alkylation reactions with various allylic side chains was carried out (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 (1 M) in *N*,*N*-dimethylformamide (DMF) or acetonitrile in the presence of alkali metal (Na, K, Cs) carbonates. We also found that an

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doi:10.1016/j.tetasy.2008.11.022

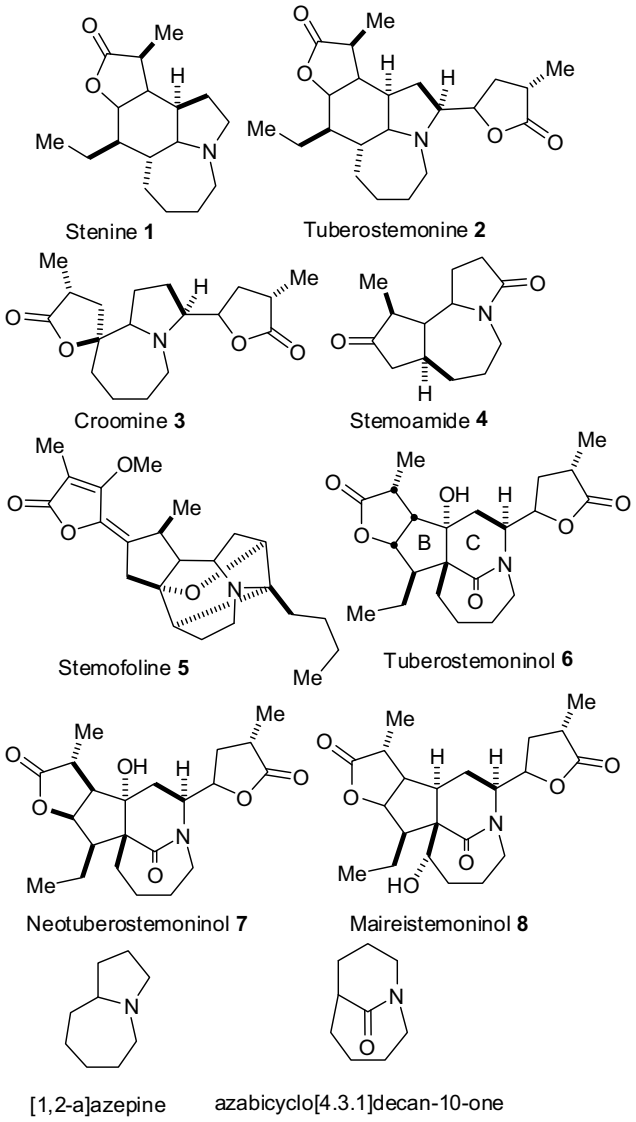
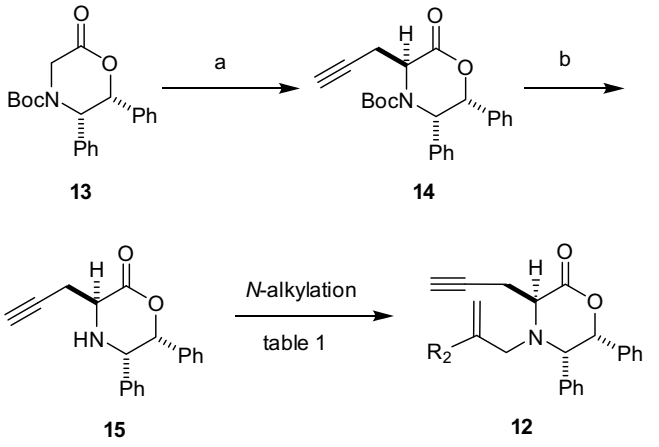


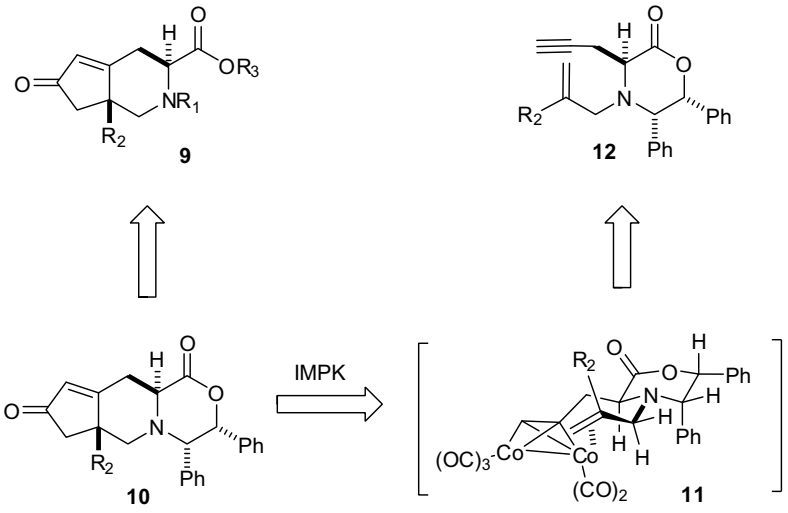
Figure 1. Examples of several *Stemona* alkaloids.

increase in 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 [$Co_2(CO)_8$] in dichloromethane followed by the addition of *N*-methyl morpholine N-oxide (NMO) to initiate the cyclization at 0 °C to room temperature (condition A, Table 2) 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 cycloadducts **10a**.[13] Substrate **12f** provided the desired product **10f** under thermal condition B ($Co_2(CO)_8$, MeCN, reflux).[14] However, neither thermal (condition B) nor Lewis base (NMO (condition A), DMSO (condition C), nBuSMe (condition D), and Me_2S (condition E)) at a temperature range of 35–75 °C in acetonitrile or toluene were able 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 of other intermediates formed in the reaction.[15] Considering the successful (with a



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 $NaHCO_3/H_2O$; 65%.



Scheme 1. Planned IMPK and stereochemistry generation.

Table 1
Preparation of IMPK precursors **12**

Entry	Allylic side chains	Conditions	Products (yields)
1	CH_2=CH–CH_2OAc	$Pd_2(dba)_3$, PPh_3, K_2CO_3, THF, rt, 2d	**12a**, 70–90%
2	CH_2=C(CH_3)–CH_2Br	K_2CO_3, TBAI, DMF, rt, 2 d	**12b**, 16% and rec S.M.
3[a]	CH_2=C(CH_2OTBS)–CH_2Br	K_2CO_3, TBAI, DMF, rt, 3 d	**12c**, 5–10%, and rec S.M.
4[b]	CH_2=C($CH_2CH_2CH_2OTBS$)–CH_2Br	$NaHCO_3$, DMF, rt, 36 h	**12d**, 5–10%, and rec S.M.
5	CH_2=C($COOCH_3$)–CH_2Br	$KHCO_3$, DMF, rt, 12–24 h	**12e**, 98%
6	CH_2=CH–COCl	Et_3N, CH_2Cl_2, 0 °C–rt, 2 h	**12f**, 61%

[a] See Ref. 11 for preparation of the allylic bromide.
[b] See Ref. 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%

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 the 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**. 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, while 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 the 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** is shown in Scheme 3, and was confirmed by single crystal X-ray diffraction of diacetate cyclopentenone **18** (Fig. 2).[17]

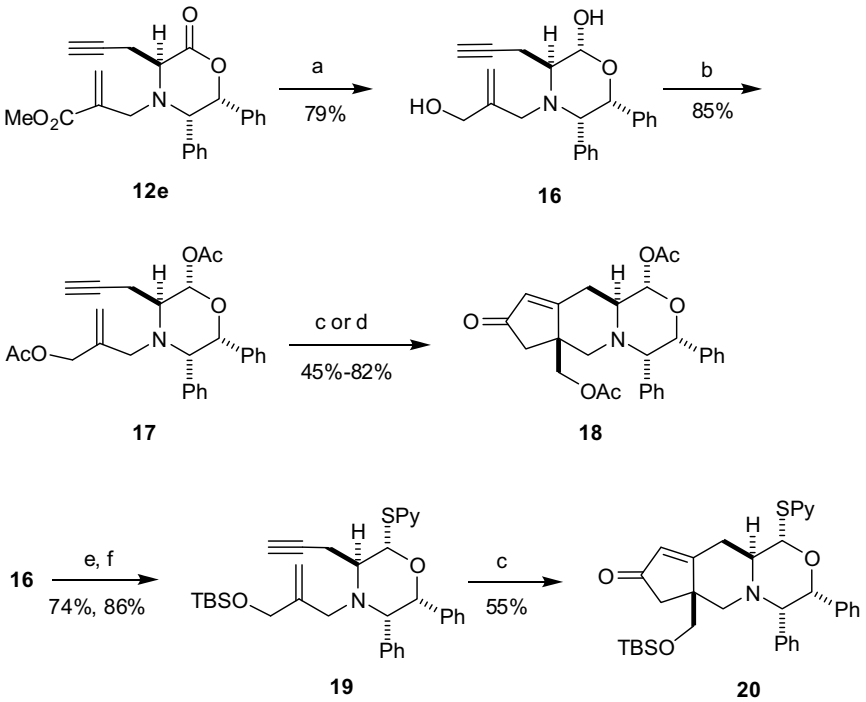
3. Conclusion

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 in due course.

4. Experimental

4.1. General

All chemicals from commercial sources were used without further purification. Both glycinates **13** (2*R*,3*S*)-*tert*-butyl 6-oxo-2,3-diphenylmorpholine-4-carboxylate and its enantiomer were used in the reactions. All dry reactions were carried out using standard syringe-septum technique. Analytical and preparative TLC used Merck silica gel 60 F254 plates, while flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Nuclear mag-



Scheme 3. Modified IMPK reactions, reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C; (b) Ac_2O, pyr., THF, 85%; (c) $Co_2(CO)_8$, NMO, CH_2Cl_2, 45–50%; (d) $Co_2(CO)_8$, DMSO, toluene, 110 °C, 82%; (e) PySSPy, Bu_3P, CH_2Cl_2, 74%; (f) TBSCl, imidazole, DMAP, CH_2Cl_2, 86%.

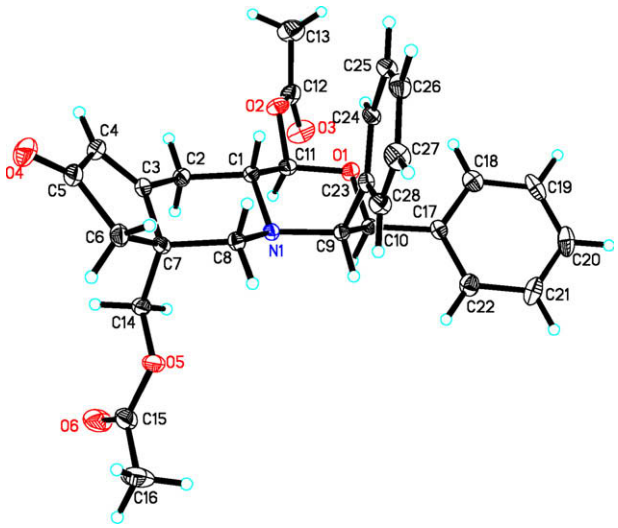


Figure 2. ORTEP diagram of compound **18**.[17]

netic resonance spectra ^{1}H NMR (300 MHz and 400 MHz) and ^{13}C NMR (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 ^{1}H) or the central line (77.23 ppm) of $CDCl_3$ (for ^{13}C). 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 a cooled solution (−78 °C) of 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 over 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, and stirred for 2.5 h under −78 °C. The reaction mixture was then carefully quenched with ammonium chloride saturated aqueous solution and diluted with ethyl acetate. The solution was allowed to warm up to above 0 °C. The reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate three times, and the combined organic layer was washed with ammonium chloride-saturated aqueous solution 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, CH_2Cl_2). IR (NaCl thin film): 3492, 3281, 2255, 1747, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 5−6.5 6 (m, 10H), 6.47 (d, J = 2.8 Hz, 1H), 5.16 (t, J = 4.8 Hz, 1H), 5.05 (d, J = 3.2 Hz, 1H), 3.32 (ddd, J = 2.4 Hz, 5.2 Hz, 17.2 Hz, 1H), 3.07 (td, J = 3.2 Hz, 17.2 Hz, 1H), 2.22 (t, J = 2.4 Hz, 1H), 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.9 0, 153.9 5, 136.5 3, 134.5 7, 128.6 1, 128.1 9, 127.8 7, 127.7 5, 127.5 6, 126.5 4, 81.6 9, 79.9 7, 79.4 1, 72.6 9, 60.7 3, 55.8 0, 27.9 1, 23.8 0. FAB-HRMS: calcd for $C_{24}H_{25}NO_4$ [MH$^+$] 392.1863, found 392.1825.

4.1.2. (3*R*,5*R*,6*S*)-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) over a 10 min period. The cooling bath was removed, and the reaction mixture was stirred for 3–5 h or until the disappearance of starting material as monitored by TLC. The solvent was then removed under reduced pressure. Diethyl ether was added to precipitate the hydrochloride salt, after which the solvent was removed. The white solid was rinsed with diethyl ether and dried to provide 6.0 g of white milky powder, which was redissolved in dichloromethane (70 ml). Saturated sodium bicarbonate (0.95 ml) was added followed by the slow 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. $[\alpha]_D^2 5 = -117.3$ (c 1, CH_2Cl_2). IR (NaCl thin film): 3326, 3287, 1732 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 7−7.1 7 (m, 6H), 7.03–7.01 (m, 2H), 6.95 (d, J = 8.0 Hz, 2H), 5.73 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 4.21 (d, J = 3.6 Hz, 1H), 3.04 (dddd, J = 0.8 Hz, 2.4 Hz, 8.8 Hz, 16.8 Hz, 1H), 2.91 (dddd, J = 1.2 Hz, 2.8 Hz, 3.6 Hz, 16.8 Hz, 1H), 2.37 (br s, 1H), 2.11 (ddd, J = 1.2 Hz, 2.8 Hz, 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4 9, 136.8 9, 134.9 3, 128.5 7, 128.3 2, 128.2 7, 127.8 6, 127.8 3, 127.2 1, 85.4 9, 80.1 2, 72.1 5, 57.0 9, 55.3 8, 24.0 3. FAB-HRMS: calcd for $C_{19}H_{17}NO_2$ [MH$^+$] 292.1338, found 292.1337.

4.1.3. (3*S*,5*S*,6*R*)-4-Allyl-5,6-diphenyl-3-(prop-2-ynyl) morpholine-2-one 12a

A mixture of $Pd_2(dba)_3$ (8 mg), PPh_3 (27 mg), and K_2CO_3 (28 mg) in anhydrous THF (2 ml) was stirred under argon. The secondary amine **15** (30 mg, 0.103 mmol) was added followed by allyl acetate (13.3 µl, 0.1236 mmol), and the resulting mixture was stirred at room temperature for 1 day during which more allyl acetate was added. The reaction mixture was filtered through a pad of Celite, and concentrated. The residue was subjected to flash chromatography (3:1 hexanes/EtOAc) to give the desired product **12a** in decent yield. ^{1}H NMR ($CDCl_3$, 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 = 3.0 Hz, 1H), 5.90–5.76 (ddd, J = 4.8 Hz, 7.8 Hz, 10.2 Hz, 1H), 5.18–517 and 5.09–5.07 (app d, J = 27.6 Hz, 1H), 5.14 (br., 1H), 4.30–4.29 (d, J = 3.0 Hz, 1H), 4.06–4.03 (t, J = 4.2 Hz, 1H), 3.30–3.23 (dddd, J = 14.4 Hz, 1.8 Hz, 1.8 Hz, 5.1 Hz, 1H), 3.17–3.10 (app dd, J = 14.4 Hz, 7.8 Hz, 1H), 3.03–2.95 (ddd, J = 16.8 Hz, 2.7 Hz, 3.6 Hz, 1H), 2.85–2.77 (dd, J = 16.8 Hz, 2.4 Hz, 4.5 Hz, 1H), 2.16–2.15 (t, J = 2.55 Hz, 1H). FAB-MS: calcd for $C_{22}H_{21}NO_2$ [MH]$^+$ 331.2, found 332.2 (low resolution MS).

4.1.4. General procedure for 12b, 12c, 12d, 12e preparation

To a 0 °C cooled solution of amine **15** in DMF (1 M) was added potassium carbonate (1.2 equiv) as a solid followed by dropwise addition of allylic bromide (1.5 or more equiv). The resulting mixture was stirred at room temperature for 12 h for two days. The reaction mixture was filtered, and the filtrate was partitioned between ammonium chloride saturated aqueous solution and ethyl acetate, and separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography gave products **12b**, **12c**, **12d**, and **12e,** respectively.

4.1.4.1. (3*S*,5*S*,6*R*)-4-(2-Methylallyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one 12b. ^{1}H NMR ($CDCl_3$, 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 = 3.0 Hz, 1H), 4.90 (br s, 1H), 4.81 (br s, 1H), 4.16 (d, J = 3.0 Hz, 1H), 3.79–3.78 (d, J = 4.2 Hz, 1H), 3.08–3.05 (d, J = 17.2 Hz, 1H), 2.96–2.90 (dd, J = 4.8 Hz, 18.0 Hz, 1H), 2.78–2.70 (ddd, J = 4.4 Hz, 9.6 Hz, 18.4 Hz, 1H), 2.51–2.44 (d, J = 24.8 Hz, 1H), 2.42–2.34 (app t, J = 14.8 Hz, 1H). 1.93–1.86 (d, J = 24.8 Hz, 1H), 1.83–1.79 (d, J = 17.2 Hz, 1H), 1.01 (s, 9H), 0.29–0.21 (d, J = 29.2 Hz, 6H).

4.1.4.2. (3*S*,5*S*,6*R*)-4-(2-((*tert*-Butyldimethylsilyloxy)methyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one 12c. ^{1}H NMR ($CDCl_3$, 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* = 3.0 Hz, 1H), 5.21 (br, 1H), 4.91 (br, 1H), 4.20–4.19 (d, *J* = 3.0 Hz, 1H), 4.03 (app t, *J* = 3.9 Hz, 1H), 3.04 (s, 2H), 3.02–2.95 (m, 1H), 2.84–2.75 (ddd, *J* = 2.7 Hz, 4.5 Hz, 16.8 Hz, 1H), 2.13 (t, *J* = 2.7 Hz, 1H). 1.85 (s, 3H).

4.1.4.3. (3*R*,5*R*,6*S*)-4-(6-(*tert*-Butyldimethylsilyloxy)-2-methylenehexyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one 12d. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.21 (m, 6H), 7.12–7.08 (m, 4H), 5.03 (d, *J* = 1.8 Hz, 1H), 4.86–4.83 (t, *J* = 2.3 Hz, 1H), 4.78–4.77 (d, *J* = 1.5 Hz, 1H), 4.05–3.97 (comp m, 4H), 3.40–3.36 (t, *J* = 3.9 Hz, 1H), 3.20–3.19 (d, *J* = 4.2 Hz, 1H), 2.57–2.52 (ddd, *J* = 2.7 Hz, 5.4 Hz, 11.1 Hz, 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 $C_{32}H_{43}NO_3$ $[MH]^+$ 518.3012, found 518.3103.

4.1.4.4. Methyl 2-(((3*R*,5*R*,6*S*)-2-oxo-5,6-diphenyl-3-(prop-2-ynyl)-morpholino)methyl)acrylate 12e. To a 0 °C cooled solution of amine **15** (6.735 g, 23.12 mmol) in DMF (23 ml) was added potassium carbonate (4.7 g, 34.68 mmol) followed by the dropwise addition of methyl 2-(bromomethyl)acrylate (4.48 g, 24.27 mmol). The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was portioned between ammonium chloride saturated aqueous solution and ethyl acetate, and separated. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layer was washed with water for three times, then washed with brine, dried over magnesium sulfate anhydrous, filtered, and concentrated. Flash chromatography (hexanes/EtOAc, 8:1) gave 8.82 g (98%) of product **12e** as a light yellow sticky solid. $[\alpha]_D^{25} = -41.3$ (*c*1, CH_2Cl_2). IR (NaCl thin film): 3293, 3061, 3031, 2950, 2922, 2849, 1742, 1635, 1603 cm^{-1}. ^{1}H NMR ($CDCl_3$, 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* = 1.4 Hz, 1H), 6.20 (d, *J* = 3.0 Hz, 1H), 5.70 (d, *J* = 1.4 Hz, 1H), 4.19 (d, *J* = 3.0 Hz, 1H), 4.16 (t, *J* = 4.0 Hz, 1H), 3.82 (s, 3H), 3.41 (d, *J* = 4.0 Hz, 1H), 3.82 (s, 3H), 3.41 (d, *J* = 4.4 Hz, 2H), 3.02 (ddd, *J* = 2.8 Hz, 3.6 Hz, 16.8 Hz, 1H), 2.91 (ddd, *J* = 2.4 Hz, 4.4 Hz, 16.8 Hz, 1H), 2.12 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.8 0, 167.2 2, 137.2 9, 135.8 7, 134.4 8, 129.5 1, 128.5 0, 128.2 2, 127.3 9, 126.3 8, 82.3 8, 80.7 7, 71.2 0, 63.1 6, 62.6 1, 52.3 7, 52.3 0, 24.71. FAB-HRMS: calcd for $C_{24}H_{23}NO_4$ $[MH^+]$ 390.1706, found 390.1700.

4.1.5. (3*S*,5*S*,6*R*)-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 stirred continously at 0 °C for 2 h or until the disappearance of the starting material spot on TLC. The solvent was removed, and the residue was subjected to flash chromatography (3:1 hexanes/EtOAc) to give 85 mg (61%) of product **12f** as colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.20 (m, 4 H), 7.15–7.10 (m, 2H), 7.01–6.98 (m, 2H), 6.63–6.62 (d, *J* = 3.0 Hz, 1H), 6.54–6.52 (app d, *J* = 7.2 Hz, 2H), 6.31–6.27 (d, *J* = 13.8 Hz, 1H), 631–6.30 (d, *J* = 1.8 Hz, 1H), 5.59–5.55 (dd, *J* = 3.0 Hz, 9.3 Hz, 1H), 5.44–5.41 (dd, *J* = 3.9 Hz, 5.7 Hz, 1H), 5.18–5.17 (d, *J* = 3.0 Hz, 1H), 3.52–3.49 (ddd, *J* = 17.3 Hz, 3.0 Hz, 6.0 Hz, 1H), 3.17–3.09 (ddd, *J* = 17.3 Hz, 2.7 Hz, 3.9 Hz, 1H), 2.25–2.23 (t, *J* = 2.7 Hz, 1H). FAB-HRMS: calcd for $C_{22}H_{19}NO_3$ $[MH]^+$ 346.1365, found 346.1445.

4.1.6. (2*S*,3*R*,5*R*,6*S*)-4-(2-(hydroxymethyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-ol 16

To a cooled solution (−78 °C) of compound **12e** (4.0 g, 10.27 mmol) was added DIBAL (41.1 ml, 1.0 M solution in dichloromethane) dropwise over a period of 20 min. The reaction mixture was stirred for an additional 20 min, and coldbath was removed. After stirring for another 20 min, the reaction mixture 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 was separated. The aqueous layer was extracted with ethyl acetate three 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%) of product **16** as white foam. $[\alpha]_D^{25} = +60.0$ (*c* 1, CH_2Cl_2). IR (NaCl thin film): 3293, 2921, 2850 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.3 4–7.31 (m, 2H), 7.17–7.04 (m, 8H), 5.25–5.21 (m, 2H), 5.19–5.18 (d, *J* = 4.0 Hz, 1H), 4.88 (s, 1H), 4.44–4.31 (app q, *J* = 17.6 Hz, 1H), 4.08–4.07 (d, *J* = 4.0 Hz, 1H), 3.77–3.76 (d, *J* = 5.6 Hz, 1H), 3.58–3.53 (d, *J* = 17.6 Hz, 1H), 3.11–3.06 (m, 1H), 2.91–2.84 (dt, *J* = 24 Hz, 3.2 Hz, 1H), 2.81–2.69 (comp m, 2H), 2.21–2.19 (t, *J* = 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{25}NO_3$ $[MH^+]$ 364.1834, found 364.1893.

4.1.7. 2-(((2*R*,3*R*,5*R*,6*S*)-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) were added pyridine (14.64 ml, 175.15 mmol) and acetic anhydride (13.64 ml, 140.10 mmol) followed by DMAP (860 mg, 20%). After removing the cold bath, the reaction mixture was stirred for 5–9 h or until the disappearance of starting material as monitored by TLC. Excess solvent was removed under rotavaporation. The residue was subjected to flash chromatography (hexanes/EtOAc, 5:1), and gave 13.38 g (85%) of product **17** as a light yellow solid. $[\alpha]_D^{25} = +57.3$ (*c* 1, CH_2Cl_2). IR (NaCl thin film): 3290, 2929, 2849, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 8–7.2 6 (m, 2H), 7.16–6.97 (m, 8H), 6.07 (d, *J* = 8.4 Hz, 1H), 5.31 (d, *J* = 3.2 Hz, 1H), 5.23 (s, 1H), 5.11 (s, 1H), 4.90 (d, *J* = 13.8 Hz, 1H), 4.73 (d, *J* = 13.8 Hz, 1H), 4.00 (d, *J* = 3.2Hz, 1H), 3.44 (d, *J* = 14.0 Hz, 1H), 3.27 (ddd, *J* = 3.6 Hz, 3.6 Hz, 7.6 Hz, 1H), 2.83 (d, *J* = 14.0 Hz, 1H), 2.58 (ddd, *J* = 2.8 Hz, 4.4 Hz, 18.0 Hz, 1H), 2.47 (dt, *J* = 18.0 Hz, 3.2 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 2.07 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7 4, 169.1 6, 141.2 7, 137.9 4, 134.7 8, 131.5 2, 127.6 8, 127.6 4, 127.3 5, 126.8 9, 115.3 6, 94.5 0, 79.6 6, 78.9 0, 77.2 2, 71.6 2, 65.2 9, 63.0 9, 54.8 8, 51.3 7, 21.2 9, 21.1 6, 18.9 6. HRMS-TOF: calcd for $C_{27}H_{29}NO_5$ $[MH^+]$ 448.2125, found 448.2128.

4.1.8. IMPK precursor 19

To a 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 Bu_3P (39 μl, 0.1513 mmol). The reaction mixture was warmed up to room temperature and stirred for 12 h. The solvent was removed, and the residue was subjected to column chromatography (5:1 to 3:1 hexanes/EtOAc), provided 53 mg (77%) of product. To a solution of the above product (53 mg, 0.1161 mmol) in DMF (0.2 ml) were added imidazole (39.6 mg, 0.5805 mmol), TBSCl (34.9 mg, 0.2322 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 36 h to remove the solid and was then concentrated. Flash chromatography (5:1 hexanes/EtOAc) gave 54 mg (81%) of product **19**. ^{1}H NMR ($CDCl_3$, 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* = 4.2 Hz, 1H), 5.14–5.12 (d, *J* = 10.0 Hz, 1H), 5.05 (s, 1H), 4.30–4.25 (d, *J* = 19.0 Hz, 1H), 4.12–4.07 (d, *J* = 19.0 Hz, m 1H), 4.05–4.04 (d, *J* = 4.2 Hz, 1H), 3.50–3.45 (d, *J* = 18.8 Hz, 1H), 3.07–3.02 (ddd, *J* = 4.8 Hz, 4.8 Hz, 10.0 Hz, 1H), 2.86–2.81 (d, *J* = 18.8 Hz, 1H), 2.67 (t, *J* = 3.2 Hz, 1H).

4.1.8.1. 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 (2.162 g, 6.292 mmol). The resulting dark purple suspension was stirred at room temperature for 2 h or until the disappearance of the starting material as monitored by TLC. The reaction solution was diluted to 114.4 ml and cooled to 0 °C. The first batch of *N*-methyl morpholine N-oxide (3.02 g, 25.74 mmol) was slowly added as a solid to the reaction, and stirred for 30 min before removing the cold bath. After 2 h, the reaction mixture was cooled down to 0 °C, and a second batch of *N*-methyl morpholine N-oxide was added and stirred for 30 min and then for 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%). $[\alpha]_D^{25} = +24.8$ (*c* 1, CH_2Cl_2). IR (NaCl thin film): 2905, 2832, 1742, 1714, 1630 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.2 9−7.0 3 (m, 10H), 5.93 (d, *J* = 8.6 Hz, 1H), 5.92 (d, *J* = 1.6 Hz, 1H), 5.41 (d, *J* = 3.2 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 3.89 (d, *J* = 3.2 Hz, 1H), 3.00 (d, *J* = 11.6 Hz, 1H), 2.99 (ddd, *J* = 3.6 Hz, 8.6 Hz, 11.6 Hz, 1H), 2.83 (dd, *J* = 3.6 Hz, 14.0 Hz, 1H), 2.45–2.41 (m, 1H), 2.43 (d, *J* = 18.4 Hz, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 1.91 (d, *J* = 18.4 Hz, 1H), 1.85 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.8 5, 176.8 9, 171.0 0, 169.2 8, 137.3 4, 134.1 5, 130.8 1, 129.9 5, 128.0 3, 128.0 0, 127.9 7, 127.9 1, 127.8 6, 127.2 0, 125.9 1, 96.3 1, 79.1 3, 67.9 2, 66.5 8, 60.3 0, 56.2 0, 47.3 5, 44.1 4, 30.0 4, 21.2 7, 20.9 6. HRMS (TOF-ESI): calcd for $C_{28}H_{29}NO_6$ $[MH]^+$ 476.1995, found 476.20495. Enantiomer: $[\alpha]_D^{25} = -24.9$ (*c* 1, CH_2Cl_2).

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 as monitored by TLC. The reaction mixture was cooled down to room temperature, and the solvent was removed by rotavaporation. The residue was subjected to flash chromatography (hexanes/EtOAc: 3:1 to 2:1 to 1:1) to give compound **18** as light yellow solid 3.21 g (82%).

4.1.8.2. Cyclopentenone 10a. ^1H NMR ($CDCl_3$, 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* = 3.6 Hz, 1H), 5.89 (s, 1H), 4.28–4.27 (d, *J* = 3.6 Hz, 1H), 3.49–3.44 (dd, *J* = 3.2 Hz, 13.6 Hz, 1H), 3.31–3.27 (dd, *J* = 6.0 Hz, 10.8 Hz, 1H), 3.01 (br, 1H), 2.71–2.64 (t, *J* = 12.4 Hz, 1H), 2.50–2.44 (dd, *J* = 6.4 Hz, 18.4 Hz, 1H), 1.88–1.83 (dd, *J* = 2.4 Hz, 21.2 Hz, 1H), 1.74–1.69 (t, *J* = 22.0 Hz, 1H). FAB-HRMS: calcd for $C_{23}H_{21}NO_3$ $[MH^+]$ 360.1521, found 374.1398.

4.1.8.3. Cyclopentenone 10b. $[\alpha]_D^{25} = +135.3$ (*c* 1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.3 2−7.0 2 (m, 10H), 6.24 (d, *J* = 3.6 Hz, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 4.25 (d, *J* = 3.6 Hz, 1H), 3.42–3.36 (dd, *J* = 3.6 Hz, 13.5 Hz, 1H), 3.26–3.21 (dd, *J* = 3.3 Hz, 12.3 Hz, 1H), 3.02 (d, *J* = 10.8 Hz, 1H), 2. 87–2.78 (m, 1H), 2.30 (d, *J* = 18.5 Hz, 1H), 2.14 (d, *J* = 18.5 Hz, 1H), 1.95 (d, *J* = 10.8 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.6 61, 181.5 5, 169.0 3, 135. 73, 129.8 8, 128.6 5, 128.5 7, 128.4 5, 128.0 4, 128.0 1, 125.6 5, 83.3 6, 66.8 4, 64.0 2, 58.6 3, 48.3 0, 43.5 0, 30.9 5, 24.6 7. HRMS-TOF: calcd for $C_{24}H_{23}NO_3$ [MH+] 374.1676, found 374.1748.

4.1.8.4. Cyclopentenone 20. ^1H NMR ($CDCl_3$, 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* = 2.0 Hz, 1H), 5.31–5.30 (d, *J* = 4.2 Hz, 1H), 4.94–4.91 (d, *J* = 10.0 Hz, 1H), 3.92 (s, 2H), 3.79–3.78 (d, *J* = 4.2 Hz, 1H), 3.08–3.05 (d, *J* = 17.2 Hz, 1H), 2.96–2.90 (dd, *J* = 4.8 Hz, 18.0 Hz, 1H), 2.78–2.70 (ddd, *J* = 4.4 Hz, 9.6 Hz, 18.4 Hz, 1H), 2.51–2.44 (d, *J* = 24.8 Hz, 1H), 2.42–2.34 (app t, *J* = 14.8 Hz, 1H). 1.93–1.86 (d, *J* = 24.8 Hz, 1H), 1.83–1.79 (d, *J* = 17.2 Hz, 1H), 1.01 (s, 9H), 0.29–0.21 (d, *J* = 29.2 Hz, 6H).

Acknowledgments

This study was financially supported by the National Institutes of Health Grant GM068011. We thank Susie Miller for the X-ray diffraction analysis and Christopher Rithner for assistance with NMR experiments.

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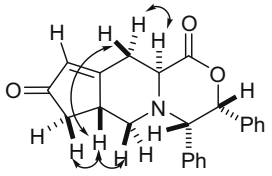
13. nOe analysis of compound **10a**



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17. CCDC 690517 contains the supplementary crystallographic data for this paper. These data can be free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/deposit.