Synthesis of Ketone Analogues of Prolyl and Pipecolyl Ester FKBP12 Ligands

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The recently discovered small-molecule ligands for the peptidyl and prolyl isomerases (PPIase) of FKBP12 have been shown to possess powerful neuroprotective and neuroregenerative effects. Ketone analogues of the prolyl and pipecolyl esters, which mimic only the FKBP binding domain portion of FK506, are proposed and an efficient synthetic strategy is presented in this report, along with the preliminary results of in vitro and in vivo biological studies.

Introduction

FKBP12 is one of the best-characterized members of the class of proteins called immunophilins. It serves as a cellular receptor for the important immunosuppressant drug FK506.[1,2] FKBP12 is also known to have peptidyl and prolyl isomerase (PPIase, or rotamase) enzyme activity, catalyzing the interconversion of cis and trans rotamers of amide bonds in proline-containing peptide and protein substrates.[3] PPIases have been found to play critical roles in a variety of biological processes other than immunosuppresion, including protein trafficking and regulation of neurite outgrowth.[4] FK506 possesses two distinct binding domains: a FKBP12 binding domain and an "effector domain", which mediates interaction of the drug−immunophilin complex with the secondary protein target calcineurin (Figure 1). Inhibition of calcineurin by the FK506−FKBP12 complexes, not blocking the catalytic rotamase activity, is the mechanistic basis for the observed immunosuppressant effects of FK506.[5] Recently, FKBP12 has been found to be present in nearly 50-fold higher concentration in the central nervous system compared to the immune system.[6] It was subsequently found that FK506 mimicked the effects of trophic factors such as nerve growth factor in vitro, promoting neurite outgrowth in neuronal cultures at picomolar concentrations.[7] In vivo, FK506 promoted regeneration and repair of damaged facial[8] and sciatic nerves[9] in rats, suggesting therapeutic utility for FKBP12 ligands in treating neurological disorders.[4,10,11]

We reported previously that small-molecule ligands, such as GPI 1046 (Figure 1, **1**), for FKBP12 possess powerful neuroprotective and neuroregenerative properties in vitro and in vivo.[10,11] The neurotrophic effects of these compounds are independent of the immunosuppressive pathways because they lack the "effector domain" of FK506. Previously, work by ourselves and other groups exploring the SAR of small molecules that mimic only the FKBP binding domain portion of FK506 has focused on esters, thioesters, and amides of proline and pipecolic acid.[12−16] As part of our program exploring various classes of FKBP12 ligands and seeking more metabolically stable ligands, we now report the synthesis and biological evaluation of a series of ketone analogues of **1**, such as compound **5h** (Figure 1).

Chemistry

Syntheses of prolyl and pipecolyl ketones are relatively uncommon in the literature. In our ongoing structural probe of novel FKBP inhibitors, the ketone analogues were found to be the most challenging synthetically.

A retrosynthetic examination of target compounds such as **5h** (shown in Figure 2), analogue of **1**, initially suggested the synthesis should start by formation of the ketone through various alkylaryl Grignard reagents (method A). This would allow extensive SAR around both the alkyl (chain length) and aryl portions of the molecule. After exploring the two most popular electrophiles used in the literature for synthesizing ketones via Grignard reactions, we have determined that the Weinreb amide electrophile[17] gave the best yield and the cleanest reaction for the proline derivatives while the 2-pyridine carbothiolate[18] was preferred for the pipecolyl ring series. Therefore, as shown in Scheme 1, addition of Grignard reagents to the commercially available Weinreb amide derivative of Boc-proline **2** yielded intermediate ketones **3**. Deprotection of the Boc group using TFA followed by acylation with methyl chlorooxoacetate provided the desired oxamate intermediates **4**. Reaction with various Grignard reagents at −78 °C resulted in highly selective addition at the more electrophilic carbonyl of the ketoamide moiety, yielding the desired products **5** (see Table 1). Similarly, as shown in Scheme 2, the pipecolyl derivatives **11** (see Table 1) were synthesized starting from commercially available L-Boc-pipecolic acid **6**. As a side note, several other electrophiles including the prolinal were explored. The aldehyde was advantageous when sterically hindered and less reactive Grignard reagents were used; however, an extra oxidation step was required to convert the resultant alcohol to the ketone.

Although method A was successful for the synthesis of several simple phenyl alkyl ketone analogues, we soon encountered several problems and limitations with this approach. First, there were a limited number of commercially available Grignard reagents, requiring syn-

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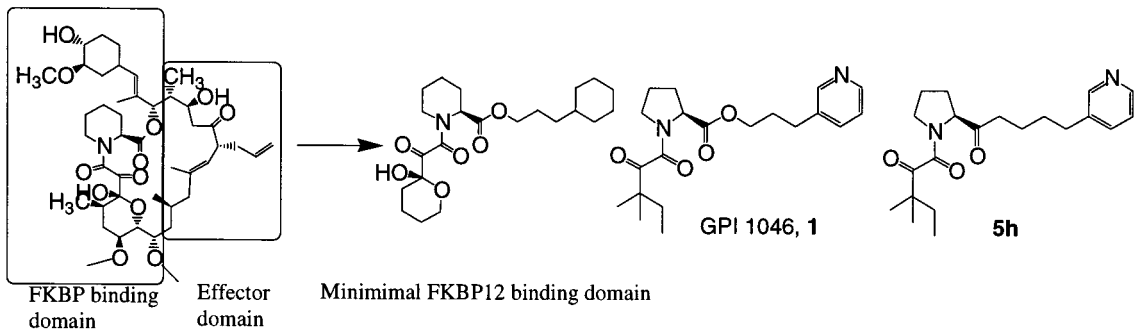


Figure 1. FK506 and small-molecule mimetics of the FKBP12 binding domain.

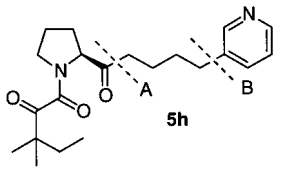
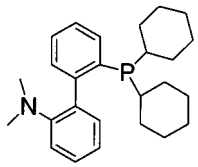


Figure 2. Synthetic approaches for the ketone compounds exemplified by **5h**.

thesis of the desired organometallic reagent from either an alcohol or halide for each compound. For instance, phenylbutyl Grignard **14** was obtained in two steps from the corresponding alcohol **12**, as shown in Scheme 3a. Second, in many cases obtaining the halide precursors, like the one for compound **5g** as shown in Scheme 3b, required a long and tedious synthesis. Alkyne **15**, reacting with **16**, was converted to **17** via palladium-mediated carbon−carbon coupling, followed by transformation of the alcohol to bromide **18**. Several attempts to make the corresponding Grignard **19** failed. Hence, **20** was obtained by saturation of the triple bond via hydrogenation, followed by benzyl protection of the phenolic alcohol. Finally, **21** was converted to the Grignard **22**. As shown in Scheme 3c, once again, we were unable to transform 4-bromobutylpyridine **23** into its Grignard **24**, which was needed for **5h**. Thus, it appeared that method A was not a practical and efficient route to obtain compounds needed particularly for SAR in the aryl region.

We therefore developed an alternative route based on bond dissection "B" in our retrosynthetic analysis (Figure 2). This route, shown in Scheme 4, proceeded through a common intermediate (**28** in Scheme 4) from which the final products could be made in the last step of the synthesis using various aromatic/heterocyclic halides through a Heck coupling.[19,20] As shown in Scheme 4, addition of the commercial Grignard reagent 3-butenylmagnesium bromide to the Boc-proline Weinreb amide of **2** yielded ketone intermediate **25**. Further elaboration via similar chemistry shown in Scheme 1 yielded **28**. Compound **28**, containing a terminal alkene, was subjected to a facile palladium-catalyzed coupling with various aromatic/heterocyclic halides, and the final products **5g,h** were obtained following the hydrogenation reaction.

When standard Heck reaction conditions were used, a significant amount (25−35%) of internal coupling side product **31** was produced from the reaction of **28** and 3-bromopyridine (Scheme 5). This was consistent with previous literature reports.[21,22] The internal coupling product compromised the yield and purification process, since it has a slightly lower R_f value than the terminal coupling product. To improve the yield of the desired terminal coupling product, we explored several different factors that may influence the product ratio, including palladium catalysts, phosphine ligands, solvents, and temperatures. We found that the recently reported bulky phosphine ligand **32**[23] could significantly suppress



the formation of the internal coupling product, and the desired product could be easily purified from the side product (<5%) by either silica chromatography or recrystallization. General application of this improved method will be the subject of a future publication.[24]

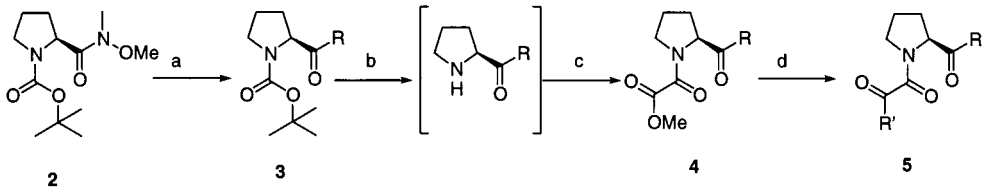
Diketopipecolic acid **33** was available in our laboratory from earlier work, and taking advantage of it as a starting material further shortened the synthesis. Compound **33** was converted to the carbothiolate **34**, and **35** was obtained after **34** was treated with a Grignard reagent made from the commercially available precursor 1-bromo-5-(trimethylsilyl)-4-pentyne (Scheme 6). The silyl protecting group on the terminal alkyne was removed to give **36**, which could be subsequently coupled to the aryl/heterocyclic group. It was interesting to note that the diketo moiety, hindered by the 1,1-dimethylpropyl or *tert*-butyl groups, showed remarkable resistance and remained intact even in the presence of excess Grignard reagent up to 0 °C. Further elaboration from **36** as described above resulted in the desired final product **11e** (see Table 1). **34** could also be converted to **11d** directly by treating it with the 5-phenylpentylmagnesium bromide.

In contrast, reaction of Grignards with the proline analogue of **38** or **39** led to significant addition to the amide carbonyl of the diketo moiety to yield **40** without producing appreciable amounts of the desired product **41** (Scheme 7). The fact that the prolylcarbonyl position was quite hindered[25] might explain partially the reactivity differences between the prolyl and pipecolyl series.

Biological Results and Discussion

Inhibition of the rotamase activity of FKBP-12 by test compounds was assayed as described previously,[13] and apparent K_i's were obtained and used as measures of relative ligand binding affinities. The compounds de-

Scheme 1[a]



[a] Reagents and conditions: (a) RMgX, THF, 0 °C; (b) 50% TFA, CH_2Cl_2; (c) methyl chlorooxoacetate, TEA, CH_2Cl_2, 0 °C; (d) R′MgX, THF, −78 °C, 3 h.

scribed are mimetics of the FKBP binding domain of FK506 (Figure 1) and, as expected, retain good affinity for FKBP12. In vitro results of compounds are shown in Table 1, and their inhibition constants range from low nanomolar to low micromolar values. By way of comparison, the ketone compounds were generally several-fold less potent as FKBP12 inhibitors than the corresponding esters or thioesters; however, they were generally an order of magnitude more potent than amides in this regard. The neurotrophic properties of these ketones were evaluated in an in vivo model of neurodegeneration. Parkinson's disease is a serious neurodegenerative disorder resulting from degeneration of the nigrostriatal dopaminergic pathway and subsequent decrease in dopaminergic transmission.[26] *N*-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin that selectively destroys dopaminergic neurons.[27] MPTP lesioning of dopaminergic neurons in mice was used to test the effectiveness of our compounds as an animal model of Parkinson's disease as described previously.[8] The data in Table 1 (both concurrent and post-MPTP) are shown as percent recovery of striatal dopaminergic innervation relative to MPTP-treated animals not receiving test drugs. Our studies indicated that these compounds were effective in restoring striatal innervation when administered orally at 10 mg/kg dose after lesioning with MPTP and they were as potent and efficacious as their ester/thioester amide analogues[12,15,16] in this mouse model. For example, compound **5h** regenerated striatal dopaminergic terminals post-MPTP-lesioning in a bell-shaped dose−response curve (Figure 3). It produced significant effects at doses as low as 0.1 mg/kg and regenerated 45% recovery somewhere between 0.4 and 1.0 mg/kg. The maximum recovery (around 50%) was consistent with what we had typically observed for many of our other compounds, such as **1**. However, compound **5h** was about 10-fold more potent (peak at 0.4 mg/kg) than **1**.

Conclusions

We have developed an efficient synthetic approach to the synthesis of (*N*-glyoxyl)prolyl and pipecolyl ketone compounds, and we believe they are the first reported examples of ketone compounds as FKBP12 ligands. Our biological results suggest that they are potent neurotrophic agents with potential therapeutic utility in treating degenerative disorders of the nervous system, such as Parkinson's disease.

Experimental Section

General Methods. All commercially available starting materials and solvents were reagent grade. Anhydrous tetrahydrofuran (THF) and diethyl ether were used as obtained from Sigma-Aldrich Inc. (*S*)-Pipecolic acid was obtained as the (*R*)-tartrate salt from Oxford Asymmetry. Analytical thin-layer chromatography was carried out using Merck DC-F_{254} precoated silica gel plates. Flash chromatography was performed using Kieselgel 60 (230−400 mesh) silica gel. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian 300 MHz or a Bruker 400 MHz instrument. Chemical shifts are reported in parts per million (ppm). Mass spectral analyses were performed by Oneida Research Services, Whitesboro, NY. Elemental analyses were determined by Atlantic Microlab, Norcross, GA, and are within ±0.4% of the calculated values unless otherwise noted.

2(*S*)-(4-Phenylbutyryl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3f). 2(*S*)-(Methoxymethylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester **2** (2.0 g, 7.74 mmol) was dissolved in anhydrous THF (10 mL), cooled to 0 °C, and treated with freshly prepared 4-phenylbutylmagnesium bromide **14** (2.1 equiv). The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. The reaction mixture was quenched with 2 × 50 mL of 1 N HCl and water. The resulting mixture was extracted with 2 × 100 mL of EtOAc. The organic phase was dried, concentrated, and purified on a silica gel column (25% EtOAc/hexane) to provide 1.33 g (54%) of the desired product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 9H); 1.66−1.87 (m, 6H); 2.32−2.42 (m, 2H); 2.49−2.52 (m, 2H); 3.32−3.51 (m, 2H); 4.12 (dd, 1H, J = 3.5, 7.0 Hz); 7.04−7.19 (m, 5H). TLC: R_f = 0.48 (25% EtOAc/hexane).

2(*S*)-Oxo-[2-(4-phenylbutyryl)pyrrolidin-1-yl]acetic Acid Methyl Ester (4f). A mixture of 2(*S*)-(4-phenylbutyryl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **3f** (1.33 g, 4.19 mmol) and trifluoroacetic acid (0.98 mL, 12.57 mmol) in methylene chloride (5 mL) was stirred overnight at room temperature. The reaction mixture was evaporated in vacuo to yield a thick oil and was used directly for the next step without purification.

A mixture of above product 2(*S*)-4-phenyl-1-pyrrolidin-2-yl-butan-1-one and triethylamine (4.05 g, 40.0 mmol) was dissolved in methylene chloride (20 mL) and stirred at 0 °C for 15 min. Methyl chlorooxoacetate (0.44 g, 4.61 mmol) was added dropwise, and the mixture was stirred for an additional 2 h at 0 °C. The reaction mixture was washed with water. The organic phase was dried, concentrated, and purified on a silica gel column (50% EtOAc/hexane) to yield a yellow oil, 0.56 g (44%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.66−1.87 (m, 4H); 2.32−2.42 (m, 2H); 2.49−2.67 (m, 4H); 3.62−3.78 (m, 2H); 3.82 (s, 3H); 4.68 (d, 1H, J = 6.8 Hz); 7.19−7.31 (m, 5H). TLC: R_f = 0.40 (50% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(4-phenylbutyryl)pyrrolidin-1-yl]butane-1,2-dione (5f). 2(*S*)-Oxo-[2-(4-phenylbutyryl)pyrrolidin-1-yl]acetic acid methyl ester **4f** (0.56 g, 1.8 mmol) was dissolved in anhydrous THF (10 mL), cooled to −78 °C, and treated with 1,1-dimethylethylmagnesium chloride (1.0 M, 2.04 mL). The reaction mixture was allowed to stir for 3 h. The reaction mixture was washed with saturated ammonium chloride. The organic phase was dried, concentrated, and purified on a silica gel column (25% EtOAc/hexane) to provide 0.44 g (72%) of the desired product as a clear oil. HPLC analysis using a chiral column indicated a sharp single peak (>95%, retention time of 5.65 min), suggesting **5f** is a single stereoisomer. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9H); 2.14−2.19 (m, 1H); 2.46−2.70 (m, 4H); 3.46 (dd, 1H, J = 6.5, 6.7, 10.4 Hz); 3.54 (dt, 1H, J = 7.1, 10.3 Hz); 4.59 (dd, 1H, J = 4.6,

Table 1. Structures, Methods, and Preliminary in Vitro and in Vivo Data for *N*-Glyoxylprolyl and Pipecolyl Ketones

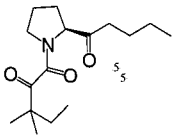
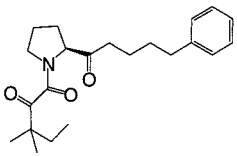
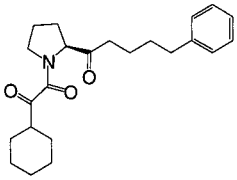
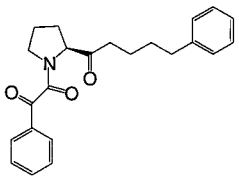
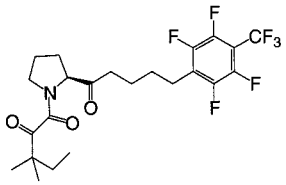
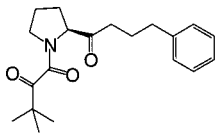
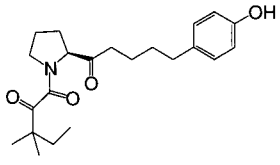
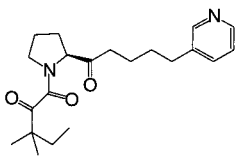
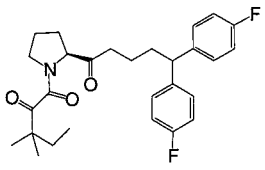
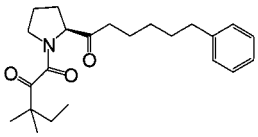
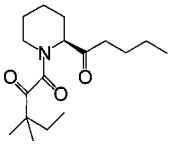
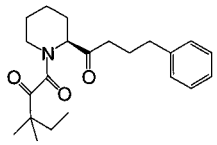
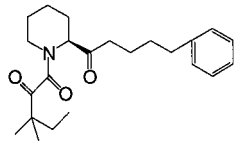
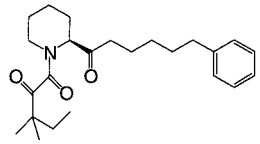
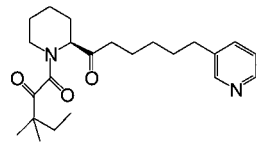
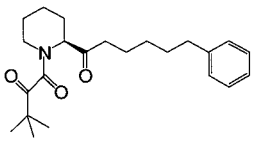
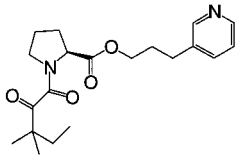
No	Structure	Method	Formula	Anal.	Inhibition[a] K_i, nM	% Recovery 4 mg/kg, s.c. Concurrent	% Recovery 10 mg/kg, p.o. post-MPTP
5a		A	$C_{16}H_{27}NO_3$	C, H, N	2000		
5b		A	$C_{22}H_{31}NO_3$	C, H, N	30	22.5 ± 3.6	
5c		A	$C_{23}H_{31}NO_3$	C, H, N	310	37.6 ± 3.6	62.2 ± 4.0
5d		A	$C_{23}H_{25}NO_3$	C, H, N	10,000		
5e		A/B	$C_{23}H_{36}NO_3F_7$	C, H, N	130	7.0 ± 3.0	27.0 ± 4.0
5f		A	$C_{20}H_{27}NO_3$	C, H, N	180	34.0 ± 7.0	35.0 ± 5.0
5g		A/B	$C_{22}H_{31}NO_4$	C, H, N	240		33.5 ± 3.0
5h		B	$C_{21}H_{30}N_2O_3$	C, H, N	210	38.0 ± 6.0	34.0 ± 5.0
5i		A	$C_{28}H_{33}NO_3F_2$	C, H, N	460	41.0 ± 6.0	54.0 ± 6.0

Table 1 (Continued)

No	Structure	Method	Formula	Anal.	Inhibition[a] K_i, nM	% Recovery 4 mg/kg, s.c. Concurrent	% Recovery 10 mg/kg, p.o. post-MPTP
5j		A	$C_{23}H_{33}NO_3$	C, H, N	3800	46.0 ± 4.0	48.0 ± 5.0
11a		A	$C_{17}H_{29}NO_3$	C, H, N	3400		
11b		A	$C_{22}H_{31}NO_3$	C, H, N	10,000		
11c		A	$C_{23}H_{33}NO_3$	C, H, N	790		
11d		A/B	$C_{24}H_{35}NO_3$	C, H, N	3000	46.3 ± 6.1	
11e		B	$C_{23}H_{34}N_2O_3$	C, H, N	900		
11f		A	$C_{23}H_{33}NO_3$	C, H, N	290	50.0 ± 6.0	36.0 ± 4.0
1					7.5[b]	39.0 ± 4.0[b]	35.0 ± 5.0[b]

[a] Values of kinetic constants are the means of at least three independent estimations. Standard deviations were generally lower than 15%. [b] Reference 14.

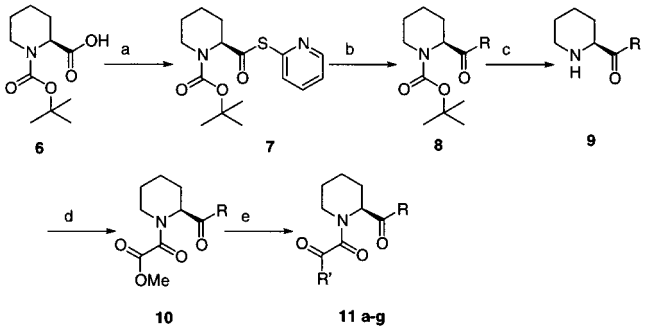
4.8 Hz); 7.19−7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.4, 207.7, 165.6, 141.9, 128.9, 128.7, 126.4, 64.2, 47.8, 43.5, 39.6, 35.3, 28.2, 26.6, 25.1, 22.7, Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25; O, 14.57. Found: C, 73.05; H, 8.34; N, 4.31. TLC: R_f = 0.52 (25% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-(2-pentanoylpyrrolidin-1-yl)pentane-1,2-dione (5a). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87−0.91 (m, 6H); 1.11 (s, 3H); 1.18 (s, 3H); 1.20−2.0 (m, 10H); 2.52 (t, 2H, J = 7.2 Hz); 3.45−3.62 (m, 2H); 4.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.6, 207.4, 165.5, 64.2, 47.7, 40.1, 32.3, 28.1, 25.6, 25.0, 24.1, 23.4, 22.6, 14.2, 9.2. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 66.59; H, 9.71; N, 4.85; O, 17.06. Found: C, 66.59; H, 9.61; N, 4.70. TLC: R_f = 0.60 (10% CH_2Cl_2/EtOAc).

2(*S*)-3,3-Dimethyl-1-[2-(5-phenylpentanoyl)pyrrolidin-1-yl]pentane-1,2-dione (5b). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, J = 7.5 Hz); 1.22 (s, 3H); 1.25 (s, 3H); 1.67 (m, 4H); 1.70−2.33 (m, 6H); 2.61 (t, 2H, J = 7.1 Hz); 3.52 (m, 2H); 4.17 (t, 2H, J = 6.2 Hz); 4.52 (m, 1H); 7.16−7.49 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.6, 207.5, 165.5, 142.8, 128.6, 128.5, 126.0, 64.3, 47.7, 43.0, 40.1, 36.2, 32.3, 28.1, 25.6, 25.0, 24.1, 22.8, 9.2. Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92; O, 13.43. Found: C, 73.48; H, 8.35; N, 3.69. TLC: R_f = 0.80 (10% CH_2Cl_2/EtOAc).

2(*S*)-1-Cyclohexyl-2-[2-(5-phenylpentanoyl)pyrrolidin-1-yl]ethane-1,2-dione (5c). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.0−1.40 (m, 6H); 1.56−2.20 (m, 12H); 2.61 (t, 2H, J = 7.2 Hz); 3.60−3.90 (m, 2H); 4.16 (t, 2H, J = 6.9 Hz); 4.48 (m, 1H); 4.85 (m, 1H); 7.14−7.28 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.2, 203.3, 164.2, 142.5, 128.8, 128.7, 126.1, 65.1, 48.2, 46.4, 40.3, 36.1, 31.3, 28.5, 27.9, 26.2, 25.9, 23.3, 22.3. Anal. Calcd

Scheme 2[a]



[a] Reagents and conditions: (a) PySSPy, TPP, MeCN, reflux or PySH, DCC, DMAP, CH_2Cl_2; (b) RMgX, THF, 0 °C; (c) 50% TFA, CH_2Cl_2; (d) methyl chlorooxoacetate, TEA, CH_2Cl_2, 0 °C; (e) R′MgX, THF, −78 °C, 3 h.

for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79; O, 12.99. Found: C, 74.78; H, 8.56; N, 3.70. TLC: R_f = 0.68 (25% EtOAc/hexane).

2(*S*)-1-Phenyl-2-[2-(5-phenylpentanoyl)pyrrolidin-1-yl]-ethane-1,2-dione (5d). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 (m, 4H); 1.70−2.20 (m, 4H); 2.63 (m, 2H); 3.71 (m, 2H); 4.19 (t, 2H, J = 7.2 Hz); 4.61 (m, 1H); 7.13−7.56 (m, 10H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.3, 197.6, 166.9, 141.9, 138.9, 132.4, 129.6, 129.3, 128.9, 128.8, 126.4, 60.0, 47.3, 39.5, 36.1, 29.1, 24.8, 23.2, 21.2. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 73.53; H, 6.71; N, 3.73; O, 13.21. Found: C, 73.48; H, 6.58; N, 3.13. TLC: R_f = 0.80 (10% CH_2Cl_2/EtOAc).

2(*S*)-1-3,3-Dimethyl-1-((2*S*)-2-{5-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]pentanoyl}-1-pyrrolidinyl)-1,2-pentanedione (5e). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, J = 7.5 Hz); 1.24 (s, 3H); 1.27 (s, 3H); 1.54−2.22 (m, 10H); 2.55 (m, 2H); 2.79 (m, 2H); 3.50 (m, 2H); 4.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 206.5, 206.0, 164.1, 146.2.0, 144.5, 142.4, 124.1, 100.3, 62.9, 45.9, 38.4, 33.2, 29.6, 27.2, 26.8, 23.8, 22.6, 22.0, 21.5, 21.0, 7.9. Anal. Calcd for $C_{23}H_{36}NO_3F_7$: C, 55.53; H, 5.27; N, 2.82. Found: C, 55.62; H, 5.32; N, 2.79. TLC: R_f = 0.70 (25% EtOAc/hexane).

2(*S*)-1-{2-[5,5-Bis-(4-fluorophenyl)pentanoyl]pyrrolidin-1-yl}-3,3-dimethylpentane-1,2-dione (5i). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, J = 7.5 Hz); 1.21 (s, 3H); 1.24 (s, 3H); 1.44−2.10 (m, 8H); 2.48 (m, 2H); 3.44−3.66 (m, 3H); 3.88 (t, 2H, J = 7.6 Hz); 4.53 (dd, 1H, J = 4.8, 8.7 Hz); 6.96 (d, 4H, J = 8.3 Hz); 7.17 (d, 4H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.9, 208.6, 167.1, 159.3, 141.4, 132.4, 119.6, 63.7, 47.5, 43.2, 40.5, 39.0, 37.8, 29.1, 24.6, 23.8, 23.2, 21.3, 9.2. Anal. Calcd for $C_{28}H_{33}NO_3F_2$: C, 71.62; H, 7.08; N, 2.98; O, 10.22; F, 8.09. Found: C, 71.53; H, 7.09; N, 2.92. TLC: R_f = 0.5 (25% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(6-phenylhexanoyl)pyrrolidin-1-yl]pentane-1,2-dione (5j). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87−0.92 (m, 3H); 1.16−1.40 (m, 8H); 1.60−1.71 (m, 6H); 1.73−2.06 (m, 5H); 2.56−2.66 (m, 3H); 3.47−3.55 (m, 2H); 4.58−4.62 (m, 1H); 7.18−7.20 (br, s, 3H); 7.27−7.32 (br s, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.6, 207.9, 165.4, 142.9, 128.8, 128.6, 126.0, 64.3, 47.8, 40.4, 36.1, 33.5, 31.6, 29.1, 28.2, 24.4, 24.1, 23.5, 23.4, 22.5, 9.35. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77; O, 12.92. Found: C, 74.14; H, 8.94; N, 3.75. TLC: R_f = 0.35 (25% EtOAc/hexane).

2-(Pyridin-2-ylsulfanylcarbonyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (7). A mixture of piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester **6** (3.0 g, 13.14 mmol), *N*,*N*′-dicyclohexylcarbodiimide (4.07 g, 19.71 mmol), 2-mercaptopyridine (1.75 g, 15.77 mmol), and 4-(dimethylamino)pyridine (0.1 g) was dissolved in methylene chloride (120 mL) and stirred overnight. The reaction mixture was filtered through Celite and concentrated to a yellow oil. The oil was purified on a silica gel column (40% EtOAc/hexane) to yield 3.0 g (71%) of the desired product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15−1.48 (m, 2H); 1.51 (s, 9H); 1.60−1.80 (m, 4H); 2.29−2.35 (m, 2H); 301−3.11 (m, 1H); 4.05−4.2 (m, 1H); 4.65 (br, s, 1H); 7.26−7.30 (m, 1H); 7.59−7.62 (m, 1H); 7.71−7.77 (m, 1H); 8.63 (br s, 1H). TLC: R_f = 0.56 (40% EtOAc/hexane).

2-(4-Phenylbutyryl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (8b). 2-(Pyridin-2-ylsulfanylcarbonyl)piperidine-1-carboxylic acid *tert*-butyl ester **7** (2.0 g, 7.74 mmol) was dissolved in anhydrous THF (10 mL), cooled to 0 °C, and treated with freshly prepared 3-phenylpropylmagnesium bromide (2.1 equiv). The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. The reaction mixture was quenched with 2 × 50 mL of water. The resulting mixture was extracted with 2 × 100 mL of EtOAc. The organic phase was dried, concentrated, and purified on a silica gel column (10% EtOAc/hexane) to provide 0.92 g (69%) of the desired product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15−1.36 (m, 2H); 1.42 (s, 9H); 1.66−1.87 (m, 4H); 1.87−1.93 (m, 2H); 2.39−2.44 (m, 2H); 2.56−2.61 (m, 2H); 2.82 (m, 1H); 4.06−4.11 (m, 1H); 4.52 (br s, 1H); 7.04−7.19 (m, 5H). TLC: R_f = 0.48 (25% EtOAc/hexane).

4-Phenyl-1-piperidin-2-yl-butan-1-one (9b). A mixture of 2-(4-phenylbutyryl)piperidine-1-carboxylic acid *tert*-butyl **8b** (0.92 g, 2.78 mmol) and trifluoroacetic acid (0.65 mL, 8.34 mmol) in methylene chloride (5 mL) was stirred overnight at room temperature. The reaction mixture was evaporated in vacuo to yield a thick oil used directly for the next step without purification.

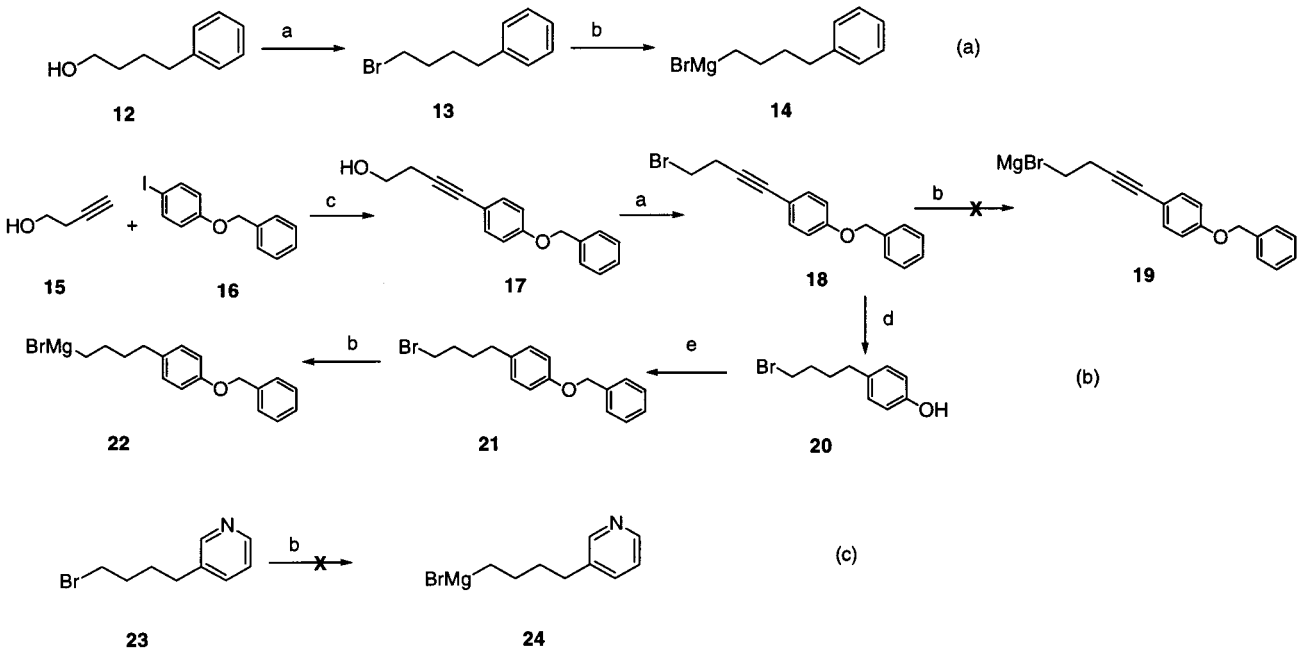
Oxo-[2-(4-phenylbutyryl)piperidin-1-yl]acetic Acid Methyl Ester (10b). A mixture of 4-phenyl-1-piperidin-2-yl-butan-1-one **9b** (0.65 g, 2.78 mmol) and triethylamine (1.16 g, 11.5 mmol) was dissolved in methylene chloride (20 mL) and stirred at 0 °C for 15 min. Methyl chlorooxoacetate (0.38 g, 3.06 mmol) was added dropwise, and the mixture was stirred for an additional 2 h at 0 °C. The reaction mixture was washed with water. The organic phase was dried, concentrated, and purified on a silica gel column (25% EtOAc/hexane) to yield clear oil, 0.77 g (88%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45−1.91 (m, 6H); 1.93−1.99 (m, 2H); 2.36−2.43 (m, 2H); 2.52−2.62 (m, 2H); 2.84 (m, 1H); 3.84 (s, 3H); 3.91−3.96 (m, 1H); 5.10 (d, 1H, J = 7.5 Hz); 7.18−7.30 (m, 5H). TLC: R_f = 0.48 (25% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(4-phenylbutyryl)piperidin-1-yl]pentane-1,2-dione (11b). Oxo-[2-(4-phenylbutyryl)piperidin-1-yl]acetic acid methyl ester **10b** (0.77 g, 2.43 mmol) was dissolved in anhydrous THF (15 mL), cooled to −78 °C, and treated with 1,1-dimethylpropylmagnesium chloride (1.0 M, 2.7 mL). The reaction mixture was allowed to stir for 3 h. The reaction mixture was washed with saturated ammonium chloride. The organic phase was dried, concentrated, and purified on a silica gel column (25% EtOAc/hexane) to provide 0.67 g (77%) of the desired product as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, 3H, J = 7.5); 1.21 (s, 3H); 1.24 (s, 3H); 1.31−1.78 (m, 7H); 1.94 (t, 2H, J = 7.3 Hz); 2.23 (br d, 1H, J = 13.5 Hz); 2.48 (t, 2H, J = 7.3 Hz); 2.63 (t, 2H, J = 8.1 Hz); 3.15 (dt, 1H, J = 12.5, 13.0 Hz); 3.37 (br d, 1H, J = 13.1 Hz); 5.10 (d, 1H, J = 5.3 Hz); 7.16−7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 210.9, 208.1, 170.7, 144.6, 131.6, 129.2, 126.4, 60.8, 49.9, 47.6, 41.5, 38.2, 35.6, 28.1, 27.1, 26.8, 26.3, 23.5, 9.2. Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92; O, 13.43. Found: C, 74.03; H, 8.80; N, 3.94. TLC: R_f = 0.55 (25% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-(2-pentanoylpiperidin-1-yl)pentane-1,2-dione (11a). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86 (t, 3H, J = 7.5 Hz); 1.15 (s, 3H); 1.18 (s, 3H); 1.11−1.72 (m, 11H); 2.19 (br, d, 1H, J = 13.5 Hz); 2.40 (t, 2H, J = 7.3 Hz); 3.09 (dt, 1H, J = 3.2, 12.4 Hz); 3.33 (br d, 1H, J = 13.9 Hz); 5.05 (d, 1H, J = 5.6 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.5, 208.3, 167.8, 62.9, 47.0, 44.8, 39.2, 33.1, 25.8, 25.5, 24.3, 23.9, 23.5, 22.7, 14.2, 9.1. Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12; H, 9.89; N, 4.74; O, 16.25. Found: C, 68.99; H, 9.83; N, 4.69. TLC: R_f = 0.83 (25% EtOAc/hexane).

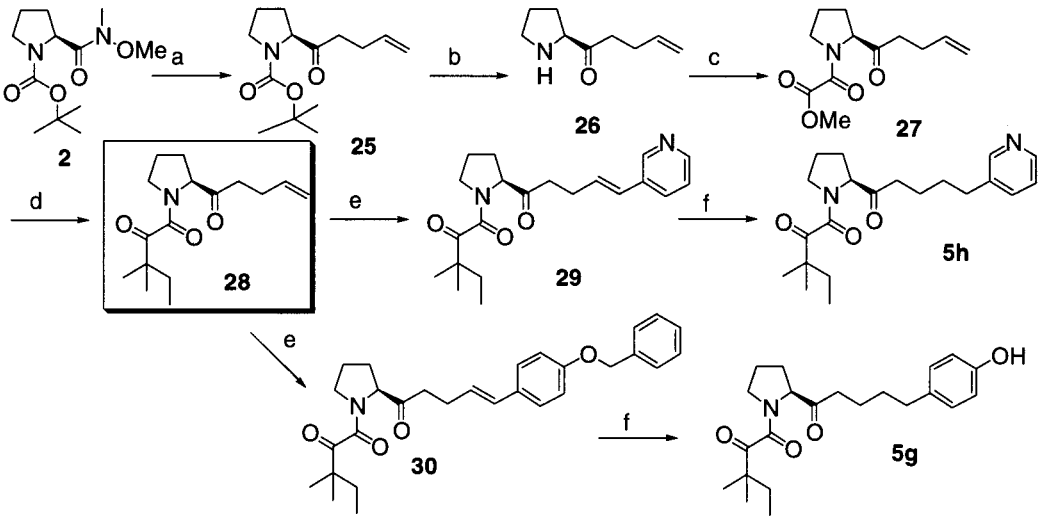
2(*S*)-3,3-Dimethyl-1-[2-(5-phenylpentanoyl)piperidin-1-yl]pentane-1,2-dione (11c). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86 (t, 3H, J = 7.5 Hz); 1.18 (s, 3H); 1.21 (s, 3H); 1.24−1.75 (m, 11H); 2.20 (br, d, 1H, J = 15.4 Hz); 2.76−2.79 (m, 2H); 2.89 (dd, 2H, J = 2.2, 8.8 Hz); 3.02 (dt, 1H, J = 12.8, 13.1 Hz);

Scheme 3[a]



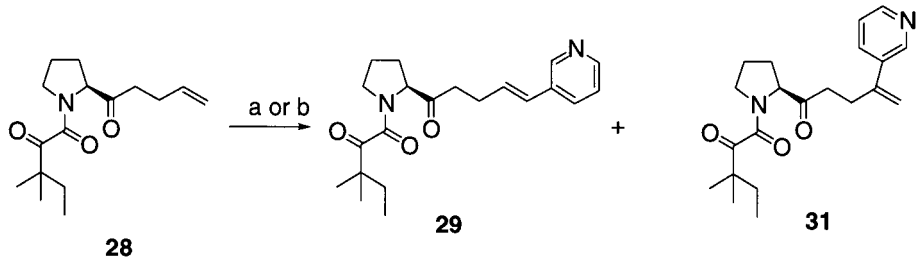
[a] Reagents and conditions: (a) CBr_4, TPP, CH_2Cl_2; (b) Mg, THF or ether, reflux; (c) $(PPh_3)_2PdCl_2$, CuI, TEA, CH_2Cl_2; (d) 10% Pd/C, H_2, EtOH; (e) benzyl bromide.

Scheme 4[a]



[a] Reagents and conditions: (a) $BrMgCH_2CH_2CHCH_2$, THF, 0 °C; (b) 50% TFA, CH_2Cl_2; (c) methyl chlorooxoacetate, TEA, CH_2Cl_2; (d) $ClMgC(CH_3)_2CH_2CH_3$, THF, −78 °C; (e) 3-bromopyridine or 4-benzyloxybromobenzene, $Pd(OAc)_2$, CuI, tri(orthotolyl)phosphine, TEA, CH_2Cl_2; (f) 10% Pd/C, H_2, EtOH.

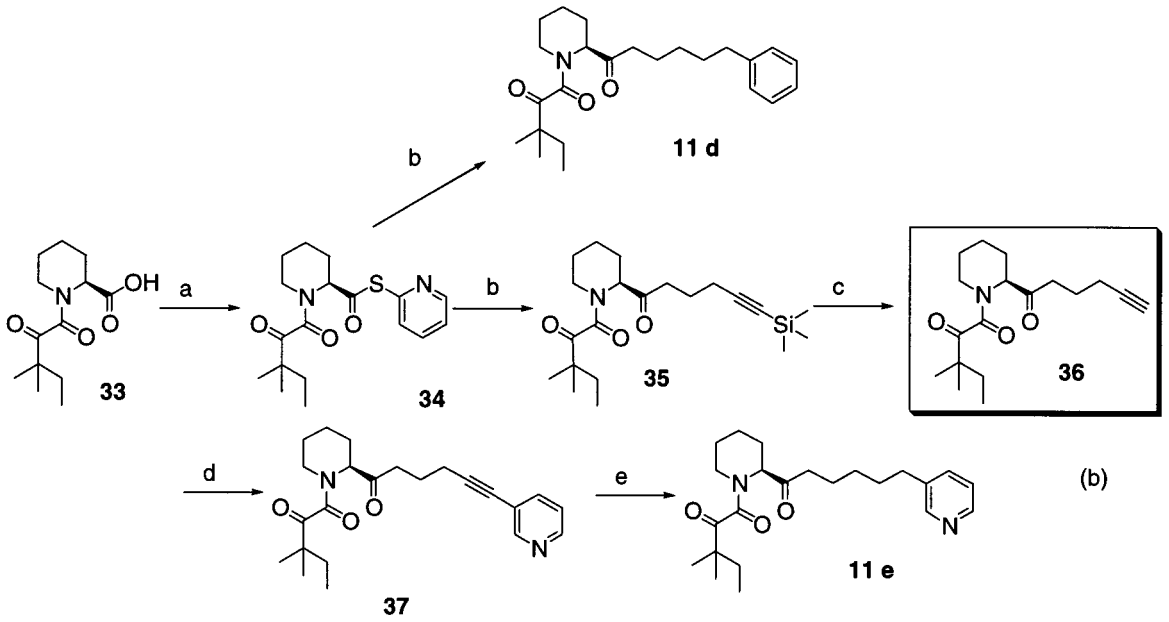
Scheme 5[a]



[a] Reagents and conditions: (a) 3-bromopyridine, $Pd(OAc)_2$, CuI, tri(orthotolyl)phosphine, TEA, CH_2Cl_2; (b) 3-bromopyridine, $Pd(OAc)_2$, **32**, TEA, CH_2Cl_2.

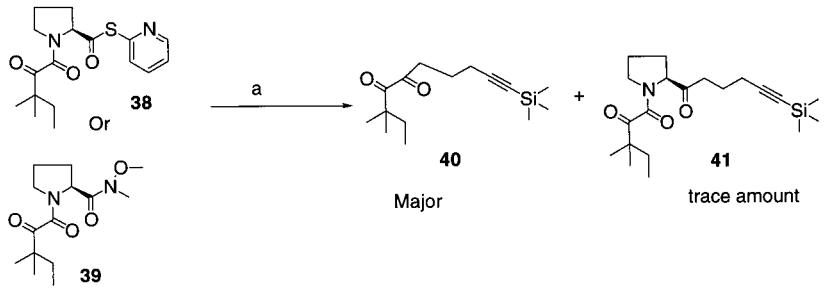
3.33 (br d, 1H, J = 13.2 Hz); 5.08 (d, 1H, J = 5.6 Hz); 7.14−7.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.3, 208.1, 167.8, 142.5, 128.8, 128.7, 126.2, 57.9, 47.0, 44.7, 39.3, 36.1, 32.9, 31.2, 25.5, 25.3, 24.3, 23.9, 23.5, 9.2. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77; O, 12.92. Found: C, 74.30; H, 8.93; N, 3.81. TLC: R_f = 0.48 (25% EtOAc/hexane).

Scheme 6[a]



[a] Reagents and conditions: (a) PySH, DCC, DMAP, CH_2Cl_2; (b) $BrMg(CH_2)_3CCSi(CH_3)_3$, THF; or $BrMg(CH_2)_5Ph$; (c) excess *t*BAF, THF; (d) 3-iodopyridine, $(PPh_3)_2PdCl_2$, CuI, TEA, CH_2Cl_2; (e) 10% Pd/C, H_2, EtOH.

Scheme 7[a]



[a] Reagents and conditions: (a) $BrMg(CH_2)_3CCSi(CH_3)_3$, THF.

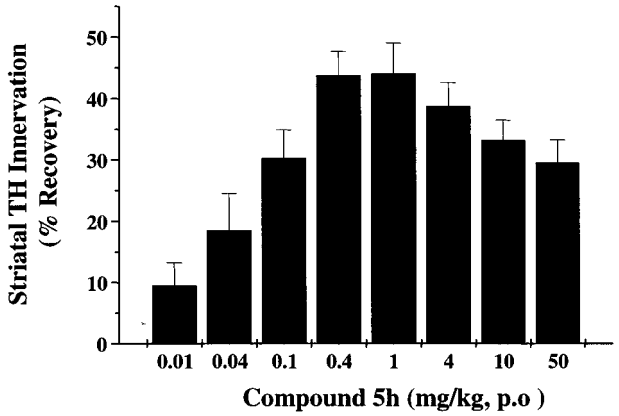


Figure 3. Dose−Rresponse curve of compound **5h** in the post-MPTP model.

2(*S*)-3,3-Dimethyl-1-[2-(6-phenylhexanoyl)piperidin-1-yl]pentane-1,2-dione (11d). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, J = 7.5 Hz); 1.22 (s, 3H); 1.24 (s, 3H); 1.32−1.78 (m, 13H); 2.21 (br, d, 1H, J = 13.5 Hz); 2.48 (t, 2H, J = 6.7 Hz); 2.64 (t, 2H, J = 7.0 Hz); 3.17 (dt, 1H, J = 12.6, 12.9 Hz); 3.38 (br d, 1H, J = 13.2 Hz); 5.10 (d, 1H, J = 5.5 Hz); 7.15−7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.4, 208.3, 167.8, 142.9, 128.8, 128.7, 126.1, 57.9, 47.1, 44.8, 39.5, 36.1, 32.9, 31.6, 29.2, 24.4, 23.9, 23.6, 23.5, 21.2, 9.18. Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.77; H, 9.15; N, 3.63; O, 12.45. Found: C, 74.80; H, 9.12; N, 3.61. TLC: R_f = 0.42 (25% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(6-phenylhexanoyl)piperidin-1-yl]butane-1,2-dione (11f). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 9H); 1.31−1.43 (m, 2H); 1.57−1.75 (m, 9H); 2.27 (br, d, 1H, J = 13.7 Hz); 2.45 (t, 2H, J = 7.4 Hz); 2.60 (t, 2H, J = 7.4 Hz); 3.19 (dt, 1H, J = 3.2, 12.4 Hz); 3.35 (br, d, 1H, J = 13.2 Hz); 5.11 (d, 1H, J = 13.2 Hz); 7.15−7.26 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.7, 208.3, 167.9, 142.9, 128.8, 128.7, 126.1, 57.9, 47.1, 44.9, 43.4, 39.5, 36.1, 31.6, 29.1, 26.6, 25.5, 23.6, 21.2. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77; O, 12.92. Found: C, 74.39; H, 8.89; N, 3.85. TLC: R_f = 0.79 (20% EtOAc/hexane).

4-(4-Benzyloxyphenyl)but-3-yn-1-ol (17). A mixture of but-3-yn-1-ol **15** (9.1 g, 128.35 mmol), 4-(4-benzyloxyphenyl) iodide **16** (43.79 g, 141.2 mmol), and triethylamine (16.88 g, 166.86 mmol) was dissolved in methylene chloride (350 mL) and stirred for 5 min at room temperature. Pd (cat.) (8.98 g, 12.8 mmol) and copper iodide (1.85 g, 9.7 0 mmol) was added to the reaction mixture and stirred for an additional hour. The mixture was refluxed at 50 °C overnight. The organic phase was concentrated and purified on a silica gel column (25−50% EtOAc/hexane) to provide 19.08 g (59%) of the desired product as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.69 (t, 2H, J = 4.0 Hz); 3.81 (t, 2H, J = 4.0 Hz); 5.07 (s, 2H); 7.36−7.45 (m, 9H). TLC: R_f = 0.5 (50% EtOAc/hexane).

4-(4-Benzyloxyphenyl)but-3-ynyl Bromide (18). A mixture of 4-(4-benzyloxyphenyl)-but-3-yn-1-ol **17** (19.08 g, 75.62 mmol) and carbon tetrabromide (30.09 g, 90.74 mmol) was dissolved in methylene chloride (400 mL) and cooled to 0 °C. Triphenylphosphine (23.8 g, 90.74 mmol) was added slowly in small portions. After being stirred for 1 h at 0 °C, the

reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated and purified on a silica gel column (5−30% EtOAc/hexane) to yield an orange solid, 21.8 g (92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.98 (t, 2H, J = 4.0 Hz); 3.54 (t, 2H, J = 4.0 Hz); 5.09 (s, 2H); 7.28−7.45 (m, 9H). TLC: R_f = 0.45 (30% EtOAc/hexane).

4-(4-Bromobut-1-ynyl)phenol (20). A mixture of 4-(4-benzyloxyphenyl)-but-3-ynl bromide **18** (21.8 g, 69.16 mmol) and 10 wt % palladium on carbon (6.0 g) was suspended in methanol (200 mL) and shaken on a Parr apparatus under hydrogen (50 psi) overnight. The reaction mixture was filtered through Celite and concentrated to a brown oil (14 g). The oil was used without further purification.

(4-Benzyloxyphenyl)butyl Bromide (21). 4-(4-Bromobut-1-ynyl)phenol **20** (14.0 g, 65.47 mmol) was dissolved in methylene chloride (200 mL). Benzyl bromide (12.3 g, 72.01 mmol) was added dropwise via a syringe and allowed to stir at room temperature for 1 h. The reaction mixture was warmed to reflux (50 °C) and stirred overnight. After cooling to room temperature, the reaction mixture was washed with water. The organic phase was dried, concentrated, and purified on a silica gel column (5−10% EtOAc/hexane) to yield the desired product as a yellow oil, 13.32 g (64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.75−1.83 (m, 2H); 1.89−1.96 (m, 2H); 2.63 (t, 2H, J = 7.5 Hz); 3.46 (t, 2H, J = 6.5 Hz); 5.09 (s, 2H); 6.96 (d, 2H, J = 9.0 Hz); 7.14 (d, 2H, J = 9.0 Hz); 7.35−7.49 (m, 5H). TLC: R_f = 0.8 (5% EtOAc/hexane).

(4-Benzyloxyphenyl)butylmagnesium Bromide (22). Magnesium turnings (1.52 g, 62.59 mmol) was stirred overnight under an inert atmosphere. (4-Benzyloxyphenyl)butyl bromide **21** (13.32 g, 41.72 mmol) and an iodine crystal were dissolved in anhydrous THF (40 mL) and added to the stirring magnesium slowly until initiation occurred. Continuous addition was allowed to sustain the reaction, at which time the reaction mixture was refluxed for an additional 2 h. The result was used directly for the next step.

***tert*-Butyl 2-Pent-4-enoylpyrrolidinecarboxylate (25).** To a solution of 3-propenylmagnesium bromide (97 mL of a 0.5 M solution; 48.4 mmol) in THF (15 mL), cooled to 0 °C and under a nitrogen atmosphere, was added dropwise with stirring a solution of *tert*-butyl 2-(*N*-methoxy-*N*-methylcarbamoyl)pyrrolidinecarboxylate **2** (5.0 g, 19.4 mmol) in 15 mL of THF. The mixture was stirred overnight while slowly warming to room temperature. The reaction was quenched by the addition of 80 mL of saturated NH_4Cl followed by 50 mL of ethyl acetate and 20 mL of water. The layers were separated, and the aqueous layer was extracted with 2 × 100 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the crude product was purified on a silica gel column with 10% EtOAc in hexane to obtain the olefin **25** as a clear oil, 4.30 g (88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 9H); 1.78−1.91 (m, 3H); 2.07−2.22 (m, 1H); 2.30−2.37 (m, 2H); 2.45−2.62 (m, 2H); 3.40−3.58 (m, 2H); 4.22−4.25 (m, 1H); 4.95−5.07 (m, 2H); 5.75−5.86 (m, 1H). TLC: R_f = 0.7 (33% EtOAc/hexane).

Methyl 2-Oxo-2-(2-pent-4-enoylpyrrolidinyl)acetate (27). Trifluoroacetic acid (65.7 g, 576 mmol) was added dropwise to a solution of 24.3 g (96 mmol) of **25** in 45 mL of methylene chloride, and the mixture was cooled to 0 °C. After being stirred for 4 h, the mixture was concentrated in vacuo to remove TFA. The residue was dissolved in 800 mL of methylene chloride and treated with triethylamine (20 g, 198 mmol) while stirring and cooling the mixture in an ice bath. Methyl oxalyl chloride (13.5 g, 106 mmol) was added as a solution in 40 mL of methylene chloride in 10 mL portions each followed by 5 mL of Et_3N. After the addition, a final 10 mL portion of Et_3N was added and the mixture was stirred overnight. It was concentrated, treated with 100 mL of 1:1 EtOAc/hexane and filtered to remove solids, and the concentrated residue was purified on silica gel, eluting with 1:1 hexane/EtOAc to obtain oxamate **2** as a brownish oil, 18.80 g (82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77−1.92 (m, 2H); 1.94−2.05 (m, 2H); 2.30−2.40 (m, 2H); 2.55−2.75 (m, 2H); 3.65−3.75 (m, 2H); 3.79 (s, 3H); 4.95−5.10 (m, 3H); 5.75−5.85 (m, 1H). TLC: R_f = 0.2 (40% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-1,2-dione (28). A solution of oxamate **27** (21.0 g, 88 mmol) in 150 mL of THF was cooled to −78 °C, under nitrogen, and treated with 200 mL (180 mmol) of 0.9 M 3,3-dimethylpropylmagnesium chloride. After the mixture was stirred for 2.5 h, TLC indicated that the reaction was complete. It was quenched with 300 mL of saturated NH_4Cl followed by 200 mL of EtOAc. The layers were separated, and the aqueous layer was extracted once more with 300 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the product was purified on silica gel with 20% EtOAc in hexane to obtain **28** as a light-yellow oil, 21.0 g (85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, J = 7.5 Hz); 1.21 (s, 6H); 1.64−1.95 (m, 5H); 2.14−2.18 (m, 1H); 2.32−2.40 (m, 2H); 2.60−2.72 (m, 2H); 3.47−3.62 (m, 2H); 4.57−4.61 (m, 1H); 4.97−5.07 (m, 2H); 5.78−5.84 (m, 1H). TLC: R_f = 0.7 (2:3 EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(5-(3-pyridyl)pent-4-enoyl)pyrrolidinyl]pentane-1,2-dione (29). To a solution of olefin **28** (500 mg, 1.78 mmol) in 7 mL of Et_3N was added 3-bromopyridine (310 mg, 1.96 mmol), palladium(II) acetate (20 mg, 0.09 mmol), and tri(orthotolyl)phosphine (108 mg, 0.36 mmol), and the mixture was refluxed overnight. The mixture was concentrated, and the products were purified on a silica gel column, eluting with a gradient from 50% EtOAc in hexane to 75% EtOAc to obtain **29** as a light-brown oil, 480 mg (75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, J = 7.5 Hz); 1.21 (s, 6H); 1.62−2.02 (m, 6H); 2.12−2.23 (m, 1H); 2.50−2.61 (m, 2H); 2.66−2.88 (m, 2H); 3.42−3.59 (m, 2H); 4.60−4.63 (m, 1H); 6.23−6.32 (m, 1H); 6.41 (d, 1H, J = 15.9 Hz); 7.19−7.23 (m, 1H); 7.65 (dt, 1H, J = 8.0, 2.0 Hz); 8.43 (dd, 1H, J = 4.5, 2.0 Hz); 8.54 (d, 1H, J = 2.0 Hz). TLC: R_f = 0.5 (80% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(5-(3-pyridyl)pentanoyl)pyrrolidinyl]pentane-1,2-dione (5h). Platinum oxide (12 mg) was added to a solution of **29** (300 mg, 0.84 mmol) in methanol (8 mL). The mixture was hydrogenated at 1 atm for 2.5 h and was then filtered through Celite and concentrated. Eluting through a short bed of silica gel (100% EtOAc) furnished analytically pure material, 260 mg (87%). HPLC analysis using a chiral column indicated a sharp single peak (>95%, retention time of 8.65 min), suggesting **5h** is a single stereoisomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, J = 7.5 Hz); 1.21 (s, 6H); 1.61−1.66 (m, 4H); 1.68−1.72 (m, 2H); 1.77−1.80 (m, 1H); 1.94−1.99 (m, 2H); 2.13−2.16 (m, 1H); 2.50−2.56 (m, 1H); 2.60−2.66 (m, 2H); 3.47−3.50 (m, 1H); 3.52−3.55 (m, 1H); 4.57 (dd, 1H, J = 8.8, 4.8 Hz); 7.18−7.22 (m, 1H); 7.49 (d, 1H, J = 7.8 Hz); 8.42−8.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 208.2, 207.6, 165.4, 150.0, 147.5, 137.8, 136.4, 123.7, 64.2, 47.3, 40.0, 38.1, 33.2, 33.1, 30.9, 28.2, 24.3, 23.4, 23.0, 9.3. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.15; H, 8.54; N, 7.76. TLC: R_f = 0.30 (4:1 EtOAc/hexane).

Note: The final hydrogenation step may be done using 10% Pd/C and hydrogenating for 5 h at 60 psi. Ethanol or ethyl acetate may be used instead of methanol.

2(*S*)-3,3-Dimethyl-1-(2-{5-[4-(phenylmethoxy)phenyl]-pent-4-enoyl}pyrrolidinyl)pentane-1,2-dione (30). A solution of 3,3-dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-1,2-dione **28** (1.73 g, 6.20 mmol), 4-benzyloxybromobenzene (1.80 g, 6.83 mmol), palladium(II) acetate (70 mg, 0.31 mmol), and tri(orthotolyl)phosphine (380 mg, 1.24 mmol) in triethylamine (23 mL) was refluxed overnight. The mixture was concentrated in vacuo and purified on a silica gel column, eluting with a gradient from 10% EtOAc/hexane to 20% EtOAc/hexane to obtain 1.72 g (60%) of **30** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, J = 7.5 Hz); 1.24 (s, 6H); 1.60−2.00 (m, 5H); 2.10−2.33 (m, 1H); 2.40−2.60 (m, 2H); 2.62−2.82 (m, 2H); 3.38−3.62 (m, 2H); 4.61 (q, 1H, J = 4.5 Hz); 5.05 (s, 2H); 6.05 (dt, 1H, J = 16.0, 4.5 Hz); 6.36 (d, 1H, J = 16.0 Hz); 6.90 (d, 2H, J = 8.5 Hz); 7.25 (d, 2H, J = 8.5); 7.28−7.46 (m, 5H). TLC: R_f = 0.7 (50% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-{2-[5-(4-hydroxyphenyl)pentanoyl]-pyrrolidinyl}pentane-1,2-dione (5g). A mixture of 1.63 g (3.53 mmol) of **30** and 400 mg of 10% Pd/C in 100 mL of EtOAc was hydrogenated at 50 psi overnight. The mixture was filtered through Celite, concentrated, and chromatographed (25% EtOAc/hexane) to obtain 800 mg (61%) of **5g**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, J = 7.50 Hz); 1.21 (s, 6H); 1.49−1.72 (m, 4H); 1.74−1.86 (m, 2H); 1.87−1.98 (m, 2H); 2.10−2.21 (m, 1H); 2.46−2.63 (m, 4H); 3.43−3.68 (m, 3H); 4.59 (q, 1H, J = 4.5 Hz); 6.72 (d, 2H, J = 8.40 Hz); 7.03(d, 2H, J = 8.40 Hz). ^{13} C NMR ($CDCl_3$, 400 MHz): δ 208.7, 208.5, 165.9, 154.3, 132.4, 129.6, 116.6, 62.1, 47.1, 41.5, 37.8, 35.7, 31.6, 29.1, 24.6, 23.8, 23.5, 21.6, 9.1. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.64; H, 8.44; N, 3.65. TLC: R_f = 0.45 (75% hexane/EtOAc).

2(*S*)-1-(3,3-Dimethyl-2-oxopentanoyl)piperidine-2-carbothioic Acid Pyridin-2-yl Ester (34). A mixture of 2(*S*)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carboxylic acid **33** (6.3 g, 24.7 mmol), *N*,*N*′-dicyclohexylcarbodiimide (7.6 g, 37.0 mmol), 2-mercaptopyridine (3.02 g, 27.2 mmol), and 4-(dimethylamino)pyridine (0.91 g, 7.41 mmol) was suspended in methylene chloride (300 mL) and stirred at room temperature overnight. The reaction mixture was filtered through Celite, and the organic phase was concentrated in vacuo to yield a clear oil. The oil was purified on a silica gel column (25−35% EtOAc/hexane) to provide 8 g (83%) of the desired product as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, 3H, J = 7.5 Hz); 1.26 (s, 3H); 1.31 (s, 3H); 1.66−1.84 (m, 7H); 2.45−2.48 (m, 1H); 3.34−3.41 (m, 1H); 3.46−3.50 (m, 1H); 5.50 (d, 1H, J = 5.5 Hz); 7.34 (dd, 1H, J = 1.0, 7.5 Hz); 7.61 (d, 1H, J = 8.0 Hz); 7.78 (dt, 1H, J = 2.0, 8.0 Hz); 8.66−8.68 (m, 1H). TLC: R_f = 0.65 (10% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(6-trimethylsilanyl-hex-5-ynoyl)-piperidin-1-yl]pentane-1,2-dione (35). 2(*S*)-1-(3,3-Dimethyl-2-oxopentanoyl)piperidine-2-carbothioic acid pyridin-2-yl ester **34** (1.5 g, 4.30 mmol) was dissolved in anhydrous THF (20 mL), cooled to 0 °C, and treated with freshly prepared (5-trimethylsilyl-pent-1-ynyl)magnesium bromide (8 mL). The reaction mixture was allowed to stir for 4 h. The reaction mixture was washed with saturated ammonium chloride. The organic phase was dried, concentrated, and purified on a silica gel column (25% EtOAc/hexane) to provide 1.35 g (83%) of desired product as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75 (t, 3H, J = 7.5 Hz); 1.08 (s, 3H); 1.11 (s, 3H); 1.22−1.76 (m, 9H); 2.12−2.21 (m, 3H); 2.46−2.50 (m, 1H); 2.98−3.10 (m, 1H); 3.25 (br d, 1H, J = 13.0 Hz); 4.98 (d, 1H, J = 5.5 Hz). TLC: R_f = 0.65 (10% EtOAc/hexane).

2(*S*)-1-(2-Hex-5-ynoylpiperidin-1-yl)-3,3-dimethylpentane-1,2-dione (36). 2(*S*)-3,3-Dimethyl-1-[2-(6-trimethylsilanyl-hex-5-ynoyl)piperidin-1-yl]pentane-1,2-dione **35** (0.5 g, 1.32 mmol) was dissolved in anhydrous THF (5 mL), cooled to −78 °C, and treated with tetrabutylammonium fluoride (1.0 M, 6.6 mL). The reaction mixture was allowed to stir for 2 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water. The organic phase was dried, concentrated, and purified on a silica gel column (25% EtOAc/hexane) to provide 0.3 g (75%) of the desired product as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75 (t, 3H, J = 7.5 Hz); 1.08 (s, 3H); 1.11 (s, 3H); 1.22−1.76 (m, 10H); 2.12−2.21 (m, 3H); 2.46−2.50 (m, 1H); 2.98−3.10 (m, 1H); 3.25 (br d, 1H, J = 13.0 Hz); 4.98 (d, 1H, J = 5.5 Hz). TLC: R_f = 0.45 (10% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(6-pyridin-3-yl-hex-5-ynoyl)piperidin-1-yl]pentane-1,2-dione (37). A mixture of 2(*S*)-1-(2-hex-5-ynoylpiperidin-1-yl)-3,3-dimethylpentane-1,2-dione **36** (0.85 g, 2.78 mmol), 3-iodopyridine (0.63 g, 3.06 mmol), and triethylamine (0.37 g, 3.64 mmol) was dissolved in methylene chloride (25 mL) and allowed to stir for 5 min at room temperature. $(PPh_3)_2PdCl_2$ (0.2 g, 0.28 mmol) and copper iodide (0.04 g, 0.21 mmol) were added to the reaction mixture and stirred for an additional hour. The mixture was refluxed at 50 °C overnight. The organic phase was concentrated and purified on a silica gel column (60% EtOAc/hexane) to provide 0.6 g (61%) of the desired product as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75 (t, 3H, J = 7.5 Hz); 1.08 (s, 3H); 1.11 (s, 3H); 1.22−1.76 (m, 9H); 2.12−2.21 (m, 3H); 2.46−2.50 (m, 1H); 2.98−3.10 (m, 1H); 3.25 (br, d, 1H, J = 13.0 Hz); 4.98 (d, 1H, J = 5.5 Hz); 7.09−7.12 (m, 1H); 7.54−7.58 (m, 1H); 8.36 (br s, 1H); 8.49 (br s, 1H). TLC: R_f = 0.52 (60% EtOAc/hexane).

2(*S*)-3,3-Dimethyl-1-[2-(6-pyridin-3-yl-hexanoyl)piperidin-1-yl]pentane-1,2-dione (11e). A mixture of 2(*S*)-3,3-dimethyl-1-[2-(6-pyridin-3-yl-hex-5-ynoyl)piperidin-1-yl]pentane-1,2-dione **37** (0.61 g, 1.59 mmol) and platinum oxide (0.1 g, 0.44 mmol) was suspended in methanol (5 mL). The reaction mixture was placed under a hydrogen atmosphere (1 atm) and was stirred overnight. It was filtered through Celite, concentrated, and purified on a silica gel column, eluting with 50% EtOAc/hexane to yield 0.45 g (73%) of the desired product as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (br s, 2H); 1.21 (s, 3H); 1.24 (s, 3H); 1.28−1.74 (m, 13H); 2.27 (br d, 1H, J = 13.0 Hz); 2.63 (t, 2H, J = 7.7 Hz); 3.22 (m, 1H); 3.40 (br, d, 1H, J = 12.8 Hz); 4.16 (t, 2H, J = 6.4 Hz); 5.22 (d, 1H, J = 5.4 Hz); 7.26 (m, 1H); 7.51 (d, 1H, J = 7.7 Hz); 8.45 (s, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 208.4, 208.3, 167.7, 150.5, 147.5, 138.1, 136.4, 124.3, 58.0, 47.1, 44.7, 39.5, 36.1, 32.9, 31.6, 29.1, 25.5, 24.3, 23.9, 23.5, 21.2, 9.2. Anal. Calcd for $C_{23}H_{34}N_2O_3 \cdot 0.6H_2O$: C, 69.52; H, 8.93; N, 7.05; O, 14.50. Found: C, 69.33; H, 8.62; N, 7.17. TLC: R_f = 0.52 (60% EtOAc/hexane).

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