Preparation of 2-diazo-2-oxopiperidin-3-yl-3-oxopropanoates. Useful reagents for Rh(II)-catalyzed cyclization-cycloaddition chemistry

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Dedicated to Lutz F. Tietze on the occasion of his 65th anniversary

Abstract
2-Diazo-2-oxopiperidin-3-yl-3-oxopropanoates containing a tethered indolyl group have been identified as useful intermediates for the Rh(II)-catalyzed cyclization-cycloaddition cascade for the synthesis of the core skeleton of various aspidosperma alkaloids. Several synthetic methods were developed to rapidly construct these important diazo imide substrates using cheap and readily available reagents.

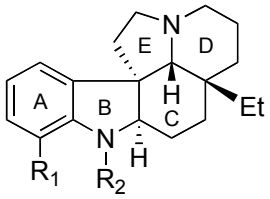
Keywords: Diazo imide, synthesis, indole, coupling, rhodium(II), lactam

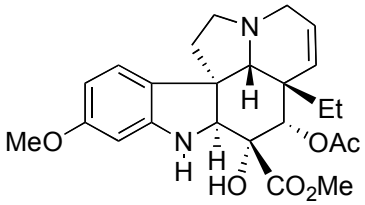
Introduction

In recent years, a widespread upsurge of activity in the stereoselective preparation of highly substituted nitrogen heterocycles, especially structurally complex alkaloids has occurred.[1] In particular, members of the *Aspidosperma* alkaloid family have occupied a central place in natural product chemistry because of their diverse biological activity.[2] This family of indole alkaloids contains over 250 members that share in their molecular structure a common pentacyclic ABCDE framework, with the C-ring being of critical importance because all six stereocenters and most of the functionalities are located in this ring.[3] Individual members differ mainly in functionality and stereochemistry. Over the years, efficient and elegant routes to this molecular framework have been developed.[4,5]

Our approach to the *Aspidosperma* skeleton was guided by a long-standing interest in developing new applications of the Rh(II) cyclization/cycloaddition cascade for the synthesis of complex natural products.[6] The generation of onium ylides by a transition-metal promoted cyclization reaction has emerged in recent years as an important and efficient method for the assembly of ring systems that are difficult to prepare by other means.[7] In earlier studies we

described the formation of cyclic carbonyl ylide dipoles by a process involving cyclization of an electrophilic metallo-carbenoid onto an adjacent carbonyl group.[8]

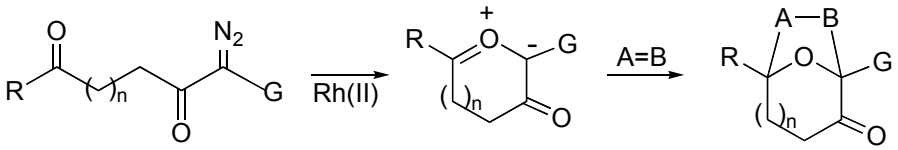




1; $R_1 = R_2 = H$ (Aspidospermidine)
2; $R_1 = OMe$; $R_2 = Ac$ (Aspidospermine)

3; Vindoline

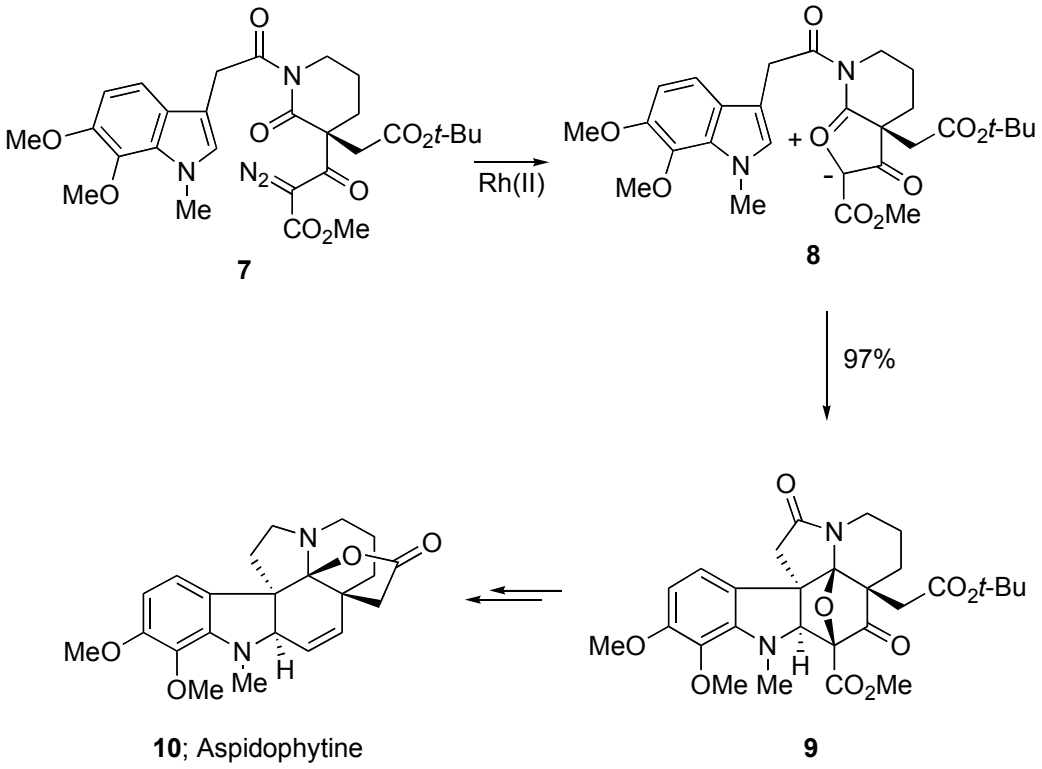
The general reaction investigated is illustrated in Scheme 1; variations in chain length (n = 0, 1, 2) and nature of the activating group (G) were explored.[9] With limited exceptions,[10] alkyl and aryl ketones were employed and dipole **5** was generated by the rhodium(II)-catalyzed decomposition of the diazoalkanedione in benzene at 80 ºC.[11]



4 **5** **6**

Scheme 1

More recently, we became interested in the formation of push-pull dipoles from the Rh(II)-catalyzed reaction of α-diazo imides[12] and noted that a smooth intramolecular 1,3-dipolar cycloaddition occurred across both alkenyl and heteroaromatic π-bonds to provide novel pentacyclic compounds in good yield and in a stereocontrolled fashion.[13,14] Our recent total synthesis of (±)-aspidophytine nicely demonstrates the utility of this cascade methodology for the construction of complex aspidosperma alkaloids.[15] Thus, the Rh(II)-catalyzed reaction of diazo imido indole **7** produced cycloadduct **9** in 97% yield *via* the intermediacy of the carbonyl ylide dipole **8**. The acid lability of cycloadduct **9** was exploited to provide the complete skeleton of aspidophytine in several additional steps (Scheme 2).



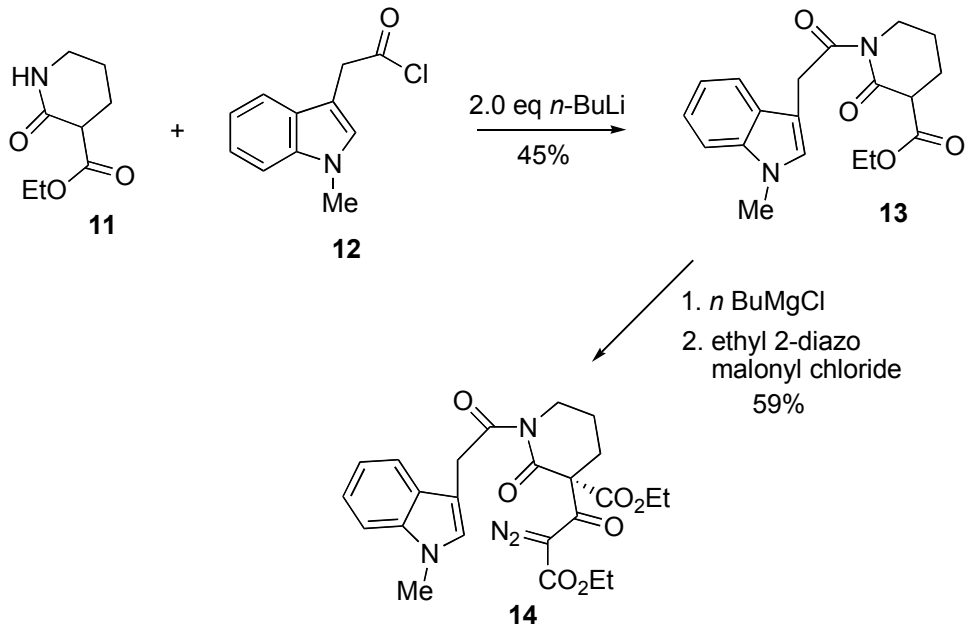
Scheme 2

Results and Discussion

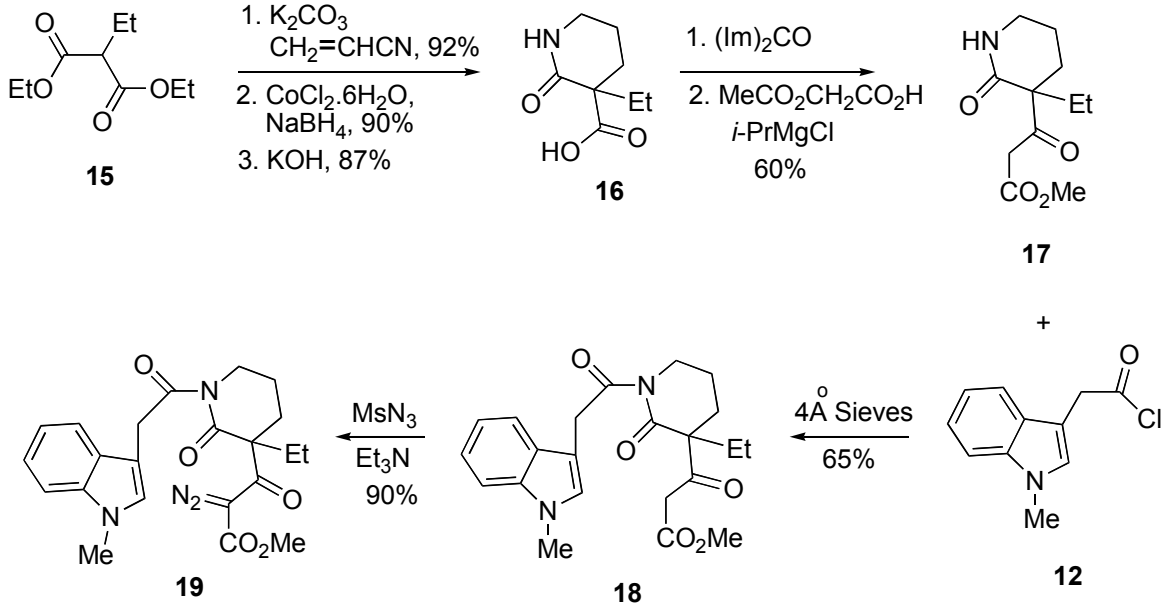
Several methods for preparing the diazo imides necessary for dipole formation have been explored. One option that we have used involves treating the commercially available 3-carboethoxy-2-piperidone (**11**) with *n*-BuLi at -78 ºC followed by the addition of an indole acid chloride such as **12**. This results in the joining of the two fragments to give imide **13** in 45% yield. A subsequent reaction of **13** with *n*-butylmagnesium chloride in THF at 0 ºC followed by the addition of ethyl 2-diazomalonyl chloride[16] afforded the indolyl substituted diazo imide **14** in 59% yield (Scheme 3).

Since the overall yield of diazo imide **14** obtained by this method was somewhat low, we opted to study some alternate procedures to prepare the starting diazo substrates. With this in mind, diazo imide **19** was synthesized in the manner outlined in Scheme 4. 3-Ethyl-2-oxopiperidine-3-carboxylic acid **16** was first prepared in three steps from diethyl ethylmalonate (**15**). Treatment of **16** with 1,1-carbonyldiimidazole followed by reaction with the dianion of mono-methyl malonate furnished β-ketoester **17** in 60% yield. This compound was then converted to the indolyl-*N*-acylamide **18** (65%) by reaction with acid chloride **12** using 4Aº molecular sieves as a neutral acid scavenger. Finally, the requisite α-diazo imide **19** was easily

obtained from **18** using standard Regitz diazo transfer conditions[17] and was isolated in 90% yield.

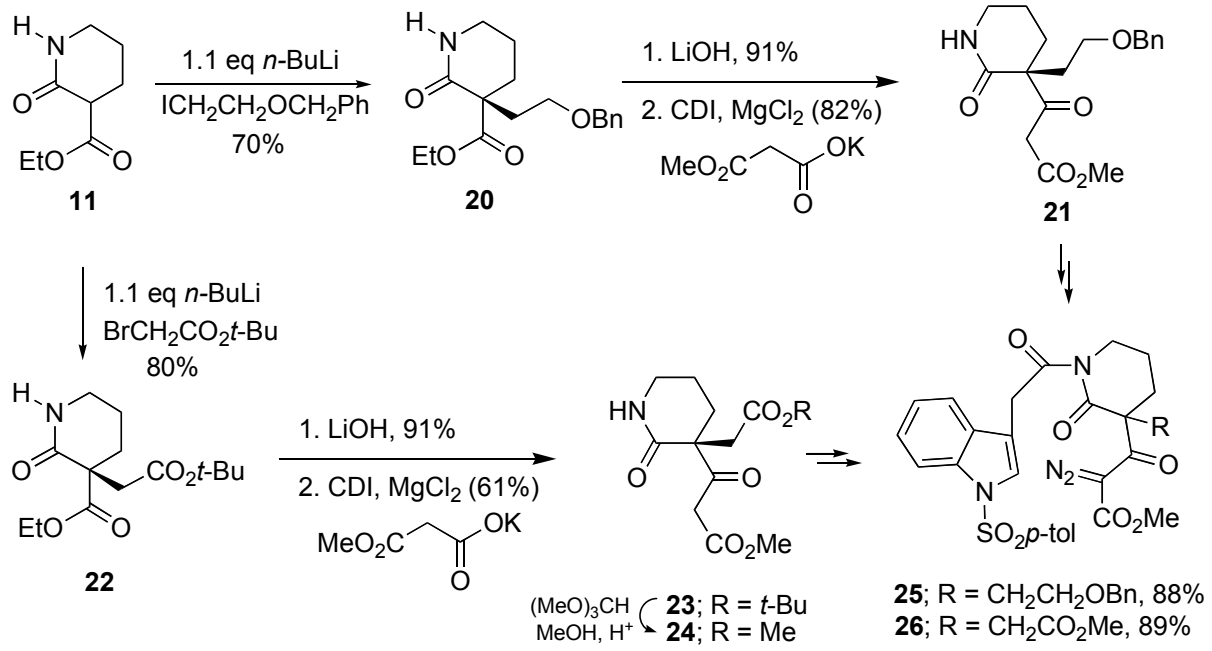


Scheme 3



Scheme 4

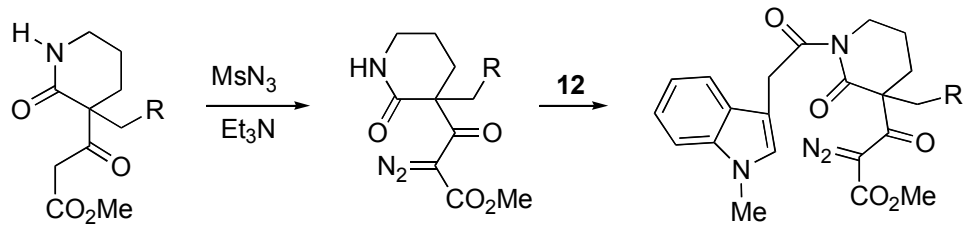
Several other 3-substituted diazo- imides related to **19** could be prepared according to the reaction sequence outlined in Scheme 5. Deprotonation of the piperidone **11** with 1.1 equiv of *n*-butyllithium followed by reaction with 2-iodoethyl benzyl ether afforded lactam **20** in 70% yield. The ethyl ester portion of **20** was converted into the methyl 3-oxopropanoate group using a modified Masamune procedure[18] which furnished β-keto ester **21** in 82% yield. A related sequence of reactions was also used to prepare lactams **23** and **24**. Thus, the anion derived from the piperidone **11** was allowed to react with *t*-butyl bromoacetate together with a catalytic amount of *t*-butyl ammonium iodide which lead to the formation of lactam **22** in 80% yield. Treatment of the resulting *t*-butyl ester **23**, derived from heating **22** with $(MeO)_3CH$/MeOH in the presence of *p*-TsOH gave the corresponding methyl ester **24** in almost quantitative yield (Scheme 5). When these lactams were allowed to react with the acid chloride derived from 2-(*N*-tosyl-1*H*-indol-3-yl)acetic acid, the expected imides were readily formed in high yield and were easily converted into the corresponding diazo substrates **25** and **26** using the Regitz diazotization procedure.[17]



Scheme 5

Still another method that was used to prepare the key diazo- imide substrates needed for the Rh(II) cascade involved the initial preparation of a methyl 2-diazo-3-(3-alkyl-2-oxopiperidin-3-yl)-3-oxopropanoate (*i.e.*, **27** or **28**) and then coupling it with an appropriate acid chloride (Scheme 6). By carrying out the synthesis of the indolyl substituted diazo imides in this manner, the Regitz diazo transfer reaction[17] can be avoided in the final step thereby simplifying the synthesis. Thus, piperidinones **21** and **23** were easily converted to the corresponding diazo lactams **27** and **28** in excellent yield. These compounds, in turn, were treated with indolyl acid

chloride **12** which resulted in the formation of the desired diazo imides **29** and **30** in 82% and 73% yield, respectively.



21; R = CH_2OBn
23; R = CO_2t-Bu

27; R = CH_2OBn, 93%
28; R = CO_2t-Bu, 96%

29; R = CH_2OBn, 82%
30; R = CO_2t-Bu, 73%

Scheme 6

In conclusion, several synthetic methods have been developed to rapidly prepare various indolyl substituted 2-diazo-2-oxopiperidin-3-yl 3-oxopropanoates in high yield. Treatment of these substrates with $Rh_2(OAc)_4$ generate push-pull 1,3-dipoles that undergo ready intramolecular dipolar cycloaddition across the indolyl π-bond. We are currently investigating the scope and limitations of the Rh(II) cyclization-cycloaddition cascade as a method for the synthesis of various *aspidosperma* alkaloids, the results of which will be disclosed in due course.

Experimental Section

2-Diazo-3-{1-[(1-methyl-1*H*-indol-3-yl)-acetyl]-3-carboethoxy-2-oxo-piperidin-3-yl}-3-oxo-propionic acid ethyl ester (14). To a solution of 0.5 g (2.9 mmol) of 2-oxo-piperidine-3-carboxylic acid ethyl ester (**11**) in 10 mL of THF at –78 °C was added 4.0 mL (6.4 mmol) of a 1.6 M *n*-butyllithium solution in hexane and the mixture was allowed to stir while warming to RT. The solution was cooled to –78 °C and 0.9 g (4.4 mmol) of *N*-methyl-3-indole-acetyl chloride (**12**) in 2 mL of CH_2Cl_2 was added over 5 min. The solution was allowed to stir for 2 h and was quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.45 g (45%) of 1-[2-(1-methyl-1*H*-indol-3-yl)-acetyl]-2-oxo-piperidine-3-carboxylic acid ethyl ester (**13**) as a yellow oil; IR (neat) 2947, 1745, 1695, 1645, and 1496 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, *J* = 7.1 Hz), 1.65-2.20 (m, 4H), 3.53 (t, 1H, *J* = 7.6 Hz), 3.60-3.80 (m, 2H), 3.73 (s, 3H), 4.25 (dq, 2H, *J* = 7.1 and 2.0 Hz), 4.35 (d, 1H, *J* = 16.9 Hz), 4.43 (d, 1H, *J* = 16.9 Hz), and 7.00-7.65 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 14.1, 20.7, 24.2, 32.7, 35.5, 43.9, 51.5, 61.7, 107.2, 109.2, 119.1, 119.2, 121.6, 128.1, 128.4, 136.8, 169.8, 170.0, and 175.1.

To a stirred solution of 0.1 g (0.29 mmol) of the above amide **13** in 5 mL of THF at 0 °C was added 0.18 mL (0.36 mmol) of a 0.2 *M* solution of *n*-butyl-magnesium chloride in THF. The solution was allowed to stir at 0 °C for 1 h and then 0.1 g (0.55 mmol) of ethyl 2-diazomalonyl chloride[16] was added. The solution was allowed to stir at 0 °C for 2 h and was then quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 2-diazo-3-{1-[(1-methyl-1*H*-indol-3-yl)-acetyl]-3-ethoxycarbonyl-2-oxo-piperidin-3-yl}-3 oxopropionic acid ethyl ester (**14**) as a yellow oil (59%); IR (neat) 2933, 2143, 1733, 1695, 1646, 1472, and 1320 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.0 Hz), 1.65-2.26 (m, 4H), 2.41 (ddd, 1H, *J* = 13.7, 9.5, and 4.3 Hz), 2.66 (dt, 1H, *J* = 9.5 and 4.3 Hz), 3.73 (s, 3H), 3.76-3.85 (m, 1H), 4.20-4.40 (m, 5H) and 7.00-7.60 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 20.7, 24.2, 28.2, 32.6, 35.5, 43.9, 51.5, 61.7, 70.0, 107.2, 107.6, 109.1, 119.0, 121.5, 128.0, 128.4, 136.8, 160.8, 166.6, 169.8, 175.4, and 187.0.

Methyl 3-(3-(2-methoxy-2-oxoethyl)-2-oxopiperidin-3-yl)-3-oxopropanoate (24). A solution of 8.8 g (28 mmol) of **23** in MeOH (40 mL) and $(MeO)_3CH$ (40 mL) was vigorously stirred for 10 min at 100 ºC-105 ºC. To this mixture was added 5.3 g (28 mmol) of *p*-TsOH•H_2O in one portion and the mixture was allowed to stir for 4 h. The solution was cooled to RT and concentrated under reduced pressure. The colorless residue obtained was subjected to flash chromatography on silica gel to give 7.5 g (99%) of **24** as a colorless oil; IR (neat) 3349, 2953, 1732, 1710, 1655, 1489, 1436, 1354, 1319, 1271, 1223, 1194, 1174 and 1002 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73-1.89 (m, 3H), 2.33-2.38 (m, 1H), 2.66 (d, 1H, *J* = 16.4 Hz), 3.01 (d, 1H, *J* = 16.4 Hz), 3.27-3.39 (m, 2H), 3.63 (s, 3H), 3.68 (s, 3H), 3.79 (dd, 1H, *J* = 19.6 and 16.8 Hz), 7.02 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.1, 28.9, 40.3, 42.7, 45.9, 52.1, 52.5, 57.8, 167.9, 170.9, 171.1 and 201.0; HRMS Calcd. for $[(C_{12}H_{17}NO_6) + H]^+$: 272.1134. Found: 272.1129.

A general procedure for the synthesis of indolyl diazo imides 25 and 26

In a 200 mL round bottomed flask a sample of 2-(1-tosyl-1*H*-indol-3-yl) acetic acid (1.5 equiv) was taken up in CH_2Cl_2. After stirring for 5 min, $(COCl)_2$ (4.0 equiv) was added dropwise together with 2 drops of DMF. The solution was stirred at RT for 4 h and was then concentrated under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 and the solution was added dropwise to a solution of the appropriate lactam **24** (1.0 mmol) containing an excess of 4Å mesh molecular sieves in CH_2Cl_2. The reaction mixture was allowed to stir at RT for 12 h, filtered through a pad of Celite and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography.

Methyl 3-(3-(2-benzyloxyethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)-acetyl)-piperidin-3-yl)-3-oxopropanoate was obtained as a colorless oil in 84% yield; IR (neat) 2954, 2872, 1752, 1683, 1593, 1446, 1360, 1290, 1160, 1115, 1086 and 976 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61-1.72 (m, 1H), 1.83 (pent, 2H, *J* = 7.2 Hz), 2.21-2.32 (m, 2H), 2.30 (s, 3H), 2.46 (dt, 1H, *J* = 10.4

and 7.2 Hz), 3.42-3.50 (m, 1H), 3.53-3.74 (m, 4H), 3.64 (s, 3H), 3.84 (d, 1H, *J* = 21.2 Hz), 4.20 (s, 2H), 4.38 (s, 2H), 7.16-7.32 (m, 9H), 7.46 (d, 1H, *J* = 8.4 Hz), 7.55 (s, 1H), 7.75 (d, 2H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.0, 21.8, 27.6, 35.6, 36.7, 44.6, 44.9, 52.6, 61.9, 65.9, 73.5, 113.8, 116.0, 120.0, 123.4, 124.9, 125.4, 127.0, 127.8, 127.9, 128.7, 130.1, 131.1, 135.1, 135.5, 137.8, 145.1, 168.0, 173.7, 174.0 and 200.1; HRMS Calcd. for $[(C_{35}H_{36}N_2O_8S) + H]^+$: 645.2271. Found: 645.2275.

Methyl 3-(3-(2-(benzyloxy)ethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)acetyl)-piperidin-3-yl)-2-diazo-3-oxopropanoate (25). To the above keto ester (1.0 equiv) in 140 mL of CH_3CN at 0 ºC was added 2.3 mL (1.0 equiv) of Et_3N. The solution was allowed to stir for 20 min and then 1.9 g (2.0 equiv) of mesyl azide was added and the reaction mixture was allowed to stir for 1.5 h. The solution was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel to give **25** as a pale yellow oil in 88% yield; IR (neat) 2982, 2864, 2167, 1707, 1687, 1446, 1368, 1303 and 1168 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.68-1.72 (m, 1H), 1.91-2.02 (m, 2H), 2.21-2.26 (m, 2H), 2.28 (s, 3H), 2.34 (dt, 1H, *J* = 14.4 and 6.0 Hz), 3.51 (dt, 1H, *J* = 10.0 and 6.0 Hz), 3.64-3.77 (m, 2H), 3.75 (s, 3H), 3.92 (d, 1H, *J* = 17.2 Hz), 4.21 (d, 1H, *J* = 17.2 Hz), 4.16-4.23 (m, 1H), 4.39 (s, 2H), 7.14-7.28 (m, 9H), 7.36 (d, 1H, *J* = 7.6 Hz), 7.43 (s, 1H), 7.72 (d, 2H, *J* = 8.0 Hz), 7.92 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 21.7, 30.5, 35.1, 35.2, 43.0, 52.7, 59.4, 67.3, 73.2, 113.7, 116.6, 119.9, 123.3, 124.8, 125.1, 127.0, 127.7, 127.8, 128.5, 130.0, 131.2, 135.1, 135.5, 138.3, 145.0, 161.8, 173.7, 174.4 and 190.6; HRMS Calcd. for $[(C_{35}H_{34}N_4O_8S) + H]^+$: 671.2176. Found: 671.2181.

Methyl 3-(3-(2-methoxy-2-oxoethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)acetyl)-piperidin-3-yl)-3-oxopropanoate was obtained as a colorless oil in 90% yield; IR (neat) 2953, 1738, 1703, 1689, 1596, 1446, 1396, 1363 and 1171 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.72-1.91 (m, 2H), 1.95-2.02 (m, 1H), 2.29 (s, 3H), 2.38 (dt, 1H, *J* = 14.0 and 4.0 Hz), 2.72 (d, 1H, *J* = 16.8 Hz), 3.19 (d, 1H, *J* = 16.8 Hz), 3.95 (dt, 1H, *J* = 12.4 and 4.4 Hz), 4.30 (dd, 1H, *J* = 25.6 and 17.2 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 7.22 (dt, 1H, *J* = 8.0 and 0.8 Hz), 7.30 (td, 1H, *J* = 8.0 and 1.2 Hz), 7.52 (d, 1H, *J* = 7.6 Hz), 7.61 (s, 1H), 7.76 (d, 2H, *J* = 8.4 Hz) and 7.97 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.7, 21.3, 28.8, 35.2, 40.1, 44.6, 52.1, 52.4, 60.8, 113.3, 115.7, 119.6, 123.0, 124.4, 125.0, 126.6, 129.7, 130.7, 134.7, 135.0, 144.7, 166.9, 170.5, 172.8, 173.6 and 199.4; HRMS Calcd. for $[(C_{29}H_{30}N_2O_9S) + H]^+$: 583.1750. Found: 583.1748.

Methyl 2-Diazo-3-(3-(2-methoxy-2-oxoethyl)-2-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)acetyl)piperidin-3-yl)-3-oxopropanoate (26). To the above keto ester (1.0 equiv) in 140 mL of CH_3CN at 0 ºC was added 2.3 mL (1.0 equiv) of Et_3N. The solution was allowed to stir for 20 min and then 1.9 g (2.0 equiv) of mesyl azide was added and the reaction mixture was allowed to stir for 1.5 h. The solution was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel to give **26** as a pale yellow solid in 89% yield, mp 79-80 ºC; IR (neat) 2954, 2143, 1688, 1649, 1437, 1356, 1329, 1294, 1195, 1170, 1127 and 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.80-1.95 (m, 2H), 2.25 (s, 3H), 2.29 (dd, 1H, *J* = 12.0 and 4.4 Hz), 2.48 (dt, 1H, *J* = 13.2 and 3.6 Hz), 2.85 (d, 2H, *J* = 4.0 Hz), 3.65 (s, 3H), 3.68-3.76 (m, 1H), 3.74 (s, 3H), 4.07 (dt, 1H, *J* = 13.2 and 4.0 Hz), 4.20 (dd, 1H, *J* = 19.6 and 17.6 Hz), 7.13 (d, 2H, *J* =

8.0 Hz), 7.17 (t, 1H, *J* = 8.0 Hz), 7.25 (td, 1H, *J* =8.0 and 1.2 Hz), 7.45 (d, 1H, *J* = 7.6 Hz), 7.52 (s, 1H), 7.71 (d, 2H, *J* = 8.4 Hz) and 7.92 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.1, 21.3, 27.3, 35.0, 37.2, 44.2, 51.7, 52.3, 60.0, 113.3, 115.9, 119.5, 122.9, 124.4, 124.8, 126.6, 129.6, 130.7, 134.7, 135.1, 144.6, 161.3, 170.7, 172.6, 173.9 and 189.2; Calcd. for $C_{29}H_{28}N_4O_9S$: C, 57.23; H, 4.64; N, 9.21. Found: C, 57.35; H, 4.75; N, 9.17.

Methyl 3-[3-(2-benzyloxyethyl)-2-oxo-piperidin-3-yl]-2-diazo-3-oxopropionate (27). To a stirred solution of 8.2 g (48 mmol) of the ethyl ester (**11**) of 2-oxopiperidine-3-carboxylic acid in 125 mL of THF at -78 °C was added 20 mL (48 mmol) of a 2.4 M *n*-butyllithium solution in hexane. The resulting solution was allowed to warm to 0 °C for 10 min and was re-cooled to -78 °C. At this point, 12.6 g (48 mmol) of 2-iodoethyl benzyl ether was added. The cooling bath was removed and the solution was heated at reflux for 3 days. The solution was allowed to cool to RT, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 10.2 g (70%) of ethyl 3-(2-benzyloxy-ethyl)-2-oxo-piperidine-3-carboxylate (**20**) as a colorless oil; IR (neat) 1729, 1669, 1194, 1119 and 1098 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 7.0 Hz), 1.78-1.90 (m, 1H), 1.95 (td, 1H, *J* = 13.2 and 4.0 Hz), 2.15-2.35 (m, 3H), 3.20-3.35 (m, 2H), 3.64 (td, 1H, *J* = 6.8 and 2.0 Hz), 4.10-4.23 (m, 2H), 4.46 (s, 2H), 6.03 (brs, 1H), and 7.20-7.73 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.3, 19.8, 30.4, 35.2, 42.5, 53.0, 61.7, 67.3, 73.1, 127.7, 127.8, 128.5, 138.6, 171.0 and 172.8.

To a solution of 23.4 g (77 mmol) the above compound in 1:1 THF (150 mL) and H_2O (150 mL) was added 3.7 g of LiOH (153 mol) and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was washed with ethyl acetate and acidified to pH 2. The aqueous layer was extracted with chloroform and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 19.2 g (91%) of 3-{2-benzyloxyethyl}-2-oxo-piperidine-3-carboxylic acid as a white solid; mp 102-103 °C; IR (neat) 1700, 1653, 1492,1454, 1202 and 1100 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.79-1.92 (m, 2H), 2.03-2.10 (m, 1H), 2.23-2.34 (m, 3H), 3.27-3.36 (m, 2H), 3.59-367 (m, 2H), 4.48 (s, 2H), 6.28 (brs, 1H), and 7.20-7.38 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 27.8, 37.9, 42.9, 50.7, 66.4, 73.4, 127.9, 128.6, 138.2 and 175.5; Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.87; H, 6.74; N, 4.96.

To a solution of 9.0 g (33 mmol) of the above carboxylic acid in CH_2Cl_2 (150 mL) was added 6.3 g (39 mmol) of 1,1'-carbonyldiimidazole, and the solution was allowed to stir at RT under N_2 for 12 h. The mixture was concentrated under reduced pressure and residue was dissolved in 150 mL of THF. In the meantime, 10.1 g (65 mmol) of potassium methyl malonate, 6.2 g (65 mmol) of powdered magnesium chloride and a catalytic amount of 4-(dimethylamino) pyridine (0.4 g (3.2 mmol)) were mixed in a solution of 0.4 L of THF and 0.2 mL of acetonitrile. After stirring for 2 h, the above lactam in THF was added dropwise to the malonate solution together with 9.0 mL (65 mmol) of triethylamine. The solution was allowed to stir at RT overnight and then 200 mL of 1*N* HCI was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and

concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 8.9 g (82%) of (*S*)-methyl 3-(3-(2-benzyloxyethyl)-2-oxopiperidin-3-yl)-3-oxopropanoate (**21**) as a colorless solid, mp 57-58 ºC; IR (neat) 1749, 1706, 1437, 1319 and 1103 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.53 (pent, 1H, *J* = 7.2 Hz), 1.66-1.75 (m, 2H), 2.08 (dt, 1H, *J* = 14.4 and 6.0 Hz), 2.28-2.42 (m, 2H), 3.14-3.21 (m, 2H), 3.37-3.43 (m, 1H), 3.49-3.54 (m, 1H), 3.58 (s, 3H), 3.64 (d, 1H, *J* = 16.6 Hz), 3.89 (d, 1H, *J* = 16.6 Hz), 3.35 (s, 2H) and 7.21-7.25 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.3, 27.4, 35.9, 41.9, 45.1, 51.7, 58.0, 65.7, 72.7, 127.2, 127.3, 128.0, 137.7, 167.9, 171.1 and 200.9; Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.91; H, 7.06; N, 4.31.

To a 3.5 g (10.4 mmol) sample of keto-ester **21** in acetonitrile (100 mL) was added 1.3 g (12.5 mmol) of triethylamine and the solution was vigorously stirred for 30 min. To this mixture was added 4.1 g (21 mmol) of mesyl azide and the solution was stirred at RT for an additional 10 h. The solution was concentrated under reduced pressure and recrystallized from ether and a trace of CH_2Cl_2 to give 3.5 g (93%) of **27** as a pale yellow solid: mp 122-124 °C; IR (neat) 2140, 1722, 1666, 1437, 1322 and 1202 cm^{-1}; ^{1}H- NMR (400 MHz, $CDCl_3$) δ 1.68-1.76 (m, 1H), 1.78-1.87 (m, 1H), 2.01-2.13 (m, 1H), 2.23-2.42 (m, 2H), 3.28-3.37 (m, 1H), 3.54-3.75 (m, 3H), 3.78 (s, 3H), 4.48 (s, 2H), 5.60 (brs, 1H) and 7.24-7.35 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.8, 29.3, 35.0, 42.6, 52.3, 56.6, 67.8, 73.2, 127.6, 127.9, 128.5, 138.8, 161.7, 172.5 and 191.2; Anal. Calcd. for $C_{18}H_{21}N_3O_5$ C, 60.16; H, 5.89; N, 11.69. Found: C, 60.32; H, 5.94; N, 11.13.

Ethyl 3-*tert*-butoxycarbonylmethyl-2-oxo-piperidine-3-carboxylate (20). To a stirred solution of 10.5 g (61 mmol) of ethyl 2-oxopiperidine-3-carboxylate (**11**) in 120 mL of THF at -78 °C was added 28 mL (67 mmol) of a 2.4 *M n*-butyllithium solution in hexane. The resulting solution was allowed to warm to 0 °C for 10 min and was re-cooled to -78 °C. At this point, 11.2 g (67 mmol) of *tert*-butyl bromoacetate was added followed by 4.5 g (13 mmol) of tetrabutylammonium iodide. The solution was allowed to warm to room temperature while stirring vigorously. After stirring for 15 h, the solvent was removed under reduced pressure and H_2O was added to the residue. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized using a mixture of ethyl acetate/hexane to give 13.9 g (80%) of the ethyl ester (**22**) of 3-*tert*-butoxycarbonylmethyl-2-oxo-piperidine-3-carboxylic acid as a white solid: mp 81-83 °C; IR (neat) 1733, 1674, 1366, 1246 and 1155 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.2 Hz), 1.38 (s, 9H), 1.70-1.76 (m, 1H), 1.86-1.96 (m, 1H), 2.25 (dt, 1H, *J* = 13.6 and 3.6 Hz), 2.11-2.18 (m, 1H), 2.71 (d, 1H, *J* = 16.8 Hz), 3.01 (d, 1H, *J* = 16.8 Hz), 3.29-3.35 (m, 2H), 4.10-4.20 (m, 2H) and 6.87 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1, 19.8, 28.1, 30.3, 40.8, 42.2, 51.7, 61.7, 81.0, 170.1, 170.3, and 172.0; Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.03; H, 8.12; N, 4.87.

A 5.4 g (19 mmol) sample of the above lactam **22** and 2.4 g of lithium hydroxide (57 mmol) in THF (50 mL) and H_2O (50 mL) was stirred at RT for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was washed with ethyl

acetate and acidified to pH 2. The aqueous phase was extracted with chloroform and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 4.5 g (91%) of 3-*tert*-butoxycarbonylmethyl-2-oxo-piperidine-3-carboxylic acid as a white solid: mp 102-104 °C; IR (neat) 3282, 1727, 1700, 1628, 1366, 1257 and 1155 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.78-2.10 (m, 3H), 2.30-2.38 (m, 1H), 2.68 (d, 1H, *J* = 16.4 Hz), 3,12 (d, 1H, *J* = 16.4 Hz), 3.32-3.46 (m, 2H) and 7.30 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.9, 28.2, 29.1, 41.8, 42.6, 51.4, 81.8, 170.0, 173.3 and 173.9; Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.03; H, 7.44; N, 5.44. Found: C, 56.28; H, 7.44; N, 5.36.

To a 2.1 g (8.3 mmol) sample of the above carboxylic acid in CH_2Cl_2 (50 mL) was added 1.6 g (10 mmol) of 1,1'-carbonyldiimidazole and the solution was allowed to stir at RT under argon for 12 h. The mixture was concentrated under reduced pressure and redissolved in 50 mL of THF. In the meantime, 2.6 g (17 mmol) of potassium methyl malonate, 1.6 g (17 mmol) of powdered magnesium chloride and a catalytic amount of 4-(dimethylamino)pyridine (0.1 g (0.8 mmol)) were mixed in a solution of 50 mL of THF and 25 mL of acetonitrile. After stirring for 2 h, the above lactam in THF was added dropwise to the malonate solution together with 2.3 mL (17 mmol) of triethylamine. The solution was allowed to stir at RT for 12 h and then 80 mL of 1 *N* HCl was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.3 g (61%) of **23** as an off-white solid: mp 102-104 °C; IR (neat) 1732, 1655, 1456, 1367, 1320 and 1156 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.75-1.90 (m, 3H), 2.42-2.49 (m, 1H), 2.69 (d, 1H, *J* = 16.4 Hz), 2.94 (d, 1H, *J* = 16.4 Hz), 3.28-3.43 (m, 2H), 3.72 (s, 1H), 3.77 (d, 1H, *J* = 16.6 Hz), 3.94 (d, 1H, *J* = 16.6 Hz) and 6.01 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.2, 28.2, 28.4, 41.9, 42.8, 45.6, 52.5, 58.1, 82.0, 168.1, 169.5, 170.7 and 200.8; Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.36; H, 7.40; N, 4.46.

To a 4.8 g (15 mmol) sample of **23** in acetonitrile (125 mL) was added 1.9 g (18 mmol) of triethylamine and the solution was vigorously stirred for 30 min. To this mixture was added 3.5 g (31 mmol) of mesyl azide and the solution was stirred at RT for an additional 10 h. The solution was concentrated under reduced pressure and recrystallized from ether which contained a trace of CH_2C_{l2} to give 5.0 g (96%) of **28** as a pale yellow solid: mp 152-154 °C; IR (neat) 2124, 1725, 1669, 1480, 1437, 1321 and 1153 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.80-2.00 (m, 2H), 2.29 (dt, 1H, *J* = 12.4 and 4.0 Hz), 2.68-2.74 (m, 1H), 2.77 (d, 1H, *J* = 16.2 Hz), 2.92 (d, 1H, *J* = 16.2 Hz), 3.28-3.39 (m, 1H), 3.64 (dt, 1H, *J* = 11.2 and 4.8 Hz), 4.22 (s, 3H) and 5.65 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.9, 25.7, 28.2, 38.4, 42.5, 52.4, 58.2, 80.8, 161.7, 170.4, 171.7 and 189.9; Anal. Calcd. for $C_{15}H_{21}N_3O_6$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.21; H, 6.43; N, 12.33.

A general procedure for the synthesis of the indoles 29 and 30. The 3-indole-acetic acid (1.1 equiv) was dissolved in CH_2Cl_2 and 4.0 equiv of oxalyl chloride was added dropwise. The solution was stirred overnight and then concentrated under reduced pressure. The resulting solid

was taken up in THF, which was immediately added to a vigorously stirred mixture containing 1.0 equiv of diazo lactam **27** or **28** and 4Å molecular sieves in THF. After stirring for 12 h, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography to give the desired coupled product (*i.e*., **29** or **30**).

Methyl ester of 3-{3-(2-benzyloxyethyl)-1-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-2-oxo-piperidin-3-yl}-2-diazo-3-oxo-propionic acid (29). Obtained as a colorless oil in 82% yield; IR (neat) 2143,1718,1685,1332 and 1146 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65-1.75 (m, 1H), 1.85-2.02 (m, 2H), 2.19-2.30 (m, 3H), 3.46-3.53 (m, 1H), 3.61-3.80 (m, 2H), 3.70 (s, 3H), 3.76 (s, 3H), 4.15-4.21 (m, 1H), 4.24 (s, 2H), 4.37 (d, 1H, *J* =15.8 Hz), 4.41 (d, 1H, *J* =15.8 Hz), 6.88 (s, 1H), 7.07-7.11 (m, 1H), 7.17-7.32 (m, 7H) and 7.54 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 30.2, 32.7, 34.7, 35.5, 44.5, 52.5, 59.3, 67.2, 73.0, 107.9, 109.3, 119.1, 119.2, 121.6, 127.6, 127.7, 128.2, 128.3, 128.5, 136.9, 138.4, 161.6, 173.6, 176.4 and 190.8.

Methyl ester of 3-{3-*tert*-butoxycarbonylmethyl-1-[2-(1-methyl-1*H*-indol-3-yl)-acetyl]-2-oxo-piperidin-3-yl}-2-diazo-3-oxo-propionic acid (30). Obtained as a colorless solid in 73% yield; mp 79-81°C; IR (neat) 2144, 1718, 1686, 1331 and 1152 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.61-1.70 (m, 1H), 1.84 (dt, 1H, *J* = 14.0 and 3.6 Hz), 1.98 (d, 1H, *J* = 15.8 Hz), 2.17 (td, 1H, *J* = 12.8 and 4.4 Hz), 2.31 (d, 1H, *J* = 15.8 Hz), 2.62-2.70 (m, 1H), 3.72 (td, 1H, *J* = 12.4 and 4.0 Hz), 3.78 (s, 6H), 4.05-4.12 (m, 1H), 4.11 (d, 1H, *J* = 16.4 Hz), 4.47 (d, 1H, *J* = 16.4 Hz), 6.96 (s, 1H), 7.10 (t, 1H, *J* = 7.6 Hz), 7.21 (t, 1H, *J* = 7.6 Hz), 7.29 (d, 1H, *J* = 7.6 Hz), and 7.51 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 26.7, 28.3, 32.8, 36.2, 36.7, 44.7, 52.6, 60.5, 80.1, 107.6, 109.4, 118.9, 119.4, 121.8, 128.1, 128.9, 136.9, 161.6, 169.8, 173.0, 177.0 and 189.9; Anal. Calcd. for $C_{26}H_{30}N_4O_7$: C, 61.17; H, 5.92; N, 10.97. Found: C, 61.02; H, 5.96; N, 10.79.

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