Direct Access to Functionalized Cyclic Enones Using Mannich, Morita–Baylis–Hillman and Elimination Reactions

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Abstract: A series of highly functionalized cyclic enones were obtained from Mannich, Morita–Baylis–Hillman and elimination reaction with cyclic enones.

Key words: Morita–Baylis–Hillman, cyclic enones, aminals, Mannich reactions, concavine

Our ongoing interest in the synthesis of natural products using the Morita–Baylis–Hillman[1] reaction (MBH)[2] resulted in the recent discovery that surfactants improve MBH yields when using cyclic enones.[3] Considering many natural products contain nitrogen, we embarked on a quest to investigate methods that might allow an aza-variation of the MBH-reaction.[4] A survey of current literature reveals a number of reports detailing the aza-MBH reaction using stabilized imines (two steps overall),[5–11] but the more traditional aza-MBH (one-step) has only been reported twice.[12,13] It was this type of one-step protocol we were most interested in utilizing as it introduces masked, unsubstituted methylene functionality which is seen, for example, in concavine (**1**) (Figure 1).[14] The one-step aza-MBH reaction, described by Kozlov and Kovaleva,[12] between formaldehyde, secondary amines and enones, however, could not be repeated and produced instead the normal type MBH product (**4** from **2** and formaldehyde) (Scheme 1). Kalinin[13] reports that treating aminals such as **6** with acetyl chloride, forms Schiff base chlorides (i.e. **7**) which, when reacted with methyl vinyl ketone, results in the formation of the aza-MBH products. Again we were unable to reproduce these results or apply the protocol to the corresponding cyclic enone system of **5**. Instead, however, the Mannich[15] product **8** was obtained in moderate yield. Although Schiff base salts like **7** have been utilized previously in Mannich reactions of cyclic ketones,[16,17] cyclic enones have yet to be exposed to these salts.

This observation encouraged us to investigate sequential Mannich and MBH reactions, as this strategy may also be useful for the synthesis of natural products of type **1** that contain nitrogen. Results of this study are discussed herein.

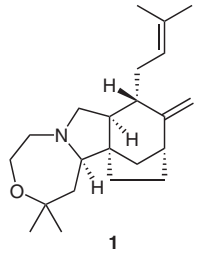

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Figure 1 Structure of concavine **1**

The Mannich reaction was demonstrated by the application of aminals di(*N*-piperidinyl)methane (**6**) and di(*N*-morpholinyl)methane (**9**), which were prepared according to a slightly modified procedure reported by Wilkins,[18] to a range of cyclic enones (Table 1). Generating aminals which allow the introduction of a free amine, for example bis(*N*,*N*-hexamethyldisilazan)methane, have so far failed. To establish a reaction protocol, aminals and cyclic enones were dissolved in anhydrous acetonitrile under an argon atmosphere, freshly distilled acetyl chloride was then added and the reaction mixture was stirred at room temperature for 4–14 hours.

Fortuitously, this protocol was found to be superior to those involving trichloromethylsilane (Cl_3MeSi) or chlorotrimethylsilane ($ClMe_3Si$), used to generate Schiff bases from aminoethers,[17,18] as neither of the latter reagents gave any improvement in either yield or purity. A further advantage of this protocol was that the product, in most cases, precipitated out of the reaction mixture and was simply collected by filtration. Interestingly, the reaction was found to be somewhat substrate specific. For example, only half the cases gave monosubstitution (Entries 1, 2, 5, 9, 10, Table 1) whereas the remainder gave disubstituted products (Entries 3, 4, 6, 7, 8, Table 1), irrespective of the number of equivalents used.

It is noteworthy that, contrary to Kalinin et al.,[13] the Mannich products were obtained exclusively. In no cases were products of a aza-Morita–Baylis–Hillman type reaction detected. Sequential MBH reactions on the Mannich products were undertaken using surfactants (i.e. SDS), according to the protocol described previously. MBH reactions with the Mannich products turned out to be capricious. In accordance with previous results, no product formation was observed with the β-substituted cyclic enones **16** and **20**.[3] All other substrates were totally consumed, but afforded complex mixtures. Conversely, good results were

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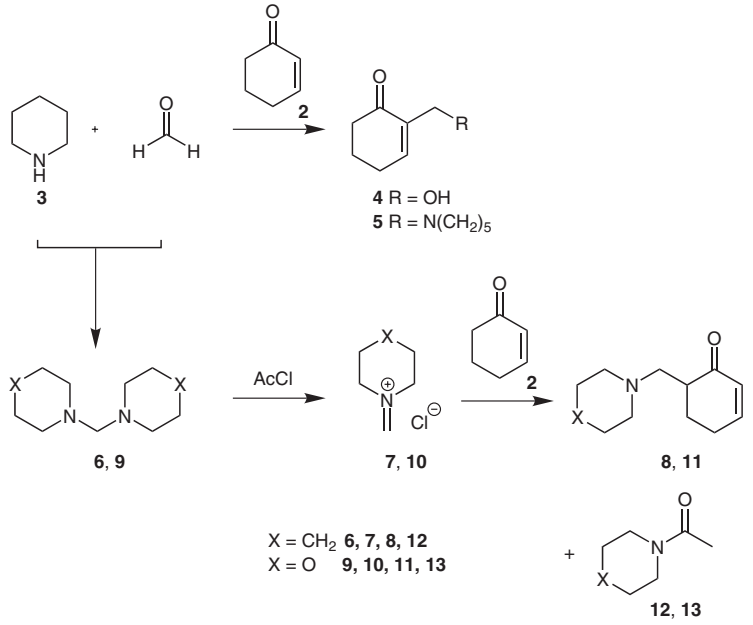
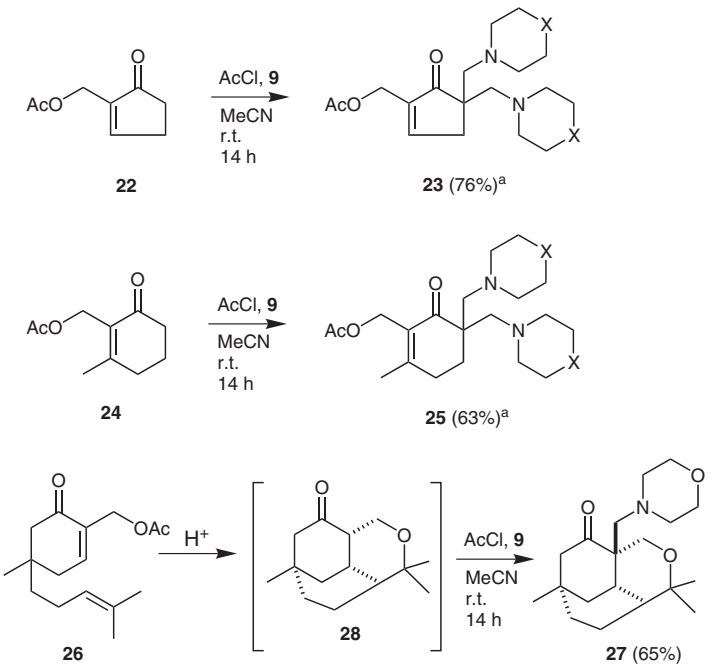


Scheme 1 Initial studies of the aza-MBH reaction

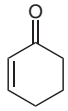
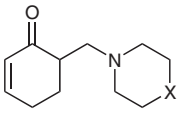
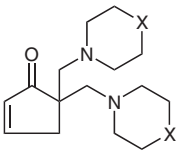
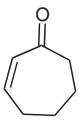
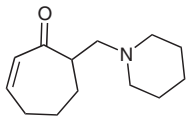
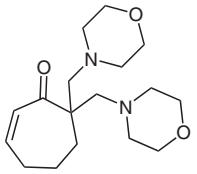
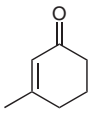
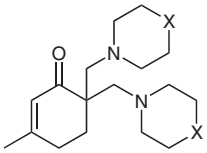
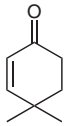
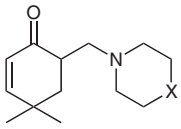


Scheme 2 Mannich reaction of MBH acetates; [a] yields based on aminal

obtained when the methylene hydroxyl functionality was introduced first, followed by acetyl protection with acetyl chloride. The MBH-acetate of cyclopentenone **22**, when reacted with **9**, gave the double alkylated product **23**, as did enone **24**, (a rare example of a Morita–Baylis–Hillmann reaction with a C-3 substituted cyclic enone) (Scheme 2).[19] Cyclopentenone and 3-methylcyclohexenone (Entries 3, 4, 7, 8, Table 1) also underwent double alkylation. Alcohol protection (i.e. acetates **22**, **24**, **26**) was essential in order to avoid side reactions. In the case of **26**, the tricyclic compound **27** was exclusively obtained, instead of the expected acetate. It is believed that the substrate **26** underwent cyclization to **28** due to catalytic amounts of HCl present in acetyl chloride. Such a cyclization to tricycle **28** is known from previous studies in our lab.[2] For authentication, **28** was reacted with **6** to give tricycle **29** in high yield (Scheme 3). Interestingly, it turned out that **26** could not be alkylated at the C-6 position. All reactions with excess aminal or triethylamine, to trap HCl, resulted in total recovery of starting material.

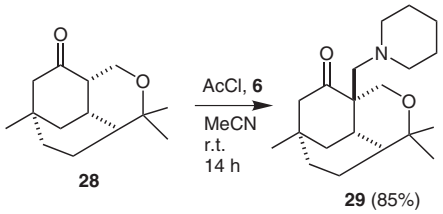
MBH-acetates **30** and **31** gave, after standard Mannich reactions, **32** and **33** in good yields. Elimination of the amino group to form the exocyclic double bond was achieved

Table 1 Mannich Reaction of Aminals with Cyclic Enones[a]

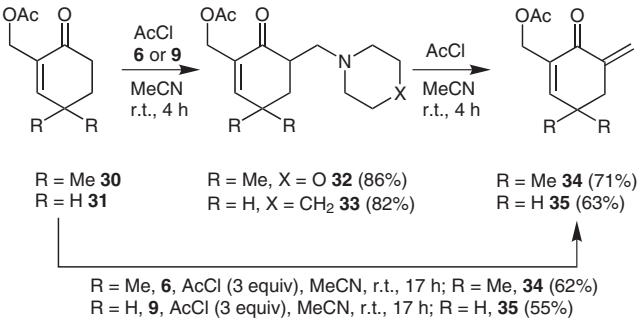
Entry	Enone	Product	Yield (%)[b]
1		 **8**; X = CH_2	80[c]
2		**11**; X = O	85[c]
3		 **14**; X = CH_2	87[c,d]
4		**18**; X = O	89[d]
5		 **15**	58[e]
6		 **19**	82[d]
7		 **16**; X = CH_2	83[d]
8		**20**; X = O	82[d,e]
9		 **17**; X = CH_2	53[c]
10		**21**; X = O	90[c]

[a] Reactions were performed at 1 mmol in anhyd MeCN (3 mL) under Ar at r.t. for 4–14 h.
[b] Yields of isolated product.
[c] Product precipitates from the reaction mixture and collected by filtration.
[d] Based on aminal.
[e] Yield of title compound obtained as a mixture with amide (**12**–**13**) by-product.

using acetyl chloride in acetonitrile at room temperature, affording good yields of products **34** and **35** (71% and 63% respectively). Attempts at a more practical, one-pot protocol, i.e. Mannich reaction and sequential elimination to introduce the double bond was successful, giving only



Scheme 3 Mannich reaction with tricycle **28**



Scheme 4 Mannich reaction of MBH acetates

slightly diminished yields (62% and 55%) as compared to the two-step procedure (Scheme 4). As expected, the products **34** and **35** were found to be heat sensitive, which possibly contributed to the moderate yields of products obtained.

In conclusion, simple cyclic enones can become highly functionalized, expediently, using the sequential MBH–Mannich protocol; methodology we believe is applicable to a range of applications. Attempts to amalgamate the MBH–Mannich–elimination sequence into a one-pot protocol are in progress.

Boiling and melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 (300 MHz, 75MHz) or Bruker 400 (400 MHz, 100 MHz) in $CDCl_3$. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High and low EI mass spectral data were obtained on a Kratos MS25 RFA. Column chromatography was conducted on silica gel (Flash Silica Gel 230–400 mesh), with distilled solvents. Petroleum ether (PE) used had boiling range 40–60 °C.

Synthesis of Aminals; General Procedure

To formalin (10–30 mmol) was added the corresponding amine (2 equiv) at 0 °C. After 30 min at 0 °C, the mixture was allowed to come to r.t. over 2 h. The pure aminals were obtained by distillation directly from the reaction mixture.

Di(*N*-piperidinyl)methane (6)[18]

Yield: 5 g (90%); colorless liquid; bp 60 °C (0.1 mmHg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79 (s, 2 H), 2.35 (br t, 8 H), 1.52–1.47 (m, 8 H), 1.41–1.36 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.73, 53.04, 25.89, 24.87.

MS (EI): *m*/*z* (%) = 98 (100) [$M^+ - NC_5H_{10}$], 84 (20), 56 (14), 41 (23).

Di(*N*-morpholinyl)methane (9)[18]

Yield: 1.7 g (92%); colorless liquid; bp 65 °C (0.1 mmHg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (m, 8 H), 2.85 (s, 2 H), 2.43 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 81.60, 66.94, 51.94.

MS (EI): *m*/*z* (%) = 186 (2) [M^+], 100 (100) [$M^+ - NC_4H_8O$], 56 (20), 42 (12).

Mannich Reaction; General Procedure

To a solution of aminal (1 mmol) and cyclic enone (1.2 mmol) in anhyd MeCN (3 mL) under argon at r.t., was added freshly distilled AcCl (0.78 mL, 1 mmol). A white precipitate formed after 10–30 s. The mixture was then stirred for a further 4–14 h, after which the precipitate was collected, dissolved in CH_2Cl_2 (5 mL) and washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). When no precipitate was formed, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). Pure products were obtained after column chromatography (EtOAc–PE).

6-[(Piperidin-1-yl)methyl]cyclohex-2-en-1-one (8)

Yield: 155 mg (80%); pale-yellow oil; R_f = 0.42 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (dt, *J* = 7.5, 1.5 Hz, 1 H), 5.95 (dt, *J* = 7.5, 1.5 Hz, 1 H), 2.73 (dd, *J* = 9.4, 3.4 Hz, 1 H), 2.53–2.49 (m, 1 H), 2.43–2.20 (m, 8 H), 1.81–1.78 (m, 1 H), 1.58–1.53 (m, 4 H), 1.43–1.38 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.34, 149.98, 129.54, 57.96, 54.78, 44.59, 26.89, 25.85, 25.06, 24.26.

MS (EI): *m*/*z* (%) = 192 (3), 180 (2), 176 (100), 148 (11), 133 (21), 118 (6), 105 (6), 98 (17), 91 (21), 65 (8), 55 (8), 41 (7).

HRMS (EI): *m*/*z* [M^+ – H] calcd for $C_{12}H_{18}NO$: 192.1388; found: 192.1386.

6-(Morpholinomethyl)cyclohex-2-en-1-one (11)

Yield: 165 mg (85%); pale-yellow oil; R_f = 0.38 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93–6.87 (m, 1 H), 5.94 (ddd, *J* = 5.2, 5.2, 4.1 Hz, 1 H), 3.66–3.62 (m, 4 H), 2.74 (dd, *J* = 12.3, 4.5 Hz, 1 H), 2.51–2.29 (m, 8 H), 2.25–2.17 (m, 1 H), 1.85–1.76 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.77, 149.77, 129.54, 66.94, 57.67, 53.86, 44.24, 26.55, 24.92.

MS (EI): *m*/*z* (%) = 195 (4), 126 (1), 100 (100), 68 (5), 56 (12), 42 (11).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{17}NO_2$: 195.1259; found: 195.1256.

5,5-[Bis(piperidin-1-yl)methyl]cyclopent-2-en-1-one (14)

Yield: 145 mg (87%); pale-yellow oil; R_f = 0.22 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.73 (m, 1 H), 6.12–6.10 (m, 1 H), 2.76 (t, *J* = 1.8 Hz, 2 H), 2.42 (d, *J* = 10.0 Hz, 2 H), 2.34–225 (m, 10 H), 1.44–1.37 (m, 8 H), 1.32–1.27 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.66, 165.35, 133.23, 63.40, 56.56, 53.48, 37.82, 26.28, 24.00.

MS (EI): *m*/*z* (%) = 276 (2) [M^+], 191 (4), 178 (4), 98 (100), 84 (11), 55 (6).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{28}N_2O$: 276.2202; found: 276.2205.

7-[(Piperidin-1-yl)methyl]cyclohept-2-en-1-one (15)

Yield: 110 mg (58%); pale-yellow oil; R_f = 0.21 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.60–6.52 (m, 1 H), 601–5.97 (m, 1 H), 2.83–2.70 (m, 2 H), 2.40–2.25 (m, 8 H), 2.05–1.95 (m, 1 H), 1.90–1.87 (m, 1 H), 1.66–1.33 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.17, 145.85, 132.78, 59.74, 54.77, 49.66, 29.70, 28.15, 25.91, 25.26, 24.25.

MS (EI): *m*/*z* (%) = 207 (2) [M^+], 182 (2), 124 (8), 98 (100), 84 (8), 81 (11), 69 (10), 55 (18), 41 (14).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{21}NO$: 207.1623; found: 207.1627.

6,6-[Bis(piperidin-1-yl)methyl]-3-methylcyclohex-2-en-1-one (16)

Yield: 128 mg (83%); slightly pale-yellow oil; R_f = 0.23 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75 (s, 1 H), 3.1 (m, 1 H), 2.60–2.02 (m, 18 H), 1.55–1.38 (m, 8 H), 1.32–1.27 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.18, 161.76, 126.31, 58.08, 54.75, 43.71, 26.64, 25.97, 25.92, 24.33, 24.14.

ESI-MS: *m*/*z* = 327 [M + Na^+].

4,4-Dimethyl-6-[(piperidin-1-yl)methyl]cyclohex-2-en-1-one (17)

Yield: 117 mg (53%); pale-yellow oil; R_f = 0.75 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (d, *J* = 7.5 Hz, 1 H), 5.78 (d, *J* = 7.5 Hz, 1 H), 2.83 (dd, *J* = 9.5, 3.1 Hz, 1 H), 2.64–2.58 (m, 1 H), 2.40–2.20 (m, 5 H), 2.05–2.02 (m, 1 H), 1.60–1.52 (m, 5 H), 1.41–1.36 (m, 2 H), 1.16 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.18, 158.87, 126.73, 58.22, 54.76, 41.10, 40.59, 33.52, 30.52, 25.98, 25.32, 24.40.

MS (EI): *m*/*z* (%) = 221 (10) [M^+], 177 (2), 162 (2), 136 (11), 121 (4), 98 (100), 93 (13), 84 (11), 77 (9), 55 (9), 41 (14).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{23}NO$: 221.1780; found: 221.1781.

5,5-[Bis(morpholinomethyl)]cyclopent-2-en-1-one (18)

Yield: 140 mg (89%); white solid; mp 78 °C (subl.); R_f = 0.19 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (dt, *J* = 5.8, 2.8 Hz, 1 H), 6.12 (dt, *J* = 5.8, 2.1 Hz, 1 H), 3.55–3.50 (m, 8 H), 2.78 (s, 2 H), 2.50 (d, *J* = 13.3 Hz, 2 H), 2.40–2.28 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.77, 165.30, 133.53, 67.06, 63.11, 55.45, 52.80, 38.17.

ESI-MS: *m*/*z* = 303 [M + Na^+].

Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.06, H, 8.70; N, 9.97.

7,7-[Bis(morpholinomethyl)]cyclohept-2-en-1-one (19)

Yield: 152 mg (82%); pale-yellow oil; R_f = 0.31 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61–6.53 (m, 1 H), 6.02–5.97 (m, 1 H), 3.65–3.61 (m, 8 H), 2.90–2.70 (m, 2 H), 2.60–2.30 (m, 8 H), 2.05–1.38 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.71, 145.72, 132.71, 66.97, 59.55, 53.89, 49.35, 29.84, 27.78, 25.21.

ESI-MS: *m*/*z* = 331 [M + Na^+].

3-Methyl-6,6-bis(morpholinomethyl)cyclohex-2-en-1-one (20)

Yield: 153 mg (82%); slightly yellow oil; R_f = 0.22 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.74 (s, 1 H), 3.60–3.53 (m, 8 H), 2.53–2.05 (m, 16 H), 1.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.49, 161.79, 126.27, 66.92, 57.79, 53.84, 43.05, 30.05, 26.41, 24.10.

ESI-MS: *m*/*z* = 331 [M + Na^+].

4,4-Dimethyl-6-(morpholinomethyl)cyclohex-2-enone (21)

Yield: 200 mg (90%); pale-yellow oil; R_f = 0.64 (EtOAc–PE, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.52 (dd, *J* = 10.0, 2.2 Hz, 1 H), 5.72 (d, *J* = 10.0 Hz, 1 H), 3.65–3.55 (m, 4 H), 2.83–2.78 (dd, *J* = 12.6, 4.3 Hz, 1 H), 2.58–2.51 (m, 1 H), 2.43–2.22 (m, 5 H), 2.01–1.94 (m, 1 H), 1.55 (t, *J* = 13.7 Hz, 1 H), 1.10 (s, 3 H), 1.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.44, 158.81, 126.51, 66.77, 57.75, 53.72, 40.85, 40.13, 33.34, 30.36, 25.16.

MS (EI): *m*/*z* (%) = 223 (10) [M$^+$], 208 (2), 176 (2), 136 (10), 121 (6), 100 (100), 93 (4), 56 810), 41 (10).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{21}NO_2$: 223.1572; found: 223.1570.

[4,4-Bis(morpholinomethyl)-5-oxocyclopent-1-enyl]methyl Acetate (23)

Yield: 134 mg (76%); pale-brown oil; R_f = 0.16 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 1 H), 4.62–4.60 (m, 2 H), 3.52–3.58 (m, 8 H), 2.7 (br s, 2 H), 2.51–2.48 (m, 2 H), 2.38–2.26 (m, 10 H), 2.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.99, 170.41, 161.71, 140.18, 66.97, 63.06, 57.77, 55.36, 53.07, 36.53, 20.69.

ESI-MS: *m*/*z* = 375 [M + Na$^+$].

[2-Methyl-5,5-bis(morpholinomethyl)-6-oxocyclohex-1-enyl]methyl Acetate (25)

Reaction scale: 0.2 mmol.

Yield: 26 mg (63%); pale-brown oil; R_f = 0.19 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83–4.65 (m, 2 H), 3.82–3.55 (m, 8 H), 2.70 (br s, 1 H), 2.48–2.22 (m, 15 H), 2.05 (s, 3 H), 1.94 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.70, 170.96, 162.62, 130.01, 68.86, 57.96, 53.87, 46.63, 43.19, 41.73, 31.96, 21.19, 20.96.

ESI-MS: *m*/*z* = 403 [M + Na$^+$].

[3,3-Dimethyl-5-(morpholinomethyl)-6-oxocyclohex-1-enyl]methyl Acetate (32)

Yield: 253 mg (86%); colorless oil; R_f = 0.7 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.53 (s, 1 H), 4.62–4.57 (m, 2 H), 3.69–3.64 (m, 4 H), 2.90 (dd, *J* = 9.5, 3.3 Hz, 1 H), 2.70–2.61 (m, 1 H), 2.50–2.45 (m, 2 H), 2.38–2.31 (m, 3 H) 2.05–2.00 (m, 1 H), 2.01 (s, 3 H), 1.61 (t, *J* = 10.3 Hz, 1 H), 1.16 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.85, 170.55, 156.73, 131.09, 66.65, 61.33, 57.75, 53.72, 40.87, 40.25, 33.15, 30.57, 25.16, 20.89.

MS (EI): *m*/*z*(%) = 295 (4) [M$^+$], 235 (9), 220 (5), 182 (3), 100 (100), 81 (5), 69 (6), 56 (6), 43 (5).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{25}NO_4$: 295.1784; found: 295.1773.

{6-Oxo-5-[(piperidin-1-yl)methyl]cyclohex-1-enyl}methyl Acetate (33)

Yield: 218 mg (82%); pale-yellow oil; R_f = 0.6 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (br t, *J* = 3.6 Hz, 1 H), 4.73–4.61 (m, 2 H), 2.71 (dd, *J* = 12.5, 4.6 Hz, 1 H), 2.54–2.46 (m, 1 H), 2.45–2.15 (m, 8 H), 2.02 (s, 3 H), 1.85–1.70 (m, 1 H), 1.57–1.45 (m, 4 H), 1.42–1.35 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.63, 170.66, 147.89, 134.00, 61.47, 57.85, 54.75, 44.57, 26.76, 25.88, 24.83, 24.24, 20.91.

ESI-MS: *m*/*z* = 298 [M + Na$^+$].

[4-Methyl(*N*-morpholino)]-1,7,7-trimethyl-6-oxatricyclo[6.2.2.0^{4,9}]dodecan-3-one (27)

Reaction scale: 0.1 mmol.

Yield: 21 mg (65%); white solid; mp 85 °C (subl.); R_f = 0.76 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.35 (d, *J* = 11.8 Hz, 1 H), 3.60 (t, *J* = 4.61 Hz, 4 H), 3.36 (d, *J* = 11.8 Hz, 1 H), 2.50–2.48 (m, 1 H), 2.41–2.35 (m, 6 H), 2.23–2.21 (m, 2 H), 2.05 (dt, *J* = 13.38, 3.15 Hz, 1 H), 1.63–1.46 (m, 2 H), 1.33–1.20 (m, 7 H), 1.05 (s, 3 H), 0.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.48, 73.37, 67.18, 62.85, 62.75, 55.62, 51.61, 50.87, 42.13, 38.93, 37.11, 34.92, 34.41, 30.88, 27.36, 22.66, 20.96.

MS (EI): *m*/*z* (%) = 321 (4) [M$^+$], 293 (3), 222 (4), 208 (5), 197 (7), 177 (2), 164 (3), 149 (4), 140 (6), 100 (100).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{31}NO_3$: 321.2304; found: 321.2306.

Anal. Calcd. for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72. Found: C, 71.02; H, 9.85.

[4-Methyl(*N*-piperidinyl)]-1,7,7-trimethyl-6-oxatricyclo[6.2.2.0^{4,9}]dodecan-3-one (29)

Yield: 122 mg (85%); white solid; mp 89 °C (subl.); R_f = 0.85 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.26 (d, *J* = 11.8 Hz, 1 H), 3.38 (d, *J* = 11.8 Hz, 1 H), 2.50–2.48 (m, 1 H), 2.41–2.35 (m, 5 H), 2.23–2.05 (m, 4 H), 1.63–1.43 (m, 7 H), 1.33–1.17 (m, 8 H), 1.05 (s, 3 H), 0.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.02, 73.38, 62.69, 62.57, 56.96, 51.72, 51.39, 42.22, 39.06, 37.15, 34.26, 30.92, 27.41, 26.54, 22.80, 21.00.

ESI-MS: *m*/*z* = 342 [M + Na$^+$].

Anal. Calcd. for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41. Found: C, 75.02; H, 10.65.

Amino-Group Elimination; General Procedure

To a solution of amine (1 mmol) in anhyd MeCN (3 mL) under argon at r.t., was added freshly distilled AcCl (1.6 mL, 2 mmol). The mixture was kept under argon and stirred for a further 17 h. CH_2Cl_2 (10 mL) was added and the mixture was washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). The pure products were obtained after column chromatography (EtOAc–PE) on silica.

3,3-Dimethyl-5-methylene-6-oxocyclohex-1-enyl)methyl Acetate (34)

Yield: 148 mg (71%); colorless oil; R_f = 0.7 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.71 (s, 1 H), 6.03 (br q, 1 H), 5.27 (br q, 1 H), 4.72 (d, *J* = 1.14 Hz, 2 H), 2.54 (s, 2 H), 2.05 (s, 3 H), 1.12 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.89, 170.58, 157.52, 140.79, 132.08, 121.80, 61.33, 45.11, 34.25, 28.15, 20.92.

ESI-MS: *m*/*z* = 203 [M + Na$^+$].

(5-Methylene-6-oxocyclohex-1-enyl)methyl Acetate (35)

Yield: 114 mg (63%); colorless oil; R_f = 0.8 (EtOAc–PE, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (t, *J* = 3.23 Hz, 1 H), 5.99 (d, *J* = 1.05 Hz, 1 H), 5.30–5.28 (m, 1 H), 4.78 (d, *J* = 1.05 Hz, 2 H), 2.71 (t, *J* = 4.74 Hz, 2 H), 2.49–2.44 (m, 2 H), 2.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.24, 170.70, 148.28, 142.34, 135.14, 120.67, 61.45, 30.71, 25.80, 20.94.

ESI-MS: *m*/*z* = 231 [M + Na$^+$].

Mannich Reaction Followed by Elimination; General Procedure

To a solution of aminal (1 mmol) and cyclic enone (1.2 mmol) in anhyd MeCN (3 mL) under argon at r.t. was added freshly distilled

AcCl (2.4 mL, 3 mmol). The mixture was kept under argon and stirred for a further 17 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). The pure products were obtained after column chromatography (EtOAc–PE) on silica.

3,3-Dimethyl-5-methylene-6-oxocyclohex-1-enyl)methyl Acetate (34)
Yield: 129 mg (62%); colorless oil; 19% of starting enone was recovered.

(5-Methylene-6-oxocyclohex-1-enyl)methyl Acetate (35)
Yield: 99 mg (55%); colorless oil; 20% of starting enone was recovered.

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