Molecules **2006**, *11*, 357-364

molecules

ISSN 1420-3049
http://www.mdpi.org

Full Paper

Synthesis of Novel Sterically Demanding Carbo- and Heterocyclic β-Ketoesters

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Received: 16 December 2005; in revised form: 10 February 2006 / Accepted: 12 February 2006 / Published: 10 May 2006

Abstract: We present an easy method for the synthesis of β-ketoesters starting from various carbocyclic and heterocyclic carboxylic acids and esters. The β-ketoester side-chain was introduced by a sequence involving α-deprotonation and quenching with CO_2, conversion to the corresponding acid chloride and subsequent chain elongation using deprotonated ethyl acetate.

Keywords: Chain elongation, β-ketoesters, ethyl acetate, heterocyclic esters

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Introduction

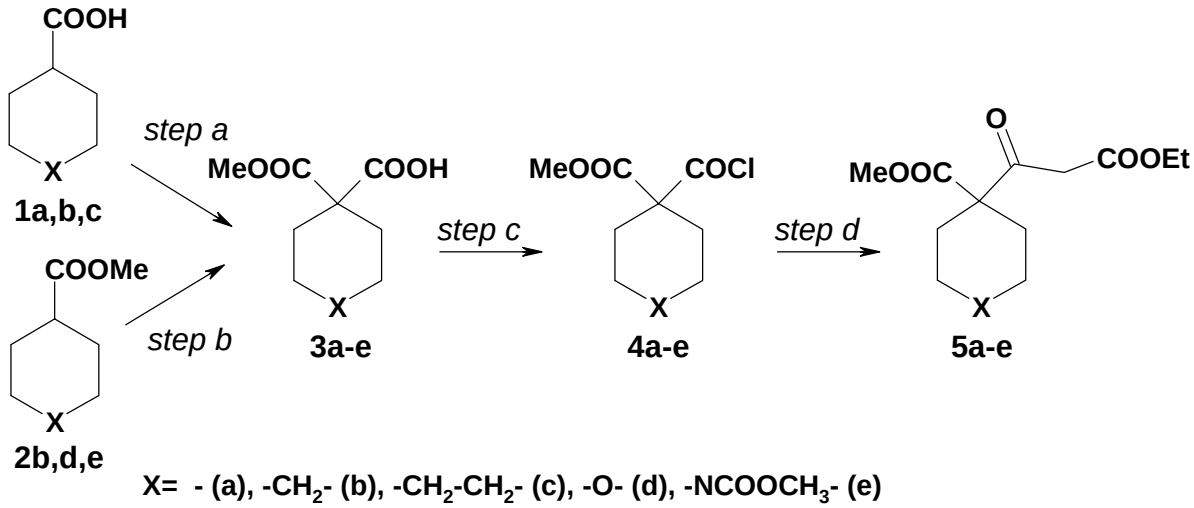
β-Ketoesters incorporating sterically demanding structural motifs have previously received attention as precursors for the synthesis of biologically active compounds such as CP-263,114 (Phomoidride B) and CP-225,917 (Phomoidride A), which were reported to inhibit *ras*-farnesyl transferase and squalene synthase [1]. Such compounds were also used as intermediates for the synthesis of bicyclononedionetetracarboxylic tetramethyl ester (BCN) metal chelates [2]. These products are of significant value in various applications such as catalysts, paint dryers, and motor fuel anti knock agents. A recent study demonstrated the applicability of β-ketoesters as key precursors for the synthesis of the C13 side chain of Taxol in a bioreductive approach [3]. Taxol and derivatives are currently used for the treatment of various kinds of cancer, such as ovarian, breast, and small cell lung cancer as well as melanoma. We envisioned such a strategy to incorporate functional groups with

increased polarity in combination with sterically demanding centers, which may improve the solubility of modified taxoids by preventing the hydrophobic collapse of the bioactive species [4].

Results and Discussion

In this contribution we present a versatile, robust, and efficient method for the synthesis of β-ketoesters with a quaternary center and a carbo- or heterocyclic structural core starting from various cyclic carboxylic acids **1** and esters **2** (Scheme 1). In a straightforward strategy, compounds **3a-e** were prepared by lithiation, either starting from the corresponding acid **1** and incorporating an ester functionality [5] with chloroacetic acid methyl ester (*step a*), or from the preceding ester **2** by introducing the acid functionality [6] with CO_2 (*step b*). Reaction conditions found in the literature were optimized to ensure complete lithiation prior to quenching with the corresponding electrophile (Table 1). For carbocyclic precursors introduction of the ester functionality via pathway *a* proved to give better yields than pathway *b*. In the case of heterocyclic starting materials, the corresponding esters were used as they are commercially available and introduction of the carboxylic acid functionality gave satisfactory yields. Formation of the acid halide **4** (*step c*) was accomplished with thionyl chloride using standard reaction conditions [7].

Scheme 1.



X= - (a), -CH_2- (b), -CH_2-CH_2- (c), -O- (d), -$NCOOCH_3$- (e)

Table 1.

conditions	step a LDA/ClCOOMe -75±5°C/THF	step b LDA/CO_2 -15°C/THF	step c $SOCl_2$ dry CH_2Cl_2/RT	step d LDA/EtOAc -80°C/THF
X	**Yields**			
-	83 %	-	99 %	58 %
-CH_2-	92 %	68 %	96 %	85 %
-CH_2-CH_2-	83 %	-	99 %	72 %
-O-	-	72 %	97 %	82 %
-$NCOOCH_3$	-	84 %	91 %	93 %

A key transformation of this synthetic pathway is the introduction of the side chain by reaction with deprotonated EtOAc to product **5** (*step d*) [8]. Following work-up protocols for related reactions from the literature under basic conditions usually led to formation of lithium enolates of compounds **5**, which were difficult to isolate. Such problems could be circumvented by hydrolyzing the crude reaction mixture with 2N HCl, which provided the required products usually in high yields.

Conclusions

In this work we developed a facile synthetic pathway for the formation of β-ketoesters incorporating a cyclic structural motif bearing a quaternary ester functionality. The reaction sequence was accomplished involving commercially available starting materials and simple steps in very good overall yields for both carbo- and heterocyclic systems.

Acknowledgements

The authors thank the Austrian Science Fund (FWF, project number P15781) for supporting this project.

Experimental

General

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40-63 μm). Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) and chemical shifts are reported in ppm using TMS as internal standard. Combustion analyses were carried out in the Microanalytic Laboratory, University of Vienna.

General procedure for the preparation of 1,1-dicarboxylic acid mono-methylesters introducing the ester functionality

Diisopropylamine (2-2.5 equiv.) in dry THF was treated with *n*-BuLi (2.5M in hexane, 2-2.5 equiv.) under nitrogen and stirred for 30 min at -40°C. Then carboxylic acid **1** (1 equiv.) was added and the mixture was heated to 50-60°C (reaction time depending on the acid). The mixture was cooled to -75±5°C, ethyl chloroformate (1 equiv.) was added, and the reaction was stirred for 30 min at this temperature. The solution was poured into the same amount of deionized water. The aqueous phase was washed three times with diethyl ether. Then the pH of the aqueous layer was adjusted to 2-3 with 2N HCl followed by triple extraction with diethyl ether. The combined organic layers were washed once with brine, dried over Na_2SO_4, and concentrated. According to NMR the products were pure and were used in the next step without further purification.

Cyclopentane-1,1-dicarboxylic acid methylester (**3a**)

Yield: 12.46cg (83%) as a yellow oil from diisopropylamine (30.7 mL, 219 mmol), dry THF (200 mL), *n*-BuLi (92.5 mL, 219 mmol), cyclopentanecarboxylic acid **1a** (10.0 g, 87.6 mmol in 30 mL dry THF) and ethyl chloroformate (6.7 mL, 87.6 mmol in 15 mL dry THF) with a deprotonation time of 3 hours at 50-60°C. ^{1}H-NMR δ: 1.36-2.35 (m, 8H, -$(CH_2)_4$-), 3.72 (s, 3H, -OCH_3), 11.36 (s, 1H, -COOH); ^{13}C-NMR δ: 25.4 (t, C3/C4), 34.6 (t, C2/C5), 52.7 (q, -OCH_3), 60.3 (s, C1), 172.8 (s, -COOMe), 178.8 (s, -COOH)

Cyclohexane-1,1-dicarboxylic acid methylester (**3b**)

Yield: 13.35 g (92%) as yellow crystals [6] from diisopropylamine (21.9 mL, 156 mmol), dry THF (150 mL), *n*-BuLi (64.7 mL, 156 mmol), cyclohexanecarboxylic acid **1b** (10.0 g, 78 mmol in 30 mL dry THF) and ethyl chloroformate (6 mL, 78 mmol in 15 mL dry THF) with a deprotonation time of 2 hours at 50-60°C. Mp: 74-77°C; ^{1}H-NMR δ: 1.39–2.06 (m, 10H, -$(CH_2)_5$-), 3.75 (s, 3H, -OCH_3), 10.17 (s, 1H, -COOH); ^{13}C-NMR δ: 22.6 (t, C3/C5), 24.9 (t, C4), 31.2 (t, C2/C6), 52.5 (q, -OCH_3), 55.0 (s, C1), 171.9 (s, -COOMe), 178.1 (s, -COOH)

Cycloheptane-1,1-dicarboxylic acid methylester (**3c**)

Yield: 11.67g (83%) as a yellow oil from diisopropylamine (29.6 mL, 210.9 mmol), dry THF (200 mL), *n*-BuLi (89.1 mL, 210.9 mmol), cycloheptanecarboxylic acid **1c** (10.0 g, 70.3 mmol in 30 mL dry THF) and ethyl chloroformate (5.4 mL, 70.3 mmol in 15 mL dry THF) with a deprotonation time of 4 hours at 50-60°C. ^{1}H-NMR δ: 1.36-2.19 (m, 12H, -$(CH_2)_6$-), 3.66 (s, 3H, -OCH_3), 9.97 (s, 1H, -COOH); ^{13}C-NMR δ: 23.8 (t, C4/C5), 29.8 (t, C3/C6), 33.6 (t, C2/C7), 52.5 (q, -OCH_3), 57.7 (s, C1), 172.9 (s, -COOMe), 178.9 (s, -COOH)

General procedure for the preparation of 1,1-dicarboxylic acid monomethylesters by introducing the acid functionality

n-BuLi (2.5M in hexane, 1.5-2 equiv.) was added to a stirred solution of diisopropylamine (1.5-2 equiv.) in dry THF (N_2, -10 to -15°C). After 15 min this mixture was treated dropwise (during 30 min) with a solution of methyl ester **2** (1 equiv.), followed by passing a fast and dry stream of CO_2 through the mixture for 15 min. The solution was then poured into the same amount of deionized water. The aqueous phase was separated and washed three times with diethyl ether. Then the pH of the aqueous layer was adjusted to 2-3 with 2N HCl and it was extracted three times with diethyl ether. The organic layer was washed once with brine, dried over Na_2SO_4 and evaporated. According to NMR the products were pure and were used in the next step without purification.

Cyclohexane-1,1-dicarboxylic acid methylester (**3b**)

Yield: 4.55 g (68%) as yellow crystals [6] from diisopropylamine (5.9 mL, 42 mmol), dry THF (50 mL), *n*-BuLi (25.2 mL, 42 mmol), and **2b** (5.09 g, 36 mmol).

Tetrahydropyran-4,4-dicarboxylic acid methylester (**3d**)

Yield: 9.5 g (72%) as colorless crystals from diisopropylamine (19.7 mL, 140.8 mmol), dry THF (200 mL), *n*-BuLi (59.5 mL, 140.8 mmol), and **2d** (10.0 g, 70.4 mmol).. Mp: 113-116°C; ^{1}H-NMR δ: 2.01-2.18 (m, 4H, H3/H5), 3.57-3.76 (m, 4H, H2/H6), 3.72 (s, 3H, -OCH_3), 10.25 (s, 1H, -COOH); ^{13}C-NMR δ: 30.8 (t, C3/C5), 52.2 (s, C4), 52.9 (q, -OCH_3), 64.6 (t, C2/C6), 170.9 (s, -COOMe), 175.1 (s, -COOH)

1,4,4-Piperidinetricarboxylic acid 1,4-dimethylester (**3e**)

Yield: 4.22 g (84%) as colorless crystals from diisopropylamine (5.8 mL, 41.1 mmol), dry THF (60 mL), *n*-BuLi (17.4 mL, 41.1 mmol), and **2e** (4.14 g, 20.55 mmol). Mp: 123-126°C; ^{1}H-NMR δ: 2.02 (t, J=6Hz, 4H, H3/H5), 3.43 (t, J=7Hz, 4H, H2/H6), 3.63 (s, 3H, -OCH_3), 3.69 (s, 3H, -$NCOOCH_3$), 10.15 (bs, 1H, -COOH); ^{13}C-NMR δ: 30.3 (t, C3/C5), 40.9 (t, C2/C6), 52.8 (q, -OCH_3), 52.9 (q, -OCH_3), 53.0 (s, C4), 156.1 (s, -NCOOMe), 170.1 (s, -COOMe), 173.9 (s, -COOH)

General procedure for the formation of acid chlorides

Thionyl chloride (2 equiv.) was added to a 10% solution of the corresponding dicarboxylic acid monomethyl ester (1 equiv.) and stirred for 2-6 days at room temperature. The crude material was isolated after evaporation of the volatiles *in vacuo*. According to NMR the products were pure and were used in the next step without further purification.

1-Chlorocarbonylcylopentane-1-carboxylic acid methyl ester (**4a**)

Yield: 4.22 g (84%) as a red brown oil from compound **3a** (12.46 g, 72.4 mmol) and thionyl chloride (10.5 mL, 144.8 mmol). ^{1}H-NMR δ: 1.36-2.35 (m, 8H, -$(CH_2)_4$-), 3.72 (s, 3H, -OCH_3); ^{13}C-NMR δ: 25.3 (t, C3/C4), 34.9 (t, C2/C5), 53.1 (q, -OCH_3), 70.4 (s, C1), 170.6 (s,-COOMe), 173.1 (s, -COCl)

1-Chlorocarbonylcyclohexane-1-carboxylic acid methyl ester (**4b**)

Yield: 15.9 g (96%) as a red brown oil from compound **3b** (14.032 g, 75.35 mmol) and thionyl chloride (10.9 mL, 150.7 mmol). ^{1}H-NMR δ: 1.33–2.15 (m, 10H, $(CH_2)_5$), 3.72 (s, 3H, -OCH_3); ^{13}C-NMR δ: 22.5 (t, C3/C5), 24.8 (t, C4), 31.8 (t, C2/C6), 52.9 (q, -OCH_3), 64.7 (s, C1), 169.9 (s, -COOMe), 173.2 (s, -COCl)

1-Chlorocarbonylcycloheptane-1-carboxylic acid methyl ester (**4c**)

Yield: 11.35 g (99%) as a red brown oil from compound **3c (**10.47 g, 52.3 mmol) and thionyl chloride (7.6 mL, 104.6 mmol). ^{1}H-NMR δ: 1.41-2.21 (m, 12H, -$(CH_2)_6$-), 3.71 (s, 3H, -OCH_3); ^{13}C-NMR δ: 23.5 (t, C4/C5), 29.6 (t, C3/C6), 33.9 (t, C2/C7), 52.9 (q, -OCH_3), 67.7 (s, C1), 170.9 (s, -COOMe), 173.7 (s, -COCl)

4-Chlorocarbonyltetrahydopyran-4-carboxylic acid methyl ester (**4d**)

Yield: 10.02 g (97%) as a red brown oil from compound **3d** (9.438 g, 50.2 mmol) and thionyl chloride (7.3 mL, 100.4 mmol). ^{1}H-NMR δ: 2.09-2.20 (m, 4H, H3/H5), 3.62-3.68 (m, 4H, H2/H6), 3.76 (s, 3H, -OCH_3); ^{13}C-NMR δ: 31.4 (t, C3/C5), 53.3 (q, -OCH_3), 61.9 (s, C4), 64.0 (t, C2/C6), 168.8 (s, -COOMe), 172.4 (s, -COCl)

4-Chlorocarbonylpiperidine-1,4-dicarboxylic acid dimethyl ester (**4d**)

Yield: 4.13 g (91%) as a red brown oil from compound **3d** (4.22 g, 17.2 mmol) and thionyl chloride (2.5 mL, 34.4 mmol). As the reaction was not complete after 3 days another 2 equiv. of thionyl chloride were added and stirring was continued for another 3 days. ^{1}H-NMR δ: 2.11-2.25 (m, 4H, H3/H5), 3.50-3.58 (m, 4H, H2/H6), 3.70 (s, 3H, -$NCOOCH_3$), 3.83 (s, 3H, -$COOCH_3$); ^{13}C-NMR δ: 30.9 (t, C3/C5), 40.4 (t, C2/C6), 52.8 (q, -OCH_3), 53.4 (q, -OCH_3), 62.8 (s, C4), 155.6 (s, -NCOOMe), 168.8 (s, -COOMe), 172.4 (s, -COCl)

General procedure for the formation of the β-ketoesters

To a solution of diisopropylamine (2 equiv.) in dry THF (N_2, -20°C) *n*-BuLi (2.5M in hexane, 2 equiv.) was added and stirred for 15 min. Then the mixture was cooled to -80°C and dry ethyl acetate was added and stirred for 15 min at this temperature. Afterwards, the corresponding acid chloride (1 equiv, in dry THF) was added dropwise and the resulting mixture was stirred for further 2 hours. The reaction mixture was hydrolyzed by adding saturated NH_4Cl-solution and stirring for another 15 min. The mixture was then poured into the same amount of 2N HCl. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed once with brine, dried over Na_2SO_4 and concentrated. Purification was carried out by column chromatography.

1-(2-Ethoxycarbonylacetyl)cyclopentanecarboxylic acid methyl ester (**5a**)

Yield: 10.00 g (57%) as a yellow oil from diisopropylamine (20.2 mL, 144 mmol), dry THF (150 mL), *n*-BuLi (60.6 mL, 144 mmol), dry ethyl acetate (7 mL, 72 mmol), and **4a** (13.69 g, 72 mmol), followed by hydrolysis with saturated NH_4Cl-solution (8 mL). Product purification was achieved by chromatography on silica gel (300 g, 20:1 LP-EtOAc). Elemental analysis: calculated: C 59.49%, H 7.49% found: C 59.67%, H.7.32%; ^{1}H-NMR *keto* δ: 1.18 (t, J=7.18Hz, 3H, -CH_3), 1.48-2.18 (m, 8H, -$(CH_2)_4$-), 3.43 (s, 2H,-CH_2-), 3.65 (s, 3H, -OCH_3), 4.11 (q, J=7.16Hz, 2H, -OCH_2-); *enol* δ: 1.18 (t, J=7Hz, 3H, -CH_3), 1.48-2.18 (m, 8H, -$(CH_2)_4$-), 3.65 (s, 3H, -OCH_3), 4.11 (q, J=7Hz, 2H, -OCH_2-), 5.03 (s, 1H, =CH-), 12.29 (s, 1H, -OH); ^{13}C-NMR *keto* δ: 13.9 (q, -CH_3), 25.5 (t, C3/C4), 32.9 (t, C2/C5), 45.7 (t, C-α), 52.5 (q, -OCH_3), 61.2 (t, -OCH_2), 66.9 (s, C1), 166.7 (s, -COOMe), 173.2 (s, -COOEt), 198.3 (s, C=O); *enol* δ: 13.9 (q, -CH_3), 25.5 (t, C3/C4), 32.9 (t, C2/C6), 52.5 (q, -OCH_3), 61.2 (t, -OCH_2-), 66.9 (s, C1), 88,1(d, C-α), 166.7 (s, -COOMe), 173.2 (s, -COOEt), 178.1 (s, =C-OH)

1-(2-Ethoxycarbonylacetyl)cyclohexanecarboxylic acid methyl ester (**5b**)

Yield: 14.2 g (80%) as a yellow oil from diisopropylamine (20.2 mL, 143.8 mmol), dry THF (150 mL), *n*-BuLi (60.6 mL, 143.8 mmol), dry ethyl acetate (7 mL, 71.9 mmol), and **4b** (15.88 g, 71.9 mmol), followed by hydrolysis using saturated NH_4Cl-solution (8 mL). Product purification was achieved by chromatography on silica gel (300 g, 10:1 LP-EtOAc). Elemental analysis: calculated: C 60.92%, H 7.80% found: C 61.12%, H.7.62%; ^{1}H-NMR *keto* δ: 1.23 (t, J=7Hz, 3H, -CH_3), 1.17-2.12 (m, 10H, -$(CH_2)_5$-), 3.45 (s, 2H, -CH_2-), 3.71 (s, 3H, -OCH_3), 4.14 (q, J=7Hz, 2H, -OCH_2-); *enol* δ: 1.23 (t, J=7Hz, 3H, -CH_3), 1.17-2.12 (m, 10H, -$(CH_2)_5$), 3.71 (s, 3H, -OCH_3), 4.14 (q, J=7Hz, 2H, -OCH_2-), 5.09 (s, 1H, =CH-), 12.38 (s, 1H, -OH); ^{13}C-NMR *keto* δ: 13.9 (q, -CH_3), 22.6 (t, C3/C5), 25.1 (t, C4), 30.4 (t, C2/C6), 44.9 (t, C-α), 52.5 (q, -OCH_3), 61.3 (t, -OCH_2), 61.4 (s, C1), 166.8 (s, -COOMe), 171.9 (s, -COOEt), 199.9 (s, C=O); *enol* δ: 13.9 (q, -CH_3), 22.6 (t, C3/C5), 25.1 (t,C4), 30.4 (t,C2/C6), 52.5 (q,-OCH_3), 61.3 (t, -OCH_2-), 61.4 (s, C1), 88.5 (d, C-α), 166.8 (s, -COOMe), 171.9 (s, -COOEt), 176.2 (s, =C-OH)

1-(2-Ethoxycarbonylacetyl)cycloheptanecarboxylic acid methyl ester (**5c**)

Yield: 10.02 g (72%) as a yellow oil from diisopropylamine (14.4 mL, 103 mmol), dry THF (100 mL), *n*-BuLi (43.5 mL, 103 mmol), dry ethyl acetate (5 mL, 51.5 mmol), and **4c** (11.26 g, 51.5 mmol) followed by hydrolysis using saturated NH_4Cl-solution (7 mL). Product purification was achieved by chromatography on silica gel (300g, 10:1 LP:EtOAc). Elemental analysis: calculated: C 62.20%, H 8.20% found: C 62.45%, H.7.93%; ^{1}H-NMR *keto* δ: 1.29 (t, J=7Hz, 3H, -CH_3), 1.39-2.12 (m, 12H, -$(CH_2)_6$-), 3.39 (s, 2H,-CH_2-), 3.66 (s, 3H, -OCH_3), 4.12 (q, J=7Hz, 2H, -OCH_2-); *enol* δ: 1.29 (t, J=7Hz, 3H, -CH_3), 1.39-2.12 (m, 12H -$(CH_2)_6$), 3.66 (s, 3H, -OCH_3), 4.12 (q, J=7.11Hz, 2H, -OCH_2-), 5.03 (s, 1H, =CH-), 12.33 (s, 1H, -OH); ^{13}C-NMR *keto* δ: 13.9 (q, -CH_3), 23.5 (t, C4/C5), 29.9 (t, C3/C6)), 32.1 (t, C2/C7), 45.1 (t, C-α), 52.4 (q, -OCH_3), 61.2 (t, -OCH_2-), 63.8 (s, C1), 166.7 (s, -COOMe), 173.3 (s, -COOEt), 199.4 (s, C=O); *enol* δ: 13.9 (q, -CH_3), 23.5 (t, C4/C5), 29.9 (t, C3/C6), 32.1 (t, C2/C7), 52.4 (q,-OCH_3), 61.2 (t, -OCH_2-), 63.8 (s, C1), 87.9 (d, C-α), 166.7 (s, -COOMe), 173.3 (s, -COOEt), 179.6 (s, =C-OH)

4-(2-Ethoxycarbonylacetyl)tetrahydropyran-4-carboxylic acid methyl ester (**5d**)

Yield: 9.39g (82%) as a yellow oil from diisopropylamine (12.56 mL, 89.6 mmol), dry THF (100 mL), *n*-BuLi (37.9 mL, 89.6 mmol), dry ethyl acetate (4.4 mL, 44.8 mmol), and **4d** (9.26 g, 44.8 mmol) followed by hydrolysis using saturated NH_4Cl-solution (6 mL). Product purification was achieved by chromatography on silica gel (300g, 20:1 LP:EtOAc). Elemental analysis: calculated: C 55.81%, H 7.02% found: C 55.65%, H.6.74%; ^{1}H-NMR *keto* δ: 1.18 (t, J=7Hz, 3H, -CH_3), 1.81-2.14 (m, 4H, H3/H5), 3.41-3.75 (m, H2/H6), 3.44 (s, 2H, -CH_2-), 3.69 (s, 3H, -OCH_3), 4.11 (q, J=7Hz, 2H, -OCH_2-); *enol* δ: 1.18 (t, J=7Hz, 3H, -CH_3), 1.81-2.14 (m, 4H, H3/H5), 3.41-3.75 (m, H2/H6), 3.69 (s, 3H, -OCH_3), 4.11 (q, J=7Hz, 2H, -OCH_2-), 5.04 (s, 1H, =CH), 12.35 (s, 1H, -OH); ^{13}C-NMR *keto* δ: 13.9 (q, -CH_3), 29.9 (t, C3/C5), 44.5 (t, C-α), 52.8 (q, -OCH_3), 58.8 (s, C4), 61.4 (t, -OCH_2-), 64.4 (t, C2/C6), 166.4 (s, -COOMe), 170.9 (s, -COOEt), 198.5 (s, C=O); *enol* δ: 13.9 (q, -CH_3), 29.9 (t, C3/C5), 52.8

(q, -OCH_3), 58.8 (s, C4), 61.4 (t, -OCH_2-), 64.4 (t, C2/C6), 88.9 (d, C-α), 166.4 (s, -COOMe), 170.9 (s, -COOEt), 176.5 (s, =C-OH)

4-(2-Ethoxycarbonylacetyl)piperidine-1,4-dicarboxylic acid dimethyl ester (**5e**)

Yield: 4.54 g (93%) as a yellow oil from diisopropylamine (4.34 mL, 31 mmol), dry THF (150 mL), *n*-BuLi (13.1 mL, 31 mmol), dry ethyl acetate (1.5 mL, 15.5 mmol), and **4e** (4.08 g, 15.5 mmol) followed by hydrolysis using saturated NH_4Cl-solution (4 mL). Product purification was achieved by chromatography on silica gel (150 g, 7:1 LP:EtOAc). Elemental analysis: calculated: C 53.33%, H 6.71%, N 4.44% found: C 53.61%, H.6.78%, N 4.33%; ^{1}H-NMR *keto* δ: 1.27 (t, J=7Hz, 3H, -CH_3), 1.78-2.27 (m, 4H, H3/H5), 3.15-3.35 (m, H2/H6), 3.53 (s, 2H, -CH_2), 3.68 (s, 3H, -OCH_3), 3.79 (s, 3H, -$NCOOCH_3$), 4.19 (q, J=7Hz, 2H, -OCH_2-); *enol* δ: 1.27 (t, J=7Hz, 3H, -CH_3), 1.78-2.27 (m, 4H, H3/H5), 3.15-3.35 (m, H2/H6), 3.68 (s, 3H, -OCH_3), 3.79 (s, 3H, -$NCOOCH_3$), 4.19 (q, J=7Hz, 2H, -OCH_2-), 5.12 (s, 1H, =CH-), 12.47 (s, 1H, -OH); ^{13}C-NMR *keto* δ: 13.9 (q, -CH_3), 29.3 (t, C3/C5), 40.6 (t, C2/C6), 44.7 (t, C-α), 52.5 (q,-OCH_3), 52.8 (q, -NCOO$\underline{CH_3}$), 59.5 (s, C4), 61.3 (t, -OCH_2-), 155.5 (s, -NCOOMe), 166.3 (s, -COOMe), 170.7 (s, -COOEt), 198.5 (s, C=O); *enol* δ: 13.9 (q, -CH_3), 29.3 (t, C3/C5), 40.6 (t, C2/C6), 52.5 (q, -OCH_3), 52.8 (q, -NCOO$\underline{CH_3}$), 59.5 (s, C4), 61.3 (t, -OCH_2-), 88.9 (d, C-α), 155.5 (s, -NCOOMe), 166.3 (s, -COOMe), 170.7 (s, -COOEt), 176.2 (s, =C-OH).

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Sample Availability: Available from the authors.