Synthesis of 1-Oxo-1-(3-pyridazinyl) Derivatives – Potent Inhibitors of Fatty Acid Amide Hydrolase (FAAH): An Improved and Optimized Procedure

Goffredo Rosini,*[a] Daniele G. Andreotti,[b] Primiano D'Ambrosio,[a] Emanuela Marotta,[a] Alessandro Tinarelli,[a] Paolo Righi[a]

[a] Dipartimento di Chimica Organica 'A. Mangini' – Alma Mater Studiorum, Università di Bologna, Viale del Risorgimento 4, 40136 Bologna, Italy
Fax +39(051)2093654; E-mail: goffredo.rosini@unibo.it

[b] GlaxoSmithKline, Medicine Research Centre, Via A. Fleming 4, 37135 Verona, Italy

Received 18 May 2007; revised 19 June 2007

Abstract: A greatly improved procedure for the preparation of long-chain α-ketopyridazines, a class of potent inhibitors of fatty acid amide hydrolase (FAAH), is described. This optimization study shows a great dependence of the yields of desired products on the pyrididazinyl lithium/Weinreb amide ratio and offers a general approach to this kind of compound.

Key words: 3-acylpyridazines, regioselective acylations, FAAH inhibitors, Weinreb amides, lithiation, drugs

Fatty acid amides (FAAs) represent a class of neuromodulatory lipids that includes the endogenous sleep-inducing substance oleamide and the endocannabinoid anandamide (Figure 1). Fatty acid amide hydrolase (FAAH) is an internal membrane protein (IMP) that hydrolyzes bioactive amides, therefore, the enzyme is responsible for the degradation of oleamide and anandamide.[1]

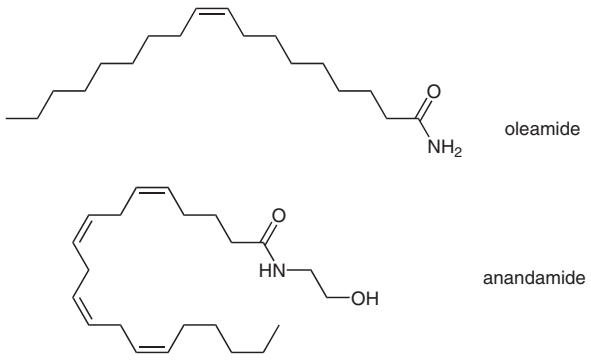
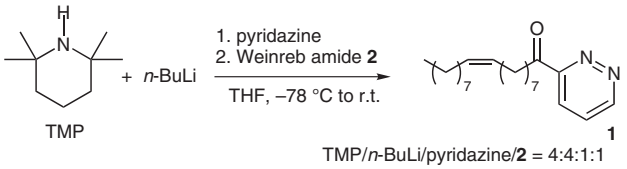


Figure 1 Endogenous fatty acid amides that serve as chemical messengers

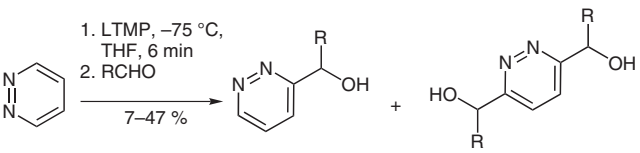
The inhibitors of FAAH may serve as useful tools to clarify the role of these two endogenous amides and may prove to be useful therapeutic agents for the treatment of sleep disorders or pain.

In 2000, Boger and co-workers[2] reported the preparation of exceptionally potent α-keto heterocycle inhibitors[3] of fatty acid amide hydrolase (FAAH). Among them (*Z*)-1-oxo-1-(3-pyridazinyl)octadec-9-ene (**1**) was unusually potent and was prepared in only 11% yield by addition of pyridazinyllithium to the Weinreb amide of oleic acid **2** (Equation 1). Pyridazinyllithium was prepared according to the procedure of Queguiner and co-workers[4] reported in 1995, when they accomplished the functionalization of diazines – π-deficient heteroaromatic systems – without the assistance of any *ortho*-directing metalation group (DMG).[5]



Equation 1 Boger's procedure for the preparation of compound **1**

They found that the optimal procedure for the metalation of pyridazine was to use a four-fold excess of lithium 2,2,6,6-tetramethylpiperidine (LTMP) as the metalating agent in THF at –75 °C. They also found that a very short metalation reaction time (6 min) was required when aldehydes were used as electrophiles, affording *ortho*-monosubstituted products obtained in 7–47% yield along with varying amounts of disubstituted products (Scheme 1).



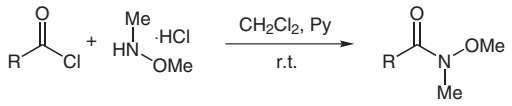
Scheme 1 Literature procedure[4] for pyridazine alkylation

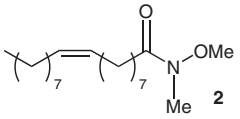
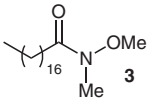
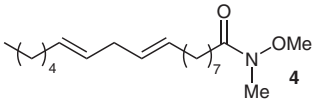
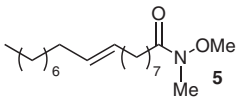
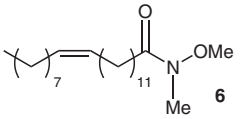
Here, we present improvements to the synthesis of compound **1** and some other significant representatives of the same family of compounds on a gram scale. Weinreb amides **2**–**6** of fatty acids were prepared[6,7] by adding *N*,*O*-dimethylhydroxylamine hydrochloride to the acyl chloride of fatty acids dissolved in dichloromethane in the presence of pyridine at room temperature (Table 1).

With these Weinreb amides in hand we first tried to reproduce the procedure developed by Boger and co-workers to convert the amide **2** into the desired α-keto hetrocycle **1**;

SYNTHESIS 2007, No. 19, pp 3051–3055
Advanced online publication: 11.09.2007
DOI: 10.1055/s-2007-990774; Art ID: P05807SS

Table 1 Preparation of Weinreb Amides[a]



Acyl chloride of	Weinreb amides	Yield (%)[b]
Oleic acid	 **2**	82
Stearic acid	 **3**	93
Linolenic acid	 **4**	81
Elaidic acid	 **5**	86
Erucic acid	 **6**	84

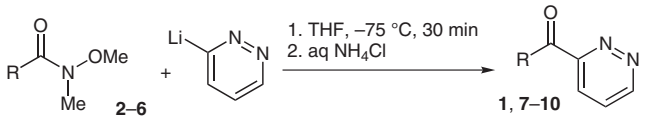
[a] All reactions were run on a 18.0–20.0 mmol scale in CH_2Cl_2 (50 mL) at r.t.
[b] Isolated yield of pure product.

(*Z*)-1-oxo-1-(3-pyridazinyl)octadec-9-ene (**1**) was isolated after flash chromatography in only 4% yield. In an initial attempt to maximize the yield of **1** the critical factor was considered to be the relative amounts of the reagents involved in the formation of the pyridazinyllithium species: TMP, *n*-BuLi, and pyridazine. In the original procedure (Equation 1) an excess of the lithiating agent, LTMP, is used with respect to the pyridazine. This excess might lead to double lithiation of pyridazine and formation of disubstitued by-products.

We changed this ratio and used a stoichiometric ratio of the lithiating agent to the pyridazine, while keeping the excess of pyridazinyllithium with respect to the Weinreb amide (TMP/*n*-BuLi/pyridazine/amide **2** = 4:4:4:1). This lowered the chances for double lithiation of pyridazine while keeping reaction times short. We also found that the reported quench of the reaction mixture with 12 N HCl–THF–EtOH (1:4.5:4.5) at low temperature followed by a slow rise to room temperature and neutralization by saturated $NaHCO_3$ is deleterious, since significant amounts of products are destroyed to give back oleic acid. Much better results were obtained by quenching the reaction at low temperature by the slow addition of aqueous saturated NH_4Cl.

The changes described above allowed a dramatic improvement of the yield of **1**, from the reported 11% to a good 78% after isolation by column chromatography. The reaction was completed in 30 minutes at –75 °C and a prolonged reaction time only allowed a slight improvement (83% yield after 120 min).

Table 2 Influence of the Pirydazinyllithium/Weinreb Amide Ratio on the Yields of 1-Oxo-1-(3-pyridazinyl) Derivatives **1**,**7**–**10**



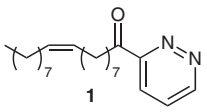
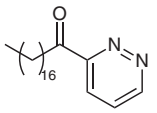
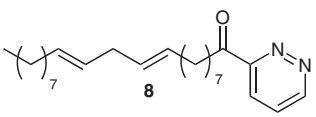
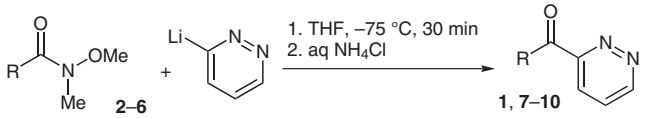
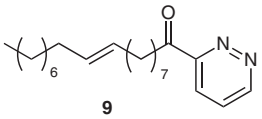
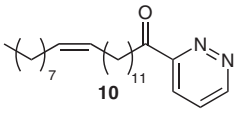
Weinreb amide (1 equiv)	Pyridazinyl Li (n equiv)	1-Oxo-1-(3-pyridazinyl) derivative	Yield (%)[a,b]	Mp (°C)
2	1.2 2.0 4.0 6.0	 **1**	17 34 78 86 (11)[c]	40–41 (Lit.[2] 40–42)
3	1.2 2.0 4.0 6.0	 **7**	–[d] –[d] 34 32 (12)[c]	93–94 (Lit.[2] 83–85)
4	1.2 2.0 4.0 6.0	 **8**	–[d] 42 67 88	oil

Table 2 Influence of the Pirydazinyllithium/Weinreb Amide Ratio on the Yields of 1-Oxo-1-(3-pyridazinyl) Derivatives **1**,**7**–**10** (continued)



Weinreb amide (1 equiv)	Pyridazinyl Li (n equiv)	1-Oxo-1-(3-pyridazinyl) derivative	Yield (%)[a,b]	Mp (°C)
5	1.2 2.0 4.0 6.0	 **9**	42 62 83 77 (42)[c]	63–65 (Lit.[2] 55–57)
6	1.2 2.0 4.0 6.0	 **10**	–[d] –[d] 22 73	54–55

[a] All reactions were run on a 4.0–5.0 mmol scale in anhyd THF at –75 °C for 30 min.
[b] Yield of isolated product after column chromatography.
[c] The reported[2] yields are given in parentheses.
[d] No appreciable result.

In order to further optimize the process, the influence of the pyridazinyllithium/Weinreb amide ratio was examined. Table 2 shows how increasing the amounts of reactants with respect to the Weinreb amide **2** raises the reaction yields. Therefore, the same protocol was applied to the conversion of Weinreb amides **3**–**6** into the corresponding 3-pyridazinyl derivatives **7**–**10** (Table 2).

In conclusion, an improved and optimized deprotonation of pyridazine was achieved, maintaining regioselectivity and greatly improving previously reported yields, and thereby allowing the preparation of a family of important FAAH inhibitors on a gram scale without the formation of disubstituted derivatives.

All chemicals were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. Flash chromatography was carried out on 300–400 mesh silica gel. IR spectra were recorded on a PerkinElmer Spectrum RX 1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz instrument and chemical shifts were referenced to TMS as internal standard. GC analyses were performed on a Agilent Technologies 6850-series GC system with a flame ionization detector (320 °C) using a capillary column (Agilent HP-5, 5% phenyl methyl siloxane, 30 m × 0.32 mm i.d. × 0.25 μm film). The column temperature was programmed from 250 °C (held for 2 min) to 275 °C (held for 4 min) at 15 °C min^{-1}. Solvents and reagents were obtained anhydrous according to the reported procedures: THF (distilled from Na-benzophenone immediately prior to use), pyridine (distilled from KH), CH_2Cl_2, 2,2,6,6-tetramethylpiperidine (TMP) and pyridazine (refluxed over and distilled from CaH_2). *n*-BuLi was titrated[7] immediately before use. Petroleum ether (PE) used refers to the fraction with boiling range 40–60 °C.

N-Methoxy-*N*-methylamides (Weinreb Amides) 2–6 of Fatty Acids; General Procedure

To a mixture containing the fatty acid (18.0 mmol) and anhyd CH_2Cl_2 (14 mL), cooled to 0 °C, was added $SOCl_2$ (2 M in CH_2Cl_2, 17.5 mL, 35 mmol). The mixture was stirred for 4 h at 50 °C. The solvent and excess reagent were removed under reduced pressure, and the crude acid chloride was dried under vacuum. The crude compound was dissolved in anhyd EtOH free CH_2Cl_2 (40 mL), and *N*-methoxy-*N*-methylamine hydrochloride (1.9 g, 19.5 mmol) was added. The mixture was cooled at 0 °C and pyridine (3.15 g, 38.95 mmol) was slowly added. The stirring was continued for 12 h at r.t. The mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with H_2O (5 × 30 mL) and then with aq sat. $CuSO_4$ (2 × 30 mL). The organic layer was dried ($MgSO_4$) and evaporated at reduced pressure to give the amide (Table 1).

(*Z*)-*N*-Methoxy-*N*-methyloctadec-9-enamide (2)

Colorless oil; R_f = 0.39 (PE–EtOAc, 4:1); GC: t_R = 2.96 min.

IR (film): 3000, 2918, 2844, 1669, 1469, 1372 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.21–1.41 (m, 20 H), 1.63 (m, 2 H), 1.96–2.07 (m, 4 H), 2.41 (t, *J* = 7.7 Hz, 2 H), 3.18 (s, 3 H), 3.68 (s, 3 H), 5.28–5.41 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.99, 22.57, 24.33, 27.08, 27.12, 29.05, 29.21, 29.31, 29.42, 29.62, 29.66, 31.79, 31.81 (by DEPT), 61.05, 129.67, 129.82.

Anal. Calcd for $C_{20}H_{39}NO_2$: C, 73.79; H, 12.08; N, 4.30. Found: C, 73.83; H, 12.15; N, 4.24.

N-Methoxy-*N*-methylstearamide (3)

White solid; mp 34–38 °C; R_f = 0.38 (PE–EtOAc, 4:1); GC: t_R = 3.22 min.

IR (KBr): 2910, 2853, 1665, 1468, 1322 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.19–1.37 (m, 28 H), 1.63 (m, 2 H), 2.41 (t, *J* = 7.7 Hz, 2 H), 3.18 (s, 3 H), 3.68 (s, 3 H).

^{13} C NMR ($CDCl_3$): δ = 14.07, 22.65, 24.62, 29.32, 29.40, 29.42, 29.48, 29.60, 29.65, 31.89, 61.11.

Anal. Calcd for $C_{20}H_{41}NO_2$: C, 73.34; H, 12.62; N, 4.28. Found: C, 73.28; H, 12.67; N, 4.23.

(9*E*,12*E*)-*N*-Methoxy-*N*-methyloctadeca-9,12-dienamide (4)

Pale yellow oil; R_f = 0.42 (PE–EtOAc, 4:1); GC: t_R = 3.08 min.

IR (film): 3003, 2921, 2847, 1673, 1459, 1141 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.25–1.42 (m, 14 H), 1.62 (m, 2 H), 1.99–2.11 (m, 4 H), 2.41 (t, *J* = 7.6 Hz, 2 H), 2.77 (t, *J* = 6.0 Hz, 2 H), 3.18 (s, 3 H), 3.68 (s, 3 H), 5.27–5.44 (m, 4 H).

^{13} C NMR ($CDCl_3$): δ = 14.00, 22.50, 24.57, 25.55, 27.13, 27.15, 29.10, 29.27, 29.35, 29.57, 31.45, 31.84, 61.11, 127.89, 127.93, 130.02, 130.12.

Anal. Calcd for $C_{20}H_{37}NO_2$: C, 74.25; H, 11.53; N, 4.33. Found: C, 74.31; H, 11.55; N, 4.25.

(*E*)-*N*-Methoxy-*N*-methyloctadec-9-enamide (5)
Pale yellow oil; R_f = 0.39 (PE–EtOAc, 4:1); GC: t_R = 3.17 min.

IR (film): 2919, 2845, 1669, 1458, 1378, 1175 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.20–1.40 (m, 20 H), 1.62 (m, 2 H), 1.91–2.01 (m, 4 H), 2.41 (t, *J* = 7.6 Hz, 2 H), 3.18 (s, 3 H), 3.68 (s, 3 H), 5.30–5.41 (m, 2 H).

^{13} C NMR ($CDCl_3$): δ = 14.02, 22.60, 24.57, 28.93, 29.10, 29.23, 29.34, 29.41, 29.52, 29.57, 31.45, 31.82, 32.53, 61.76, 130.17, 130.32.

Anal. Calcd for $C_{20}H_{39}NO_2$: C, 73.79; H, 12.08; N, 4.30. Found: C, 73.85; H, 12.15; N, 4.28.

(*E*)-*N*-Methoxy-*N*-methyldocos-13-enamide (6)
Pale yellow oil; R_f = 0.46 (PE–EtOAc, 4:1); GC: t_R = 5.23 min.

IR (film): 3049, 2920, 2848, 2295, 1652, 1421, 1261, 1176 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.20–1.40 (m, 28 H), 1.62 (m, 2 H), 1.95–2.06 (m, 4 H), 2.41 (t, *J* = 7.7 Hz, 2 H), 3.18 (s, 3 H), 3.68 (s, 3 H), 5.29–5.39 (m, 2 H).

^{13} C NMR ($CDCl_3$): δ = 14.05, 22.62, 24.61, 27.15, 29.26, 29.33, 29.41, 29.47, 29.50, 29.57, 29.72, 31.85, 61.11, 129.81, 130.32.

Anal. Calcd for $C_{24}H_{47}NO_2$: C, 75.53; H, 12.41; N, 3.67. Found: C, 75.61; H, 12.47; N, 3.61.

Pyridazines 1, 7–10; General Procedure
2,2,6,6-Tetramethylpiperidine (2.07 mL, 12.3 mmol, 4.0 equiv) was dissolved in anhyd THF (70.0 mL) and cooled to –30 °C. *n*-BuLi (1.5 M in hexane, 8.2 mL, 12.3 mmol, 4 equiv) was added dropwise, keeping the temperature below –25 °C. After the addition of *n*-BuLi was complete, the mixture was warmed to 0 °C with an ice bath and stirred at this temperature for 45 min. The mixture was then cooled to –70 °C (internal) and a solution of pyridazine (0.89 mL, 12.3 mmol, 4 equiv) in anhyd THF (10 mL) was added dropwise. The color of the mixture turned to red brown. Then a solution of Weinreb amide **2–6** (3.07 mmol) in THF (5 mL) was added, maintaining the temperature as close as possible to –70 °C. The mixture was stirred for 30 min. The workup of the mixture was performed by adding aq sat. NH_4Cl (40 mL, initially dropwise) while allowing the temperature to rise to r.t. The mixture was extracted with Et_2O (3 × 40 mL). The ethereal solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product that was purified by flash column chromatography (Table 2).

(*Z*)-1-(Pyridazin-3-yl)octadec-9-en-1-one (1)
White solid; mp 40–41 °C (Lit.[2] mp 40–42 °C); R_f = 0.24 (PE–EtOAc, 4:1); GC: t_R = 2.96 min.

IR (KBr): 3052, 3009, 1700, 1567, 1465, 1267 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 6.8 Hz, 3 H), 1.20–1.48 (m, 20 H), 1.79 (quint, *J* = 7.2 Hz, 2 H), 1.96–2.08 (m, 4 H), 3.41 (t, *J* = 7.5 Hz, 2 H), 5.29–5.41 (m, 2 H), 7.67 (dd, J_o = 5.1 Hz, J_o = 8.5 Hz, 1 H), 7.84 (dd, J_o = 8.3Hz, J_m = 1.7 Hz, 1 H), 9.34 (dd, J_o = 5.0 Hz, J_m = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 18.81, 22.38, 22.51, 26.88, 26.91, 28.85, 28.96, 29.01, 29.05, 29.22, 29.42, 29.47, 31.60, 37.88, 124.39, 126.93, 129.47, 129.66, 152.94, 155.47, 200.42.

Anal. Calcd for $C_{22}H_{36}N_2O$: C, 76.69; H, 10.53; N, 8.13. Found: C, 76.59; H, 10.47; N, 8.07.

1-(Pyridazin-3-yl)octadecan-1-one (7)
White solid; mp 91–93 °C (Lit.[2] mp 83–85 °C); R_f = 0.18 (PE–EtOAc, 4:1); GC: t_R = 5.08 min.

IR (KBr): 3047, 2920, 2849, 1699, 1572, 1469, 1259, 1017, 891 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.21–1.46 (m, 28 H), 1.79 (quint, *J* = 7.5 Hz, 2 H), 3.40 (t, *J* = 7.5 Hz, 2 H), 7.66 (dd, J_o = 4.9 Hz, J_o = 8.4 Hz, 1 H), 8.14 (dd, J_o = 8.4 Hz, J_m = 1.9 Hz, 1 H), 9.33 (dd, J_o = 5.0 Hz, J_m = 1.9 Hz, 1 H).

^{13} C NMR ($CDCl_3$): δ = 13.79, 22.36, 23.52, 28.97, 29.04, 29.13, 29.19, 29.31, 29.34, 29.38, 31.61, 37.87, 124.37, 126.92, 152,91, 155.46, 200.42.

Anal. Calcd for $C_{22}H_{38}N_2O$: C, 76.25; H, 11.05; N, 8.08. Found: C, 76.16; H, 11.04; N, 8.15.

(9*E*,12*E*)-1-(Pyridazin-3-yl)octadeca-9,12-dien-1-one (8)
Yellow oil; R_f = 0.26 (PE–EtOAc, 4:1); GC: t_R = 4.88 min.

IR (KBr): 2926, 2856, 1701, 1457, 1380 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.20–1.48 (m, 14 H), 1.79 (quint, *J* = 7.0 Hz, 2 H), 1.99–2.12 (m, 4 H), 2.78 (t, *J* = 5.7 Hz, 2 H), 3.41 (t, *J* = 7.6 Hz, 2 H), 5.28–5.44 (m, 4 H), 7.66 (dd, J_o = 4.9 Hz, J_o = 8.4 Hz, 1 H), 8.15 (dd, J_o = 8.4 Hz, J_m = 1.8 Hz, 1 H), 9.33 (dd, J_o = 5.0 Hz, J_m = 1.7 Hz, 1 H).

^{13} C NMR ($CDCl_3$): δ = 13.83, 22.32, 23.57, 25.58, 26.95, 26.97, 28.91, 29.00, 29.10, 29.38, 31.27, 37.93, 124.46, 126.99, 127.68, 127.77, 129.83, 129.94, 153.00, 155.52, 200.50.

Anal. Calcd for $C_{22}H_{34}N_2O$: C, 77.14; H, 10.01; N, 8.18. Found: C, 77.34; H, 10.08; N, 8.11.

(*E*)-1-(Pyridazin-3-yl)octadec-9-en-1-one (9)
White solid; mp 63–64 °C (Lit.[2] mp 55–57 °C); R_f = 0.16 (PE–EtOAc, 4:1); GC: t_R = 4.92 min.

IR (KBr): 2905, 2843, 1695, 1467, 1399, 958, 808, 714 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3 H), 1.28–1.54 (m, 20 H), 1.85 (quint, *J* = 7.4 Hz, 2 H), 2.01–2.10 (m, 4 H), 3.47 (t, *J* = 7.4 Hz, 2 H), 5.42–5.48 (m, 2 H), 7.75 (dd, J_o = 5.2 Hz, J_o = 8.5 Hz, 1 H), 8.22 (dd, J_o = 8.3 Hz, J_m = 1.8 Hz, 1 H), 9.42 (dd, J_o = 5.0 Hz, J_m = 1.9 Hz, 1 H).

^{13} C NMR ($CDCl_3$): δ = 14.00, 22.57, 23.75, 28.89, 29.08, 29.14, 29.21, 29.39, 29.48, 29.55, 31.79, 32.47, 32.50, 38.07, 124.71, 127.22, 130.13, 130.33, 153,04, 155.66, 200.55.

Anal. Calcd for $C_{22}H_{36}N_2O$: C, 76.69; H, 10.53; N, 8.13. Found: C, 76.81; H, 10.58; N, 8.09.

(*Z*)-1-(Pyridazin-3-yl)docos-13-en-1-one (10)
White solid; mp 54.0–55.5 °C; R_f = 0.16 (PE–EtOAc, 4:1); GC: t_R = 8.93 min.

IR (KBr): 2926, 2833, 1721, 1596, 1498, 1249, 864, 810 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.14–1.46 (m, 28 H), 1.79 (quint, *J* = 7.5 Hz, 2 H), 1.98–2.05 (m, 4 H), 3.04 (t, *J* = 7.4 Hz, 2 H), 5.42–5.48 (m, 2 H), 7.66 (dd, J_o = 5.2 Hz, J_o = 8.5 Hz, 1 H), 8.14 (dd, J_o = 8.3 Hz, J_m = 1.6 Hz, 1 H), 9.34 (dd, J_o = 5.0 Hz, J_m = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.74, 22.38, 23.48, 26.85, 28.93, 28.96, 29.09, 29.16, 29.19, 29.26, 29.41, 31.54, 37.06, 37.82, 124.34, 126.88, 129.51, 152.86, 155.41, 200.55.

Anal. Calcd for $C_{26}H_{44}N_2O$: C, 77.94; H, 11.07; N, 6.99. Found: C, 77.85; H, 11.09; N, 6.94.

Acknowledgment

This research was supported in part by Alma Mater Studiorum – Università di Bologna and MiUR, Italy (PRIN 2005: 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni').

References

(1) (a) Cravatt, B. F.; Giang, D. K.; Mayfield, S. P.; Boger, D. L.; Lerner, R. A.; Gilula, N. B. *Nature (London)* **1996**, *384*, 83. (b) McKinney, M. K.; Cravatt, B. F. *Ann. Rev. Biochem.* **2005**, *74*, 411.

(2) (a) Boger, D. L.; Sato, H.; Lerner, A. E.; Hedrick, M. P.; Fecik, R. A.; Miyauchi, H.; Wilkie, G. D.; Austin, B. J.; Patricelli, M. P.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 5044. (b) Boger, D. L. (The Scripps Research Institute) US Patent 6462054 B1, **2002**; *Chem. Abstr.* **2002**, *137*, 279215.

(3) The use of α-keto heterocycles as inhibitors was first disclosed by Edwards et al. in 1992: Edwards, P. D.; Meyer, E. F. Jr.; Vijayalakshimi, J.; Tuthill, P. A.; Andisik, D. A.; Gomes, B.; Strimpler, A. *J. Am. Chem. Soc.* **1992**, *114*, 1854.

(4) Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *J. Org. Chem.* **1995**, *60*, 3781.

(5) (a) More recently, a new strategy for deprotonative functionalization of aromatics with excellent chemoselectivity and unique regioselectivity using *t*-Bu-P4 base in the presence of ZnI_2 has appeared in the literature: Imahori, T.; Kondo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 8082. (b) Using this approach, pyridazine was treated with diphenyl ketone and gave a 4-substituted 1,2-adduct in 91% yield.

(6) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Ballini, R.; Marcantoni, E.; Torreggiani, E. *J. Nat. Prod.* **1997**, *60*, 505.

(7) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.