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Synthesis and characterization of permethylated 1,3,5-tri- and 1,3,5,7-tetracarbonyl compounds

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ABSTRACT

Permethylated 1,3,5-tri- and 1,3,5,7-tetracarbonyl compounds were prepared and structurally characterized. 2,2,4,4-Tetramethyl-3,5-dioxoesters were prepared by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with acid chlorides and subsequent reaction with methyl iodide. 2,2,4,4,6,6-Hexa-substituted 3,5-dioxopimelates were prepared by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with methyl 3-chloro-3-oxopropanoate and subsequent methylation. The use of caesium carbonate as the base for the methylation proved to be important to achieve good yields. The conformation of the products was studied by experimental and theoretical methods (DFT calculations).

1. Introduction

1,3-Dicarbonyl compounds constitute one of the most important building blocks in organic chemistry and have found widespread applications. 1,3,5-Tricarbonyl compounds have also found several applications in organic and medicinal chemistry. A great variety of pharmacologically important natural products are biosynthetically derived from poly(β-oxo)carboxylic acids (polyketides).[1] This includes various anticancer drugs and antibiotics, which are clinically used.[1] Polyketides and related 1,3-oligocarbonyl derivatives represent important synthetic building blocks (e.g., for the synthesis of polyols by stereoselective reduction).[2] 1,3,5,7-Tetracarbonyl compounds and their higher homologues are mostly unstable and rapidly undergo an intramolecular aldol condensation to give polyhydroxylated arenes. Harris and co-workers reported the biomimetic synthesis of various polyketides, which rapidly undergo intramolecular aldol condensations, based on condensations of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with carboxylic acid derivatives.[3] We have reported the synthesis of various 3,5-dioxopentanoates based on condensation reactions of 1,3-bis(silyloxy)-1,3-butadienes with acid chlorides.[4] 3,5-Dioxopimelates are stable 1,3,5,7-tetracarbonyl compounds containing two terminal ester groups, which cannot undergo an intramolecular aldol condensation. Recently, we have reported the synthesis and first detailed spectroscopic characterization of 3,5-dioxopimelates by condensation of 1,3-bis(silyloxy)-1,3-butadienes with methyl 3-chloro-3-oxopropanoate.[5] Cyclopropanated and peralkylated polycarbonyl compounds cannot undergo intramolecular aldol condensations because they lack CH-acidic methylene groups. Recently, we have reported the synthesis of cyclopropanated 1,3,5-tricarbonyl compounds based on a combination of Claisen condensations and cyclopropanations.[6]

The dialkylation of 1,3-dicarbonyl compounds is frequently carried out in undergraduate student courses and often used in organic synthesis.[7] The first synthesis of a peralkylated 1,3,5-tricarbonyl compound, i.e., diethyl 2,2,4,4-tetraethylacetonedicarboxylate, has been reported in 1891 by von Pechmann and Dünschmann.[8a] Ried and co-workers reported the first synthesis of dimethyl 2,2,4,4-tetramethylacetonedicarboxylate (**A**) by reaction of dimethyl acetonedicarboxylate with methyl iodide in the presence of sodium methanolate (Fig. 1).[8b] However, all these products were not characterized by spectroscopic methods. Despite their structural simplicity and aesthetic attraction, peralkylated 1,3,5,7-tetracarbonyl compounds, such as **B** (Fig. 1) have, to the best of our knowledge, not been described in the literature so far.

Herein, we report the synthesis and characterization of a great variety of permethylated 1,3,5-tricarbonyl- and 1,3,5,7-tetracarbonyl compounds based on a new and convenient synthetic protocol. In addition, we report studies related to the conformation of the products by experimental and theoretical methods (DFT calculations). To our opinion, the molecules reported herein combine the

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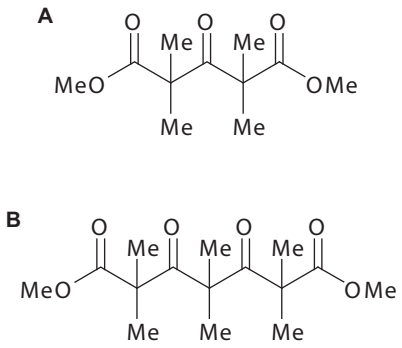
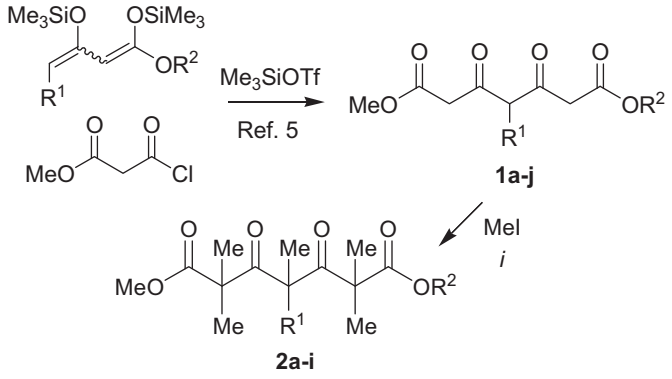


Fig. 1. Symmetrical permethylated diesters.

features of structural simplicity, aesthetic attraction, structural interest and novelty and are, therefore, of fundamental chemical and theoretical interest. In addition, polyketides are of interest as potential anticancer drugs and antibiotics as outlined above.

2. Results and discussion

Our original plan was to prepare permethylated 1,3,5-tricarbonyl and 1,3,5,7-tetracarbonyl compounds by base-mediated Claisen condensations. All attempts to realize this concept failed, due to fragmentation of the products by retro-Claisen reactions under the reaction conditions employed. The employment of silyl enol ethers instead of enolates also proved to be unsuccessful. Therefore, we changed our strategy and envisaged the direct base-mediated methylation of 1,3,5-tricarbonyl and 1,3,5,7-tetracarbonyl compounds. 1,3,5,7-Tetracarbonyl compounds **1a**–**j** were prepared, following our recently published procedure,[5] by reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with methyl 3-chloro-3-oxopropanoate (Scheme 1). The synthesis of derivatives **1a**,**b**,**h**–**j** has been previously reported.[5] All derivatives exist, as previously studied,[5] as mixtures of keto–enol tautomers (mainly in the form of the enolized central 1,3-diketone unit).



Scheme 1. Synthesis of **2a**–**i**. Conditions: i: MeI (7.0 equiv), Cs_2CO_3 (7.0 equiv), DMSO, 12 h (see Table 1); for products **1a**–**j** only the keto-form is depicted for clarity.

As a test reaction, we studied the transformation of dimethyl 3,5-dioxopimelate (**1a**) into hitherto unknown dimethyl 2,2,4,4,6,6-hexamethyl-3,5-dioxopimelate (**2a**) (Scheme 1, Table 1). The reaction of a DMSO solution of **1a** with methyl iodide (7.0 equiv), in the presence of potassium carbonate (K_2CO_3, 7.0 equiv), afforded the desired product **2a**, however, in only 12% yield (14 h, 20 °C, Table 1, entry 1). The low yield is a result of the formation of a complex mixture. Extension of the reaction time did not result in an improvement. An even more complex mixture was formed and no product at all could be isolated when the reaction was carried out at elevated temperature (55 °C, entry 2). A dramatic improvement of the yield (57%) was observed when caesium carbonate (Cs_2CO_3) instead of K_2CO_3 was employed (entry 4). While the concentration had no major influence on the yield (entry 6), the yield again dropped when the reaction was carried out at 55 instead of 20 °C (entry 5). The advantageous effect of the use of Cs_2CO_3 might be explained by its higher basicity. The low yields in case of K_2CO_3 can be explained by incomplete methylation and decomposition under the reaction conditions.

Table 1
Optimization of the synthesis of **2a**

Entry	*c* (**1a**) [M]	Base	*T* [°C]	Yield[a] [%] (**2a**)
1	1.0	K_2CO_3	20	12
2	1.0	K_2CO_3	55	0
3	0.85	K_2CO_3	20	12
4	1.0	Cs_2CO_3	20	57
5	1.0	Cs_2CO_3	55	30
6	0.5	Cs_2CO_3	20	56

[a] Yields of isolated products.

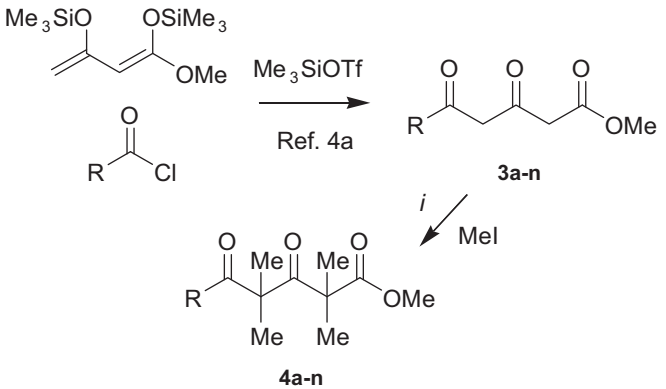
The preparative scope was next studied (Scheme 1, Table 2). All reactions were carried out following the optimized conditions discussed above (Table 1, entry 4). The reaction of unsymmetrical 3,5-dioxopimelates **1b**–**g** afforded the desired 1,3,5,7-tetracarbonyl compounds **2b**–**g** in good yields. The reaction of 3,5-dioxopimelates **1h**–**j**, containing a substituent R^1 located at the central carbon atom, afforded the corresponding permethylated products **2a** and **2h**,**i**. All products were isolated in good yields (45–77%) and are stable at −20 °C under an argon atmosphere.

Table 2
Synthesis of **2a**–**i**

1	**2**	R^1	R^2	Yield[a] [%] (**1**)	Yield[a] [%] (**2**)
a	**a**	H	Me	86[b]	57
b	**b**	H	Et	77[b]	74
c	**c**	H	*i*-Pr	58	47
d	**d**	H	*i*-Bu	69	64
e	**e**	H	*i*-Pent	62	55
f	**f**	H	*n*-Oct	57	74
g	**g**	H	Bn	70	77
h	**a**	Me	Me	84[b]	62
i	**h**	Et	Et	46[b]	66
j	**i**	4-(MeO)C_6H_4	Et	62[b]	45

[a] Yields of isolated products.
[b] Ref. 5.

1,3,5-Tricarbonyl compounds **3a**–**h** and **3j** are available by condensation of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with various acid chlorides ROCl (Scheme 2). Dimethyl acetone-



Scheme 2. Synthesis of **4a**–**n**. Conditions: i: procedure A: MeI (7.0 equiv), Cs_2CO_3 (7.0 equiv), DMSO, 20 °C, 12 h; procedure B: MeI (5.0 equiv), K_2CO_3 (5.0 equiv), DMSO, 20 °C, 8 h.

1,3-dicarboxylate (**3i**) is commercially available. The methylation of **3a**–**d** and **3f**–**j**, in the presence of Cs_2CO_3 (7.0 equiv), afforded the 2,2,4,4-tetramethyl-3,5-dioxoesters of **4a**–**d** and **4f**–**j** in 20–73% yields (Scheme 2, Table 3). Interestingly, the employment of K_2CO_3 (5.0 equiv) instead of Cs_2CO_3 resulted in a significant decrease of the yields. An exception is the synthesis of cyclopropyl-substituted derivative **4e**, which completely failed when Cs_2CO_3 was used. In contrast, product **4e** could be isolated, albeit in only 22% yield, when K_2CO_3 was employed. Products **4m**,**n** were prepared using K_2CO_3 because the new protocol was not available at that time when the experiments were carried out. The low yields in case of K_2CO_3 can be explained by incomplete methylation and decomposition under the reaction conditions. All products are stable at −20 °C under an argon atmosphere.

Table 3
Synthesis of **4a**–**n**

3, **4**	R	Yield[a] [%] (**3**)	Yield[a] [%] (**4**, A)	Yield[a] [%] (**4**, B)
a	4-$(NO_2)C_6H_4$	65[b]	20	24
b	4-MeC_6H_4	55[c]	58	12
c	3-ClC_6H_4	61[c]	55	7
d	2-ClC_6H_4	59[b]	65	—[e]
e	*c*-Pr	91[b]	0	22
f	2-Furyl	67	73	17
g	2-Thienyl	61[d]	73	16
h	2-Naphthyl	62[b]	62	32
i	MeO	—[e]	65	—[g]
j	4-$(MeO)C_6H_4$	42[c]	33	—[g]
k	*c*-Hex	62	82	—[g]
l	2,6-$F_2C_6H_3$	48	31	—[g]
m	2-(NO_2)–3-MeC_6H_3	86[f]	—[g]	17
n	2-(NO_2)–5-FC_6H_3	86[f]	—[g]	11

[a] Yields of isolated products using procedure A or B (see legend of Scheme 2).
[b] See Ref. 4a.
[c] See Ref. 6b.
[d] See Ref. 4b.
[e] Commercially available.
[f] See Ref. 12.
[g] Experiment was not carried out.

The structure of **4a** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[9]

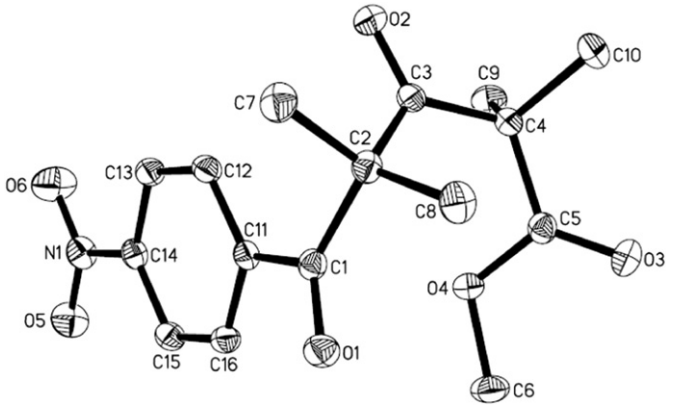


Fig. 2. The molecular structure of compound **4a**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

In a preceding paper[6] we had shown by DFT calculations[10,11] that bis-cyclopropanated 1,3,5-triketones are able to adopt conformations that can be designated *syn*/*anti* (with respect to the central carbonyl group). In such an arrangement, the substituents at both ends of the chain should be able to approach each other, which was proven by NMR spectroscopy (^{1}H NOESY measurements at dichloromethane solutions). These compounds are closely related to those investigated in the present paper by formally 'clipping' the three-membered rings and thus converting them into CMe_2 units. So we again conducted such experiments with the esters **4e**, **4a** and **4h**, and got indeed similar results. Despite averaged mirror symmetry for the molecules (C_s, planar zig–zag chain as in the drawings), we find NOE cross peaks incompatible with such a conformation. In both **4a** and **4h**, the aryl *ortho* protons exhibit contact with the adjacent (γ position) CMe_2 group (which is not surprising) as well as with the remote Me groups (α position). Furthermore, weak, positive NOE cross peaks occur between the methoxy singlet and the Me groups in γ position and the *ortho* aryl protons. These observations could not be made for **4e** because of insufficient signal separation (<0.01 ppm) of the methyl singlets. These results can only be explained by contribution of a distorted, probably *syn*/*anti*-like conformation (as described above) that allows the ends of the chain to approach each other.

Several conformations are possible for tetraketides **2**. In the ^{1}H and ^{13}C NMR spectra at ambient temperature only sharp signals are displayed, which indicate, that either one conformer is predominantly present or the interconversion of possible conformers is too fast for separate NMR detection. Temperature lowering to −80 °C for **2h** resulted only in minor line broadening of signals. Therefore, we have carried out ^{1}H NOESY experiments with **2h** and **2i**, respectively. These measurements gave hints for the existence of at least two conformers in the equilibria for both **2h** and **2i**. For example, in the NOESY spectrum of **2h** cross peaks were obtained between the CH_2 protons of the ethyl group at C-4 and both the OCH_3 and the OCH_2 protons. This points out a conformation where the substituents at both ends of the chain can approach the ethyl group at 4-position (picture A of compound **2h** in Fig. 3). Furthermore, we found also cross peaks between the protons of OCH_3 and CH_3-6 groups as well as between the protons of OCH_2CH_3 and CH_3-2. Such NOEs could only be expected for a conformation with a neighbourhood of the dimethyl groups in 2- or 6-position with the ethoxy, and methoxy groups, respectively (picture B of compound **2h** in Fig. 3). A statement concerning the conformations at the C-2,C-3 and C-5,C-6 bonds is not possible for **2h**, since the resonances of the methyl groups were not sufficiently separated. Similarly, the spectra of **2i** showed NOEs, which also prove the existence of at least two species in the conformational equilibrium. For example, cross peaks between the protons of *o*-Ph, *m*-Ph and CH_3-4 with OCH_3 and OCH_2 indicate to exist as well a conformer corresponding to A in Fig. 3. Furthermore, it was found that the CH_3-4 signal correlates with both the signals of CH_3-2 and CH_3-6 protons. The signals of both CH_3-2 groups also show cross peaks with OCH_2 and the signals for the CH_3-6 groups with OCH_3. These cross peaks point out as well a conformation which is represented by picture B (Fig. 3).

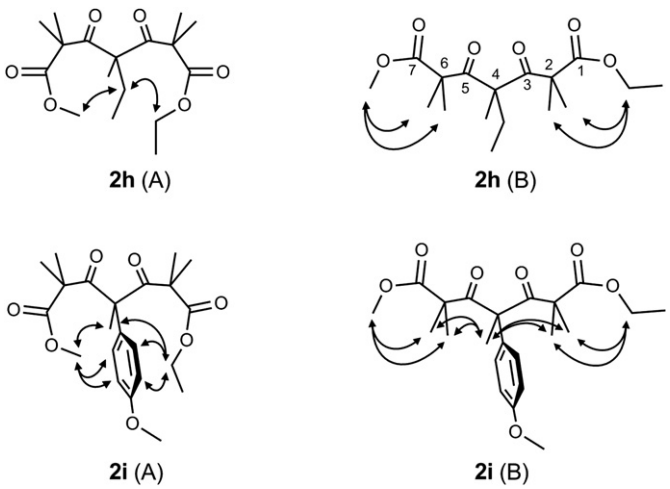


Fig. 3. Relevant NOE cross peaks found for compounds **2h** and **2i**.

Since the X-ray structural data of ester **4a** are available (Fig. 2, vide supra), we carried B3LYP/6-311+G** DFT calculations[10,11] on the conformational changes for reasons of comparison (see computational part and Supplementary data for details). On the basis of our analysis discussed above, we have found two stable conformers (Fig. 4). One conformer agrees well with the data reported by X-ray analysis (Fig. 2), which is also the more stable one; and the O2–C3–C2–C1 torsional angle is 115.1° (106.7° from X-ray analysis). The second conformer has the O2–C3–C2–C1 torsional angle of −22.7° and is less stable by 3.02 kcal/mol. The approximated equilibrium ratio should be more than 99 to 1 at room temperature. For analyzing the dynamic process, we have also computed the rotational barrier of the *para*-nitrophenyl around C1–C11 bond. For searching the potential energy surface, we have rotated the torsional angle O1–C1–C11–C16 by 360° for relaxed scan at the HF/6-31G* level. Two identical energy minimum structures and two identical energy maximum structures have been located. Further optimization of the maximum structures results in a transition state; the O1–C1–C11–C16 torsional angle is 117.4°, while that of the minimum structure is 11.0°; indicating a rotation of about 106°. As expected, the computed rotational barrier of 3.83 kcal/mol is rather small, in dictating the free rotation in solution.

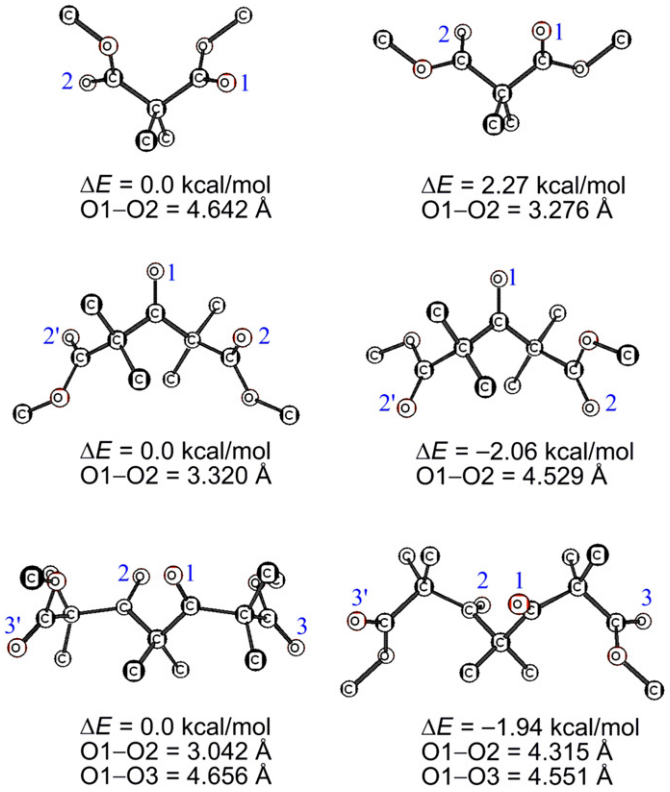
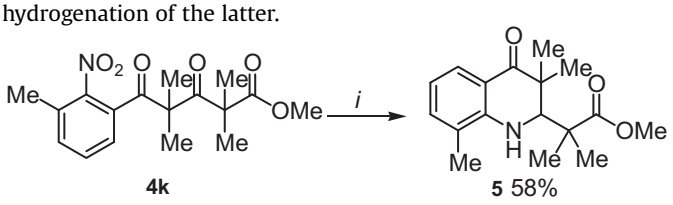


Fig. 4. Calculated relative energies and the O1–O2 distances at the B3LYP/6-311+G** level of theory of dimethyl dimethylmalonate (top), **4i** (middle) and **2a** (bottom). Hydrogen atoms are omitted for clarity.

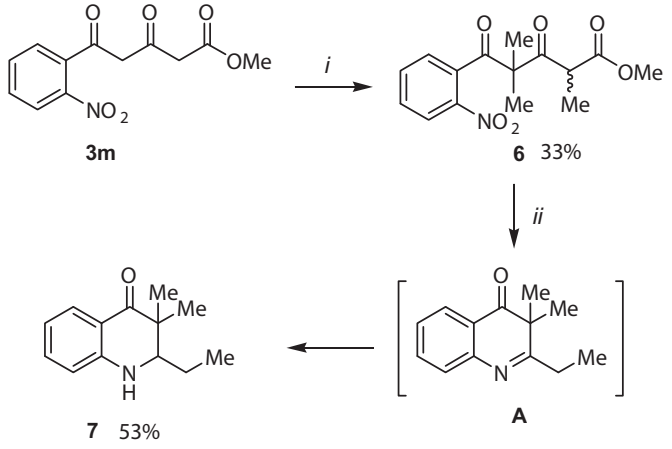
On the basis of our above discussion, conformations of tetraketide **2a** were also calculated. Since no crystal structure exists as a reference, the conformations of dimethyl dimethylmalonate as benchmark were calculated first. As shown in Fig. 4, two conformers were calculated for dimethyl dimethylmalonate. The energy difference at B3LYP/6-311+G** is 2.27 kcal/mol; the more stable conformer has a longer O1–O2 distance (4.642 Å) than the less stable conformer (3.276 Å). This indicates that the longer the distance of the two C=O groups, the more stable the isomer. On the basis of these results and also of the results obtained for cyclopropyl-polyketides,[6] two stable conformers have also been found for **4i**. The conformer with longer O1–O2 distance (4.529 Å) is 2.06 kcal/mol more stable than that one with shorter O1–O2 distance (3.320 Å). On the basis of our results, we have built the isomers of **2a** with the distances of the carbonyl groups as long as possible and two conformers of **2a** were obtained. The more stable conformer possesses, as expected, a longer O1–O2 distance (4.315 Å) than the less stable conformer (3.042 Å); the O1–O3 distance of the more stable isomer is 4.551 Å, which is close to that of the less stable conformer (4.656 Å).

Triketide **4k** was transformed by hydrogenation (H_2, Pd/C 10 mol %, MeOH), using our recently reported procedure,[12] into 4-quinolone **5** (Scheme 3). The formation of the product can be explained by transformation of the nitro to an amino group, attack of the latter to the carbonyl group to give an imine and subsequent hydrogenation of the latter.



Scheme 3. Synthesis of **5**. Conditions: i, Pd/C (10 mol %), H_2, MeOH, 12 h, 20 °C.

Surprisingly, the reaction of **3m** with 5.0 equiv of iodomethane, in the presence of potassium carbonate, resulted only in threefold methylation and formation of methyl 2,4,4-trimethyl-3,5-dioxopentanoate (**6**) (Scheme 4). The exact structure of **6** could be



Scheme 4. Synthesis of **7**. Conditions: i, MeI (5.0 equiv), K_2CO_3 (5.0 equiv), DMSO, 8 h, 20 °C; ii, Pd/C 10%, H_2, MeOH, 12 h, 20 °C.

clarified by its transformation into product **7** by hydrogenation (H_2, Pd/C 10 mol %, MeOH). The structure of **7** was independently confirmed by X-ray crystal structure analysis (Fig. 5).[8] The formation of **7** can be explained by reduction of the nitro to an amino group, attack of the latter to the carbonyl group to give imine **A** and subsequent hydrogenation of the imine.

In conclusion, we have reported the synthesis of permethylated 1,3,5-tri- and 1,3,5,7-tetracarbonyl compounds. 2,2,4,4-Tetramethyl-3,5-dioxoesters were prepared by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with acid chlorides and subsequent reaction with methyl iodide. 2,2,4,4,6,6-Hexa-substituted 3,5-dioxopimelates were prepared by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with methyl 3-chloro-3-oxopropanoate and subsequent methylation. The use of caesium carbonate as the base for the methylation proved to be important to achieve good yields. The structure and the conformation of the products were studied by combined experimental and computational methods.

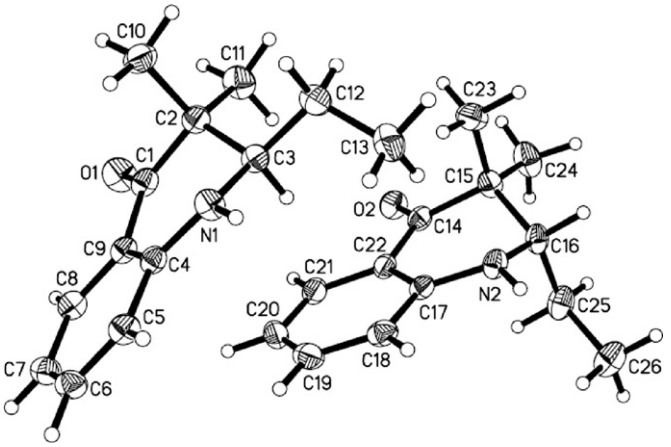


Fig. 5. The molecular structure of compound **7**. Displacement ellipsoids are drawn at the 30% probability level.

3. Experimental section

3.1. General

^{1}H NMR (300.13 MHz, 400.13 MHz and 500.13 MHz) and ^{13}C NMR spectra (75.5 MHz, 100.6 MHz and 125.8 MHz) were recorded on Bruker spectrometers AVANCE 300, AVANCE 400 and AVANCE 500. The chemical shifts are referenced to solvent signals ($CDCl_3$: δ ^{1}H=7.26, δ ^{13}C=77.0). The melting points are uncorrected.

3.2. Typical procedure for the synthesis of 3,5-dioxopimelates (1c–g)

To a CH_2Cl_2 solution (70 mL) of the 1,3-bis(trimethylsilyloxy)-1,3-butadiene (18.0 mmol) were added methyl malonyl chloride (0.819 g, 6.0 mmol, 0.64 mL) and TMSOTf (0.267 g, 1.2 mmol, 0.22 mL) at −78 °C under argon atmosphere. The solution was allowed to warm to 20 °C within 6 h and was stirred at this temperature for 12 h. To the solution was added a saturated aqueous solution of NH_4Cl (30 mL), the organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3×30 mL). The combined organic layers were extracted with a saturated aqueous solution of NaCl, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc=3:1). The products reside as mixtures of keto–enol tautomers. Only the enol signals (main tautomer) are listed. Products **1a**,**b**,**h**–**j** were prepared as previously reported.[5]

*3.2.1. 1-Isopropyl 7-methyl 3,5-dioxoheptanedioate (**1c**).* Starting with 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (2.31 g, 8 mmol), methyl malonyl chloride (0.43 mL, 4 mmol) and Me_3SiOTf (0.14 mL, 0.8 mmol) in CH_2Cl_2 (24 mL), the product was isolated as a yellow oil (0.567 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): *enol*: δ=1.22 (d, ^3J=6.3 Hz, 6H, CH_3), 2.92 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2), 5.00 (m, 1H, CH), 6.33 (s, 1H, CH), 12.05 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): *enol*: δ=21.7 (CH_3), 41.8 (C-7), 45.2 (C-3), 51.6 (OCH_3), 69.6 (CH), 100.3 (C-5), 168.1 (C-2,8) (CO), 190.1 (C-6), 198.9 (C-4). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2995 (w), 2934 (w), 2886 (w), 1736 (s), 1606 (m), 1434 (m), 1403 (w), 1248 (s), 1152 (s), 1017 (s). HRMS (ESI): calcd for $C_{11}H_{16}O_6$ ($[M+H]^+$) 245.03708, found 245.03722.

*3.2.2. 1-Isobutyl 7-methyl 3,5-dioxoheptanedioate (**1d**).* Starting with 1-isobutoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (2.42 g, 8 mmol), methyl malonyl chloride (0.43 mL, 4 mmol) and Me_3SiOTf (0.14 mL, 0.8 mmol) in CH_2Cl_2 (24 mL), the product was isolated as a yellow oil (0.713 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): *enol*: δ=0.95 (d, ^3J=6.7 Hz, 6H, CH_3), 1.86–1.99 (m, 1H, CH), 2.92 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.86 (d, ^3J=6.6 Hz, 2H, CH_2), 3.90 (s, 2H, CH_2), 6.33 (s, 1H, CH), 12.02 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): *enol*: δ=19.4, 19.4 (CH_3), 27.6 (CH), 41.5 (C-7), 45.2 (C-3), 51.6 (OCH_3), 70.8 (CH_2), 100.3 (C-5), 168.9 (C-2,8), 190.1 (C-6), 198.9 (C-4). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2991 (w), 2942 (w), 2891 (w), 1740 (s), 1600 (m), 1437 (m), 1409 (w), 1244 (s), 1150 (s), 1016 (s). HRMS (ESI): calcd for $C_{12}H_{18}O_6$ ($[M+H]^+$) 259.08403, found 259.08438.

*3.2.3. 1-Isopentyl 7-methyl 3,5-dioxoheptanedioate (**1e**).* Starting with 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (2.53 g, 8 m mol), methyl malonyl chloride (0.43 mL, 4 mmol) and Me_3SiOTf (0.14 mL, 0.8 mmol) in CH_2Cl_2 (24 mL), the product was isolated as a yellow oil (0.675 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): *enol*: δ=0.92 (d, ^3J=6.3 Hz, 6H, CH_3), 1.48–1.56 (m, 2H, CH_2), 1.58–1.74 (m, 1H, CH), 2.92 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2), 4.13 (t, ^3J=6.9 Hz, 2H, CH_2), 6.33 (s, 1H, CH), 12.04 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): *enol*: δ=22.9, 22.9 (CH_3), 24.3 (CH), 38.7 (CH_2), 41.5 (C-7), 45.2 (C-3), 51.6 (OCH_3), 62.5 (CH_2), 100.3 (C-5), 168.1 (C-2,8), 190.1 (C-6), 198.9 (C-4). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2990 (w), 2929 (w), 2878 (w), 1730 (s), 1610 (m), 1443 (m), 1399 (w), 1241 (s), 1155 (s), 1014 (s). HRMS (ESI): calcd for $C_{13}H_{20}O_6$ ($[M+H]^+$) 273.05273, found 273.05296.

*3.2.4. 1-Methyl 7-ocytl 3,5-dioxoheptanedioate (**1f**).* Starting with 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (2.51 g, 8 mmol), methyl malonyl chloride (0.43 mL, 4 mmol) and Me_3SiOTf (0.14 mL, 0.8 mmol) in CH_2Cl_2 (24 mL), the product was isolated as a yellow oil (0.717 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): *enol*: δ=0,86 (t, ^3J=6.6 Hz, 3H, CH_3), 1.25–1.40 (m, 28H, $5CH_2$, $6CH_3$), 1.61 (m, 2H, CH_2), 2.92 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2), 4.07 (t, ^3J=6.7 Hz, 2H, OCH_2), 6.33 (s, 1H, CH), 12.01 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): *enol*: δ=14.1 (CH_3), 22.6, 25.8, 28.3, 29.1, 29.1, 31.7 (CH_2), 41.5 (C-7), 45.2 (C-3), 51.6 (OCH_3), 65.3 (OCH_2), 100.3 (C-5), 168.1 (C-2,8), 190.1 (C-6), 198.9 (C-4). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2989 (w), 2936 (w), 2881 (w), 1739 (s), 1611 (m), 1437 (m), 1399 (w), 1253 (s), 1148 (s), 1015 (s). HRMS (ESI): calcd for $C_{16}H_{26}O_6$ ($[M+H]^+$) 315.11533, found 315.11567.

*3.2.5. 1-Benzyl 7-methyl 3,5-dioxoheptanedioate (**1g**).* Starting with 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (2.69 g, 8 m mol), methyl malonyl chloride (0.43 mL, 4 mmol) and Me_3SiOTf (0.14 mL, 0.8 mmol) in CH_2Cl_2 (24 mL), the product was isolated as a yellow oil (0.818 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): *enol*: δ=2.92 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2), 5.20 (s, 2H, CH_2Ph), 6.33 (s, 1H, CH), 7.32–7.35 (m, 5H, Ph), 12.05 (br, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): *enol*: δ=41.5 (C-7), 45.2 (C-3), 51.6 (OCH_3), 66.5 (CH_2Ph), 100.3 (C-5), 128.3, 128.4, 128.6, 135.1 (Ph), 168.1 (C-2,8), 190.1 (C-6), 198.9 (C-4). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2996 (w), 2933 (w), 2885 (w), 1732 (s), 1601 (m), 1429 (m), 1407 (w), 1254 (s), 1148 (s), 1010 (s). HRMS (ESI): calcd for $C_{15}H_{16}O_6$ ($[M+H]^+$) 293.16228, found 293.16231.

3.3. Procedure A for the synthesis of 2,2,4,4,6,6-hexamethyl-3,5-dioxopimelates 2a–i

To a DMSO solution (1 mL/1.0 mmol of **1**) of **1** (1 equiv) was added dry Cs_2CO_3 (7 equiv). Subsequently, MeI (7 equiv) was added at 0 °C. After 30 min the cooling was removed and the solution was stirred for 12 h. Brine (10 mL) and diethyl ether (10 mL) were added to the solution and the aqueous and organic layers were separated. The latter was extracted again with brine (3×10 mL). The organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The

residue was purified by column chromatography (silica gel, heptanes/EtOAc).

*3.3.1. Dimethyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2a**).* Starting with dimethyl 3,5-dioxoheptanedioate (**1a**) (0.500 g, 2.3 mmol), Cs_2CO_3 (5.24 g, 16.2 mmol) and iodomethane (1.02 mL, 16.2 mmol) in DMSO (2.3 mL), **2a** was isolated as a colourless oil (0.395 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 (s, 6H, CH_3), 1.42 (s, 12H, CH_3), 3.71 (s, 6H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.6, 24.2 (CH_3), 52.3 (OCH_3), 55.4, 64.1 (C), 174.0, 206.8 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988 (w), 2952 (w), 1738 (m), 1687 (s), 1459 (w), 1435 (w), 1387 (w), 1369 (w), 1254 (m), 1193 (m), 1142 (s), 1023 (m), 993 (m), 975 (m), 921 (w), 902 (w), 844 (w), 777 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 300 (M^+, 0.4), 199 (22), 171 (11), 129 (86), 101 (100), 73 (95), 70 (26), 69 (22), 59 (11), 42 (14), 41 (25). Anal. Calcd for $C_{15}H_{24}O_6$ (300.35): C, 59.98; H, 8.05. Found: C, 59.81; H, 8.04.

*3.3.2. 1-Ethyl 7-methyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2b**).* Starting with 1-ethyl 7-methyl 3,5-dioxoheptanedioate (**1b**) (0.500 g, 2.2 mmol), Cs_2CO_3 (4.95 g, 15.2 mmol) and iodomethane (0.95 mL, 15.2 mmol) in DMSO (2.2 mL), product **2b** was isolated as a colourless oil (0.508 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.21 (t, ^3J=7.3 Hz, 3H, CH_2CH_3), 1.34 (s, 6H, CH_3-4), 1.35 (s, 12H, CH_3-2,6), 3.65 (s, 3H, OCH_3), 4.10 (q, ^3J=7.3 Hz, 2H, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=13.8 (CH_2CH_3), 23.6, 24.0, 24.1 (CH_3-2,4,6), 52.2 (OCH_3), 55.3, 55.5 (C-2,6), 61.3 (OCH_2), 63.9 (C-4), 173.9 (C-7), 173.4 (C-1), 206.89, 206.92 (C-3,5). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2985 (w), 2949 (w), 1737 (m), 1709 (m), 1687 (s), 1468 (m), 1386 (m), 1367 (w), 1253 (m), 1142 (s), 1023 (m), 990 (m), 954 (w), 902 (w), 859 (w), 842 (w), 776 (w), 427 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 314 (M^+, 0.7), 269 (13), 237 (18), 213 (20), 199 (22), 185 (10), 143 (64), 129 (70), 115 (48), 111 (10), 101 (79), 87 (100), 73 (74), 70 (45), 69 (32), 59 (34), 43 (10), 42 (22), 41 (35), 29 (10). Anal. Calcd for $C_{16}H_{26}O_6$ (314.37): C, 61.13; H, 8.34. Found: C, 61.29; H, 8.56.

*3.3.3. 1-iso-Propyl 7-methyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2c**).* Starting with 1-isopropyl 7-methyl 3,5-dioxoheptanedioate (**1c**) (0.500 g, 2.0 mmol), Cs_2CO_3 (4.67 g, 14.3 mmol) and iodomethane (0.90 mL, 14.3 mmol) in DMSO (2.0 mL), **2c** was isolated as a colourless oil (0.310 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (d, ^3J=6.3 Hz, 6H, CH_3), 1.38 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 1.41 (s, 6H, CH_3), 3.69 (s, 3H, OCH_3), 5.00 (m, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 23.7, 23.9, 24.3 (CH_3), 52.3 (OCH_3), 55.4, 55.8 (C-2,6), 63.9 (C-4), 69.1 (CH), 173.0, 174.0, 207.1, 207.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2983 (w), 2942 (w), 2876 (w), 1734 (m), 1708 (m), 1687 (s), 1468 (m), 1386 (m), 1373 (w), 1254 (m), 1144 (s), 1103 (s), 1022 (m), 990 (m), 954 (w), 902 (m), 864 (w), 842 (w), 777 (w), 425 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 328 (M^+, 0.7), 269 (23), 255 (14), 237 (24), 199 (30), 185 (48), 157 (47), 140 (22), 139 (15), 129 (77), 115 (70), 111 (12), 102 (12), 101 (100), 87 (42), 73 (73), 71 (18), 70 (57), 69 (31), 59 (37), 43 (34), 42 (22), 41 (41). HRMS (ESI): calcd for $C_{17}H_{29}O_6$ ($[M+H]^+$) 329.1959, found 329.1963.

*3.3.4. 1-iso-Butyl 7-methyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2d**).* Starting with 1-isobutyl 7-methyl 3,5-dioxoheptanedioate (**1d**) (0.500 g, 1.9 mmol), Cs_2CO_3 (4.42 g, 13.5 mmol) and iodomethane (0.85 mL, 13.5 mmol) in DMSO (1.9 mL), product **2d** was isolated as a colourless oil (0.425 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (d, ^3J=6.7 Hz, 6H, CH_3), 1.39 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 1.41 (s, 6H, CH_3), 1.86–1.99 (m, 1H, CH), 3.69 (s, 3H, OCH_3), 3.86 (d, ^3J=6.6 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.0, 23.6, 24.1, 24.3 (CH_3), 27.6 (CH), 52.3 (OCH_3), 55.4, 55.7 (C-2,6), 64.0 (C-4), 71.4 (CH_2), 173.5, 174.0, 206.7, 207.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 2876 (w), 1736 (m), 1710 (m), 1688 (s), 1469 (m), 1386 (m), 1368 (w), 1253 (m), 1142 (s), 1022 (m), 989 (m), 952 (w), 922 (w), 842 (w), 776 (w), 430 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 342 (M^+, 1), 269 (23), 255 (14), 237 (24), 199 (38), 185 (38), 171 (50), 157 (13), 143 (13), 139 (18), 129 (94), 115 (76), 111 (13), 101 (100), 87 (23), 73 (90), 71 (24), 70 (63), 69 (36), 59 (46), 57 (52), 43 (16), 42 (27), 41 (56), 39 (11). Anal. Calcd for $C_{18}H_{30}O_6$ (342.43): C, 63.14; H, 8.83. Found: C, 63.10; H, 8.86.

*3.3.5. 1-iso-Pentyl 7-methyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2e**).* Starting with 1-isopentyl 7-methyl 3,5-dioxoheptanedioate (**1e**) (0.500 g, 1.8 mmol), Cs_2CO_3 (4.19 g, 12.8 mmol) and iodomethane (0.81 mL, 12.8 mmol) in DMSO (1.8 mL), product **2e** was isolated as a slight yellow oil (0.360 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (d, ^3J=6.3 Hz, 6H, CH_3), 1.42 (s, 12H, CH_3), 1.43 (s, 6H, CH_3), 1.48–1.56 (m, 2H, CH_2), 1.58–1.74 (m, 1H, CH), 3.71 (s, 3H, OCH_3), 4.13 (t, ^3J=6.9 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.4, 23.6, 24.1, 24.2 (CH_3), 25.0 (CH), 36.9 (CH_2), 52.3 (OCH_3), 55.4, 55.6 (C-2,6), 64.0 (C-4), 64.1 (CH_2), 173.6, 174.0, 206.9, 207.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (m), 2929 (m), 2871 (w), 1737 (s), 1711 (m), 1689 (s), 1466 (m), 1386 (m), 1368 (w), 1253 (m), 1142 (s), 1022 (m), 991 (m), 921 (w), 842 (w), 773 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 356 (M^+, 0.4), 237 (11), 199 (22), 185 (31), 129 (100), 101 (56), 73 (48), 71 (52), 70 (34), 69 (24), 59 (13), 43 (27), 42 (13), 41 (24). Anal. Calcd for $C_{19}H_{32}O_6$ (356.45): C, 64.02; H, 9.05. Found: C, 63.77; H, 9.32.

*3.3.6. 1-Methyl 7-octyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2f**).* Starting with 1-methyl 7-octyl 3,5-dioxoheptanedioate (**1f**) (0.500 g, 1.6 mmol), Cs_2CO_3 (3.63 g, 11.1 mmol) and iodomethane (0.70 mL, 11.1 mmol) in DMSO (1.6 mL), product **2f** was isolated as a colourless oil (0.470 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (t, ^3J=6.6 Hz, 3H, CH_3), 1.25–1.40 (m, 28H, $5CH_2$, $6CH_3$), 1.61 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 4.07 (t, ^3J=6.7 Hz, 2H, OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (CH_3), 22.6 (CH_2), 23.6, 24.1, 24.2 (CH_3), 25.8, 28.3, 29.1, 29.1, 31.7 (CH_2), 52.3 (OCH_3), 55.4, 55.6 (C-2,6), 64.0 (C-4), 65.6 (OCH_2), 173.6, 174.0, 206.9, 207.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 2928 (m), 2856 (w), 1738 (m), 1710 (m), 1688 (s), 1467 (m), 1386 (m), 1368 (w), 1253 (m), 1144 (s), 1022 (m), 991 (m), 903 (w), 842 (w), 775 (w), 723 (w), 429 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 398 (M^+, 0.9), 269 (16), 237 (14), 227 (27), 199 (48), 185 (42), 171 (21), 157 (13), 139 (13), 129 (100), 115 (16), 111 (40), 101 (81), 87 (12), 73 (45), 71 (39),70 (40), 69 (37), 59 (26), 57 (18), 55 (10), 43 (19), 42 (13), 41 (24). Anal. Calcd for $C_{22}H_{38}O_6$ (398.53): C, 66.30; H, 9.61. Found: C, 66.18; H, 9.56.

*3.3.7. 1-Benzyl 7-methyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2g**).* Starting with 1-benzyl 7-methyl 3,5-dioxoheptanedioate (**1g**) (0.500 g, 1.7 mmol), Cs_2CO_3 (3.90 g, 11.9 mmol) and iodomethane (0.75 mL, 11.9 mmol) in DMSO (1.7 mL), product **2g** was isolated as a slight yellow oil (0.494 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 6H, CH_3), 1.39 (s, 6H, CH_3), 1.43 (s, 6H, CH_3), 3.69 (s, 3H, OCH_3), 5.14 (s, 2H, CH_2), 7.32–7.35 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.6, 24.1, 24.2 (CH_3), 52.3, 55.4 (C-2,6), 55.7 (OCH_3), 64.0 (C-4), 67.1 (CH_2Ph), 128.3, 128.4, 128.6, 135.1 (Ph), 173.3, 174.0, 206.7, 207.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3090 (w), 3065 (w), 2987 (w), 2949 (w), 1736 (m), 1709 (m), 1687 (s), 1498 (w), 1456 (m), 1387 (m), 1368 (w), 1254 (m), 1132 (s), 989 (m), 737 (m), 697 (m), 602 (w), 424 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 376 (M^+, 0.1), 129 (15), 101 (18), 91 (100), 73 (17), 70 (10). Anal. Calcd for $C_{21}H_{28}O_6$ (376.44): C, 67.00; H, 7.50. Found: C, 67.25; H, 7.41.

*3.3.8. Dimethyl 2,2,4,4,6,6-hexamethyl-3,5-dioxoheptanedioate (**2a**) prepared from **1h**.* Starting with dimethyl 4-methyl-3,5-dioxoheptanedioate (**1h**) (0.500 g, 2.1 mmol), Cs_2CO_3 (4.95 g, 15.2 mmol) and iodomethane (0.96 mL, 15.2 mmol) in DMSO (2.1 mL), product **2a** was isolated as a colourless oil (0.404 g, 62%).

*3.3.9. 1-Ethyl 7-methyl 4-ethyl-2,2,4,6,6-pentamethyl-3,5-dioxoheptanedioate (**2h**).* Starting with 1-ethyl 7-methyl 4-ethyl

3,5-dioxoheptanedioate (**1i**) (0.600 g, 2.3 mmol), Cs_2CO_3 (5.30 g, 16.3 mmol) and iodomethane (1.0 mL, 16.3 mmol) in DMSO (2.3 mL), product **2h** was isolated as a slight yellow oil (0.506 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.72 (t, ^3J=7.3 Hz, 3H, CCH_2CH_3), 1.25 (t, ^3J=7.3 Hz, 3H, OCH_2CH_3), 1.37 (s, 3H, CH_3-4), 1.390 (s, 3H, CH_3-6), 1.394, 1.40 (2s, 2× 3H, CH_3-2,6), 1.41 (s, 3H, CH_3-2), 1.93 (m, AB part of ABX_3, 2H, CCH_2CH_3), 3.68 (s, 3H, OCH_3), 4.14 (q, ^3J=7.3 Hz, 2H, OCH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=9.2 (CCH_2CH_3), 13.8 (OCH_2CH_3), 19.3 (CH_3-4), 24.0, 24.3, 24.7, 24.8 (CH_3-2,6), 30.0 (CCH_2CH_3), 52.2 (OCH_3), 55.8, 56.0 (C-2,6), 61.3 (OCH_2), 68.3 (C-4), 173.4 (C-1), 173.9 (C-7), 205.6, 205.7 (C-3,5). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 2948 (w), 2884 (w), 1731 (m), 1686 (s), 1461 (m), 1385 (m), 1365 (w), 1251 (m), 1141 (s), 1062 (w), 1023 (m), 983 (m), 927 (w), 859 (m), 814 (w), 772 (w), 733 (w), 427 (w). HRMS (ESI): calcd for $C_{17}H_{29}O_6$ ([M+H]$^+$) 329.1959, found 329.1962. Anal. Calcd for $C_{17}H_{28}O_6$ (328.40): C, 62.17; H, 8.59. Found: C, 62.31; H, 8.55.

*3.3.10. 1-Ethyl 7-methyl 4-(4-methoxyphenyl)-2,2,4,6,6-pentamethyl-3,5-dioxoheptanedioate (**2i**).* Starting with 1-ethyl 7-methyl 4-(4-methoxyphenyl)-3,5-dioxoheptanedioate (**1j**) (0.260 g, 0.8 mm ol), Cs_2CO_3 (1.76 g, 5.4 mmol) and iodomethane (0.34 mL, 5.4 mmol) in DMSO (0.77 mL), product **2i** was isolated as a colourless oil (0.140 g, 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.15 (s, 3H, CH_3-6), 1.18 (s, 3H, CH_3-2), 1.18 (t, ^3J=7.3 Hz, 3H, OCH_2CH_3), 1.33 (s, 3H, CH_3-6), 1.34 (s, 3H, CH_3-2), 1.94 (s, 3H, CH_3-4), 3.55 (s, 3H, OCH_3), 3.80 (s, 3H, *p*-OCH_3), 4.00 (m, 2H, OCH_2), 6.85 (m, 2H, *m*-C_6H_4), 7.17 (m, 2H, *o*-C_6H_4). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=13.8 (OCH_2CH_3), 19.9 (CH_3-4), 23.63, 23.65, 24.88, 24.93 (CH_3-2,6), 52.1 (OCH_3), 55.2 (*p*-OCH_3), 55.8, 55.9 (C-2,6), 61.2 (OCH_2), 70.6 (C-4), 113.5 (*m*-C_6H_4), 127.7 (*i*-C_6H_4), 130.0 (*o*-C_6H_4), 159.3 (*p*-C_6H_4), 173.2 (C-1), 173.7 (C-7), 206.3, 206.4 (C-3,5). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (m), 2941 (w), 2839 (w), 1735 (m), 1709 (m), 1688 (m), 1608 (m), 1579 (w), 1512 (m), 1463 (m), 1385 (m), 1296 (m), 1252 (s), 1187 (m), 1142 (s), 1062 (w), 1025 (m), 989 (m), 928 (w), 836 (m), 797 (m), 731 (w), 682 (w), 632 (m), 593 (m), 533 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 406 (M$^+$, 13), 278 (11), 277 (70), 264 (13), 263 (87), 231 (58), 203 (45), 175 (24), 162 (35), 161 (49), 135 (14), 134 (51), 133 (100), 119 (19), 115 (16), 101 (21), 91 (18), 87 (38), 73 (30), 59 (18), 41 (10). Anal. Calcd for $C_{22}H_{30}O_7$ (406.47): C, 65.01; H, 7.44. Found: C, 65.18; H, 7.44.

3.4. General procedure for the synthesis of 1,3,5-tricarbonyl compounds 3

To a suspension of the 1,3-bis(silyl enol ether) (2.0 equiv) in CH_2Cl_2 (2 mL/mmol) was added the acid chloride (1.0 equiv) at −78 °C. The reaction mixture was allowed to warm to 20 °C and stirred for 12 h. After aqueous work-up using a saturated $NaHCO_3$ solution, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=2:1) to give product **3**. The synthesis of **3a**,**d**,**e**,**h**,[4a] **3g**,[4b] **3b**,**c**,**j**[6b] and **3m**,**n**[12] has been previously reported.

*3.4.1. Methyl 5-(2-furyl)-3,5-dioxopentanoate (**3f**).* Starting with 1-furoylchloride (0.75 mL, 5.76 mmol) dissolved in CH_2Cl_2 (10 mL) and 1,3-bis(silyl enol ether) (3.00 g, 11.52 mmol), **3f** was isolated as an orange oil (0.88 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$, keto/enol=0:100): δ=3.44 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 6.19 (s, 1H, CH), 6.56 (dd, ^3J=3.59, 1.73 Hz, 1H, CH), 7.19 (dd, ^3J=3.57 Hz, ^4J=0.75 Hz, 1H, CH), 7.59 (dd, ^3J=1.73 Hz, ^4J=0.77 Hz, 1H, CH), 15.22 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=44.4 (CH_2), 52.5 (CH_3), 96.5, 112.7, 116.4, 146.5 (CH), 149.8 (C), 168.0, 175.0, 185.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3133 (w, br), 2955 (w), 1738 (s), 1598 (s, br), 1466 (s), 1436 (s), 1387 (m), 1255 (s, br), 1227 (s), 1154 (s), 1090 (m), 1011 (s), 927 (m), 883 (s), 835 (m), 758 (s, br). MS (EI, 70 eV) *m*/*z*=210 (M$^+$, 31.2), 178 (54.1), 150 (17.2), 137 (90.9), 110 (19.5), 95 (100), 69 (26.7). Anal. Calcd for $C_{10}H_{10}O_5$ (210.18): C, 57.14; H, 4.80. Found: C, 57.15; H, 4.90.

*3.4.2. Methyl 5-cyclohexyl-3,5-dioxovalerate (**3k**).* Starting with 1-cyclohexanecarboxylic acid chloride (844 mg, 5.56 mmol) dissolved in CH_2Cl_2 (10 mL) and 1,3-bis(silyl enol ether) (3.00 g, 11.52 mmol), **3k** was isolated as a colourless oil (0.81 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$, keto/enol=0:100): δ=1.26–1.43 (m, 4H, CH_2), 1.67–1.96 (m, 6H, CH_2), 2.13–2.22 (m, 1H, CH), 3.35 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 5.59 (s, 1H, CH), 15.22 (br s, 1H, OH). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2929 (s), 2854 (s), 1744 (s), 1597 (s). HRMS (ESI): calcd for $C_{12}H_{19}NaO_4$ ([M+Na]$^+$) 249.10973, found 249.10989.

*3.4.3. Methyl 5-(2,6-Difluorophenyl)-3,5-dioxovalerate (**3l**).* Starting with 2,6-difluorobenzoyl chloride (1.02 g, 5.76 mmol) dissolved in CH_2Cl_2 (10 mL) and 1,3-bis(silyl enol ether) (3.00 g, 11.52 mmol), **3l** was isolated as an orange oil (0.79 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$, keto/enol=0:100): δ=3.47 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 6.02 (t, 1H, $^5J_{H,F}$=1.51 Hz, CH), 6.94–6.99 (m, 2H, Ph), 7.36–7.45 (m, 1H, Ph), 15.13 (s, 1H, OH). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−110.29. ^{13}C NMR (75 MHz, $CDCl_3$): δ=45.0 (CH_2), 52.5 (OCH_3), 103.7 (t, $^4J_{C,F}$=3.30 Hz, CH), 112.16 (d, $^2J_{C,F}$=23.11 Hz, CH–Ar), 112.2 (d, $^2J_{C,F}$=23.11 Hz, CH–Ar), 132.6 (t, $^3J_{C,F}$=11.00 Hz, CH–Ar), 160.3 (d, $^1J_{C,F}$=256.39 Hz, CF), 160.4 (d, $^1J_{C,F}$=256.39 Hz, CF), 167.6 (COH), 177.7 (CO_2Me), 187.7 (CO). MS (EI, 70 eV) *m*/*z*=241 (M−Me$^+$, 4), 224 (30), 196 (24), 183 (86), 141 (100), 113 (19), 69.

3.5. General procedure A for the synthesis of 2,2,4,4-tetramethyl-3,5-dioxopentanoates 4

To a DMSO solution (1 mL/1.0 mmol of **3**) of **3** (1 equiv) was added dry Cs_2CO_3 (7 equiv). Subsequently, MeI (7 equiv) was added at 0 °C. After 30 min, the cooling bath was removed and the solution was stirred for 12 h. Brine (10 mL) and diethyl ether (10 mL) were added to the solution and the aqueous and organic layers were separated. The latter was extracted again with brine (3×10 mL). The organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate).

*3.5.1. Methyl 2,2,4,4-tetramethyl-5-(4-nitrophenyl)-3,5-dioxopentanoate (**4a**).* Starting with methyl 5-(4-nitrophenyl)-3,5-dioxopentanoate (**3a**) (0.500 g, 1.9 mmol), Cs_2CO_3 (4.3 g, 13.2 mmol) and iodomethane (0.83 mL, 13.2 mmol) in DMSO (1.9 mL), product **4a** was isolated as a colourless solid (0.123 g, 20%); mp 67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.38 (s, 6H, CH_3), 1.52 (s, 6H, CH_3), 3.57 (s, 3H, OCH_3), 8.00 (AA′XX′, 2H, Ar), 8.27 (AA′XX′, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.0, 25.0, 52.1 (CH_3), 55.7, 62.4 (C), 123.6 (CH *meta*), 130.0 (CH *ortho*), 141.2 (C *ipso*), 149.8 (C *para*), 173.7, 196.2, 208.7 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3118 (w), 3003 (w), 2983 (w), 2959 (w), 2945 (w), 1742 (m), 1698 (m), 1671 (s), 1605 (w), 1520 (s), 1457 (w), 1441 (w), 1428 (w), 1393 (m), 1387 (m), 1346 (s), 1271 (m), 1241 (m), 1189 (m), 1167 (m), 1134 (s), 1042 (s), 1003 (m), 965 (s), 910 (m), 887 (m). MS (EI, 70 eV) *m*/*z*=321 (M$^+$, 0.2), 150 (100), 129 (10), 104 (15), 101 (14), 76 (10), 73 (18). Anal. Calcd for $C_{16}H_{19}NO_6$ (321.33): C, 59.81; H, 5.96; N, 4.36. Found: C, 60.10; H, 6.079; N, 4.39.

*3.5.2. Methyl 2,2,4,4-tetramethyl-3,5-dioxo-5-p-tolylpentanoate (**4b**).* Starting with methyl 3,5-dioxo-5-*p*-tolylpentanoate (**3b**) (0.641 g, 2.7 mmol), Cs_2CO_3 (6.2 g, 19.1 mmol) and iodomethane (1.2 mL, 19.1 mmol) in DMSO (2.7 mL), product **4b** was isolated as a colourless oil (0.459 g, 58%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (s, 6H, CH_3), 1.49 (s, 6H, CH_3), 2.38 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 7.20 (m, 2H, Ar), 7.76 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6, 24.4, 24.6 (CH_3), 52.0 (OCH_3), 56.0, 62.1 (C), 129.2, 129.3 (CH_{Ar}), 133.7, 143.7

(C_{Ar}), 173.6, 196.6, 209.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3017 (w), 3000 (w), 2978 (w), 2958 (w), 2942 (w), 2870 (w), 1733 (m), 1697 (m), 1661 (s), 1603 (m), 1570 (w), 1467 (m), 1438 (m), 1408 (w), 1382 (m), 1369 (w), 1271 (m), 1247 (m), 1196 (m), 1172 (m), 1142 (s), 1123 (m), 996 (m), 957 (m), 915 (m), 883 (w), 837 (s). MS (EI, 70 eV) *m*/*z*=290 (M^+, 0.6), 119 (100), 91 (15), 73 (5). Anal. Calcd for $C_{17}H_{22}O_4$ (290.35): C, 70.32; H, 7.64. Found: C, 70.48; H, 7.63.

*3.5.3. Methyl 5-(3-chlorophenyl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4c**).* Starting with methyl 5-(3-chlorophenyl)-3,5-dioxopentanoate (**3c**) (0.500 g, 1.9 mmol), Cs_2CO_3 (4.5 g, 13.7 mmol) and iodomethane (0.86 mL, 13.7 mmol) in DMSO (1.9 mL), product **4c** was isolated as a colourless oil (0.338 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.35 (s, 6H, CH_3), 1.49 (s, 6H, CH_3), 3.56 (s, 3H, OCH_3), 7.36 (dd, ^3J=8.0, 8.0 Hz, 1H, Ar), 7.50 (ddd, ^3J=8.0 Hz, ^4J=2.0, 2.0 Hz, 1H, Ar), 7.70 (ddd, ^3J=8.0 Hz, ^4J=2.0, 2.0 Hz, 1H, Ar), 7.85 (dd, ^4J=2.0, 2.0 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.2, 24.8 (CH_3), 52.1 (OCH_3), 56.0, 62.2 (C), 127.1, 129.2, 129.7, 132.7 (CH_{Ar}), 134.8, 137.8 (C_{Ar}), 173.6, 196.1, 208.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3071 (w), 2998 (w), 2986 (w), 2875 (w), 2950 (w), 1740 (m), 1699 (m), 1674 (s), 1570 (w), 1469 (m), 1434 (w), 1386 (m), 1368 (w), 1254 (m), 1142 (s), 1040 (m), 971 (s), 903 (w), 841 (w). MS (EI, 70 eV) *m*/*z*=312 (M^+, ^{37}Cl, 0.3), 310 (M^+, ^{35}Cl, 0.8), 209 (4), 141 (33), 140 (7), 139 (100), 129 (5), 111 (17), 101 (9), 73 (11). Anal. Calcd for $C_{16}H_{19}ClO_4$ (310.77): C, 61.84; H, 6.16; Cl, 11.41. Found: C, 62.14; H, 6.167; Cl, 11.22.

*3.5.4. Methyl 5-(2-chlorophenyl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4d**).* Starting with methyl 5-(2-chlorophenyl)-3,5-dioxopentanoate (**3d**) (0.450 g, 1.7 mmol), Cs_2CO_3 (4.0 g, 12.3 mmol) and iodomethane (0.78 mL, 12.3 mmol) in DMSO (1.9 mL), product **4d** was isolated as a colourless oil (0.354 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 6H, CH_3), 1.42 (s, 6H, CH_3), 3.56 (s, 3H, OCH_3), 7.17–7.34 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.4, 24.0 (CH_3), 52.2 (OCH_3), 55.4, 63.5 (C), 126.0, 127.4, 130.1 (CH_{Ar}), 130.4 (C_{Ar}), 130.4 (CH_{Ar}), 138.6 (C_{Ar}), 174.0, 203.0, 207.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988 (w), 2940 (w), 1742 (m), 1707 (s), 1682 (m), 1589 (w), 1456 (m), 1442 (m), 1431 (m), 1391 (w), 1367 (w), 1264 (m), 1235 (w), 1186 (w), 1155 (m), 999 (m), 969 (m), 894 (w), 772 (m), 744 (m), 703 (m), 469 (m), 399 (w). MS (EI, 70 eV) *m*/z=312 (M^+, ^{37}Cl, 0.1), 310 (M^+, ^{35}Cl, 0.3), 209 (1), 141 (34), 139 (100), 111 (14), 73 (12). Anal. Calcd for $C_{16}H_{19}ClO_4$ (310.77): C, 61.84; H, 6.16; Cl, 11.41. Found: C, 61.52; H, 6.27; Cl, 11.29.

*3.5.5. Methyl 5-cyclopropyl-3,5-dioxo-2,2,4,4-tetramethylpentanoate (**4e**).* Starting with **3e** (0.55 g, 3.0 mmol), K_2CO_3 (2.06 g, 14.9 mmol), DMSO (1.8 mL) and iodomethane (0.93 mL, 14.9 mmol), **4e** was isolated as a colourless oil (0.16 g, 22%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (m, 2H, CH_2), 1.02 (m, 2H, CH_2), 1.38 (s, 6H, CH_3), 1.39 (s, 6H, CH_3), 2.01 (m, 1H, CH), 3.67 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.4 (CH_2), 16.9 (CH), 22.4, 23.7, 52.3 (CH_3), 55.4, 63.3 (C), 173.9, 207.6, 207.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2999 (w), 2986 (w), 2951 (w), 1744 (m), 1707 (w), 1686 (s), 1469 (w), 1386 (m), 1258 (m), 1194 (m), 1141 (s), 1100 (w), 1061 (m), 1034 (m), 1020 (m), 992 (s), 953 (w), 917 (w), 861 (w). HRMS (ESI): calcd for $NaC_{13}H_{20}O_4$ ($[M+Na]^+$) 263.1254, found 263.1254. Anal. Calcd for $C_{13}H_{20}O_4$ (240.30): C, 64.98; H, 8.39. Found: C, 65.02; H, 8.30.

*3.5.6. Methyl 5-(furan-2-yl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4f**).* Starting with methyl 5-(furan-2-yl)-3,5-dioxopentanoate (**3f**) (0.400 g, 1.9 mmol), Cs_2CO_3 (4.4 g, 13.4 mmol) and iodomethane (0.84 mL, 13.4 mmol) in DMSO (1.9 mL), product **4f** was isolated as a colourless oil (0.377 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.33 (s, 6H, CH_3), 1.45 (s, 6H, CH_3), 3.58 (s, 3H, OCH_3), 6.51 (dd, ^3J=3.6, 1.7 Hz, 1H, CH), 7.17 (dd, ^3J=3.6 Hz, ^4J=0.7 Hz, 1H, CH), 7.53 (dd, ^3J=1.7 Hz, ^4J=0.7 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.0, 24.5 (CH_3), 52.1 (OCH_3), 55.7, 60.8 (C), 112.4, 118.4, 146.0 (CH), 151.5 (C), 173.7, 186.5, 207.0 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3138 (w), 2986 (w), 2949 (w), 1736 (m), 1703 (m), 1664 (s), 1566 (w), 1462 (s), 1384 (m), 1367 (w), 1275 (s), 1229 (m), 1194 (m), 1144 (s), 1082 (w), 1045 (m), 1012 (m), 971 (s), 898 (m), 885 (m), 865 (m), 838 (m). MS (EI, 70 eV) *m*/*z*=266 (M^+, 20), 165 (43), 137 (43), 129 (14), 123 (10), 109 (78), 101 (33), 95 (100), 73 (44), 41 (16), 39 (14). Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.21; H, 6.82.

*3.5.7. Methyl 2,2,4,4-tetramethyl-3,5-dioxo-5-(thien-2-yl)pentanoate (**4g**).* Starting with methyl 3,5-dioxo-5-(thien-2-yl)pentanoate (**3g**) (0.500 g, 2.2 mmol), Cs_2CO_3 (5.0 g, 15.5 mmol) and iodomethane (0.97 mL, 15.5 mmol) in DMSO (2.2 mL), product **4g** was isolated as a colourless oil (0.460 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (s, 6H, CH_3), 1.51 (s, 6H, CH_3), 3.59 (s, 3H, OCH_3), 7.06 (dd, ^3J=5.0, 3.9 Hz, 1H, CH), 7.56 (dd, ^3J=3.9 Hz, ^4J=1.0 Hz, 1H, CH), 7.61 (dd, ^3J=5.0 Hz, ^4J=1.0 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.1, 24.4 (CH_3), 52.2 (OCH_3), 55.9, 61.8 (C), 128.3, 132.9, 134.0 (CH), 143.4 (C), 173.6, 190.0, 208.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3104 (w), 2986 (w), 2949 (w), 1737 (m), 1699 (m), 1647 (s), 1515 (w), 1467 (m), 1410 (s), 1386 (m), 1368 (w), 1354 (m), 1255 (s), 1192 (m), 1139 (m), 1082 (w), 1062 (m), 1033 (s), 996 (m), 951 (m), 927 (m), 901 (m), 875 (w), 848 (m), 831 (m), 724 (s). MS (EI, 70 eV) *m*/*z*=282 (M^+, 6), 181 (8), 125 (6), 111 (100), 101 (11), 73 (17). Anal. Calcd for $C_{14}H_{18}O_4S$ (282.36): C, 59.55; H, 6.43; S, 11.36. Found: C, 59.81; H, 6.45; S, 11.35.

*3.5.8. Methyl 2,2,4,4-tetramethyl-5-(naphth-2-yl)-3,5-dioxopentanoate (**4h**).* Starting with methyl 5-(naphth-2-yl)-3,5-dioxopentanoate (**3h**) (0.500 g, 1.8 mmol), Cs_2CO_3 (4.2 g, 12.9 mmol) and iodomethane (0.81 mL, 12.9 mmol) in DMSO (1.8 mL), product **4h** was isolated as a colourless oil (0.367 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.35 (s, 6H, CH_3), 1.58 (s, 6H, CH_3), 3.52 (s, 3H, OCH_3), 7.51–7.62 (m, 2H, Ar), 7.84–7.98 (m, 4H, Ar), 8.36–8.38 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.6, 24.7, 52.1 (CH_3), 56.2, 62.3 (C), 124.9, 126.8, 127.7, 128.4, 128.7, 129.8, 130.9 (CH_{Ar}), 132.3, 133.6, 135.2 (C_{Ar}), 173.7, 197.0, 209.4 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 2985 (w), 2948 (w), 2873 (w), 1736 (m), 1697 (m), 1666 (s), 1626 (m), 1596 (w), 1466 (m), 1434 (m), 1386 (m), 1368 (w), 1264 (m), 1226 (m), 1193 (m), 1145 (m), 1120 (m), 1038 (m), 1021 (m), 972 (m), 937 (m), 909 (m), 865 (m), 854 (m), 826 (m), 779 (m), 760 (m), 634 (w), 601 (w), 586 (w), 560 (w), 476 (m). MS (EI, 70 eV) *m*/*z*=326 (M^+, 4), 155 (100), 141 (6), 128 (14), 127 (83), 126 (11), 101 (15), 73 (14). Anal. Calcd for $C_{20}H_{22}O_4$ (326.39): C, 73.60; H, 6.79. Found: C, 73.39; H, 6.80.

*3.5.9. Dimethyl 2,2,4,4-tetramethyl-3-oxopentanedioate (**4i**).* Starting with dimethyl 3-oxopentanedioate (**3i**) (0.600 g, 3.4 mmol), Cs_2CO_3 (7.86 g, 24.1 mmol) and iodomethane (1.5 mL, 24.1 mmol) in DMSO (3.4 mL), product **4i** was isolated as a colourless oil (0.508 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.39 (s, 12H, CH_3), 3.68 (s, 6H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.8 (CH_3), 52.3 (OCH_3), 55.2 (C), 173.8, 205.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2990 (w), 2953 (w), 1732 (m), 1699 (s), 1434 (m), 1385 (w), 1367 (m), 1260 (m), 1192 (m), 1035 (m), 1000 (m), 980 (m), 935 (w), 923 (w), 901 (w), 852 (w), 827 (w), 772 (w), 693 (w), 655 (w), 415 (w). MS (EI, 70 eV) *m*/*z*=230 (M^+, 0.6), 199 (12), 129 (55), 102 (10), 101 (76), 73 (100), 70 (11), 69 (11), 59 (13), 42 (10), 41 (20). Anal. Calcd for $C_{11}H_{18}O_5$ (230.26): C, 57.38; H, 7.88. Found: C, 57.57; H, 7.90.

*3.5.10. Methyl 5-(4-methoxyphenyl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4j**).* Starting with methyl 5-(4-methoxyphenyl)-3,5-dioxopentanoate (**3j**) (0.400 g, 1.6 mmol), Cs_2CO_3 (3.64 g, 11.2 mmol) and iodomethane (0.70 mL, 11.2 mmol) in DMSO (1.9 mL), product **4j** was isolated as a colourless oil (0.160 g, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (s, 6H, CH_3), 1.44 (s, 6H, CH_3), 3.51 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.84 (m, 2H, Ar), 7.82 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.3, 24.5 (CH_3), 51.9 (OCH_3), 55.3 (OCH_3), 56.0, 61.8 (C), 113.5 (CH_{Ar}), 129.0 (C_{Ar}), 131.5 (CH_{Ar}), 163.1 (C_{Ar}), 173.5,

195.2, 209.3 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 2947 (w), 2841 (w), 1736 (m), 1697 (m), 1664 (s), 1598 (s), 1573 (m), 11,510 (m), 1460 (m), 1385 (m), 1367 (w), 1312 (m), 1153 (s), 1028 (m), 996 (m), 952 (m), 912 (w), 840 (m), 803 (w), 771 (m), 694 (w), 635 (w), 613 (m), 520 (m), 423 (w). MS (EI, 70 eV) *m*/*z*=306 (M^+, 0.8), 136 (12), 135 (100). Anal. Calcd for $C_{17}H_{22}O_5$ (306.35): C, 66.65; H, 7.24. Found: C, 66.57; H, 7.32.

*3.5.11. Methyl 5-cyclohexyl-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4k**).* Starting with methyl 5-cyclohexyl-3,5-dioxopentanoate (**3k**) (0.226 g, 1.0 mmol), Cs_2CO_3 (2.281 g, 7.0 mmol) and iodomethane (0.44 mL, 7.0 mmol) in DMSO (1.0 mL), product **4k** was isolated as a colourless oil (0.231 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.20–1.26 (m, 4H, CH_2), 1.37 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 1.61–1.77 (m, 6H, CH_2), 2.74–2.84 (m, 1H, CH), 3.69 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ=22.6, 23.8 (CH_3), 25.6, 25.6, 30.3 (CH_2), 45.9 (CH), 52.1 (OCH_3), 55.0, 63.4 (C_q), 174.1 (*C*$OOCH_3$), 207.4, 211.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 2930 (s), 2854 (m), 1746 (s), 1715 (s), 1687 (s). MS (EI, 70 eV): *m*/*z*=282 (M^+, 1), 172 (11), 140 (10), 111 (35), 83 (100), 55 (21), 41 (16). Anal. Calcd for $C_{16}H_{26}O_4$ (282.375): C, 68.06; H, 9.28. Found: C, 67.593; H, 9.252.

*3.5.12. Methyl 5-(2,6-difluorophenyl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4l**).* Starting with methyl 5-(2,6-difluorophenyl)-3,5-dioxopentanoate (**3l**) (0.256 g, 1.0 mmol), Cs_2CO_3 (2.281 g, 7.0 mmol) and iodomethane (0.44 mL, 7.0 mmol) in DMSO (1.0 mL), product **4l** was isolated as a colourless oil (0.095 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.44 (s, 6H, CH_3), 1.49 (s, 6H, CH_3), 3.70 (s, 3H, OCH_3), 6.90–6.95 (m, 2H, Ar), 7.36–7.41 (m, 1H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$) δ=−109.7 (s, C_{Ar}F). ^{13}C NMR (75 MHz, $CDCl_3$) δ=22.7, 23.3 (CH_3), 52.3 (OCH_3), 55.4, 64.0 (C_q), 111.7 (m, CH_{Ar}), 116.8 (t, $^2J_{C,F}$=24.0 Hz, C_{Ar}), 131.3 (t, $^3J_{C,F}$=9.9 Hz, CH_{Ar}), 158.4 (dd, $^1J_{C,F}$=249 Hz, $^3J_{C,F}$=8.3 Hz, CF), 174.0 (*C*$OOCH_3$), 199.1, 204.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3102 (w), 3065 (w), 2989 (m), 2952 (m), 2845 (w), 1745 (m), 1716 (s), 1693 (s), 1622 (s), 1588 (m). MS (EI, 70 eV): *m*/*z*=312 (M^+, 1), 211 (9), 141 (100), 129 (16), 101 (17), 73 (21). Anal. Calcd for $C_{16}H_{18}F_2O_4$ (312.309): C, 61.53; H, 5.81. Found: C, 61.523; H, 698.

3.6. General procedure for the synthesis of 4m,n

To a suspension of K_2CO_3 (5.0 equiv) in DMSO (0.3–0.5 mL/mmol) was added **3** (1.0 equiv). To the reaction mixture was dropwise added iodomethane (5.0 equiv) at 20 °C with vigorous stirring. After stirring at 20 °C for 8 h, K_2CO_3 was removed by filtration. The solid was thoroughly washed with diethyl ether. The filtrate was washed with water until the yellow colour disappears, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=2:1) to give product **4**.

*3.6.1. Methyl 5-(3-methyl-2-nitrophenyl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4m**).* Starting with **3k** (1.00 g, 3.58 mmol) dissolved in a suspension of K_2CO_3 (2.48 g, 17.91 mmol) in DMSO (2.1 mL) and iodomethane (1.11 mL, 17.91 mmol), **4m** was isolated as a yellow oil (0.21 g, 17%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.46 (s, 6H, CH_3), 1.51 (s, 6H, CH_3), 2.40 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 7.40–7.42 (m, 2H, Ar), 7.47–7.49 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.1, 23.9, 24.3, 52.3 (CH_3), 55.8, 63.0 (C), 125.7, 129.9 (CH_{Ar}), 131.9, 132.7 (C_{Ar}), 134.1 (CH_{Ar}), 173.6, 199.1, 208.0 (CO) (one signal not found). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988 (w), 2951 (w), 1744 (m), 1707 (m), 1683 (s), 1601 (w), 1533 (s), 1463 (m), 1387 (m), 1363 (m), 1262 (s), 1193 (m), 1141 (s), 1067 (w), 1029 (m), 978 (s), 902 (w), 856 (m), 826 (w). HRMS (ESI): calcd for $NaC_{17}H_{21}NO_6$ ($[M+Na]^+$) 358.12611, found 358.12581. Anal. Calcd for $C_{17}H_{21}NO_6$ (335.35): C, 60.89; H, 6.31; N, 4.18. Found: C, 60.76; H, 6.45; N, 3.95.

*3.6.2. Methyl 5-(5-fluoro-2-nitrophenyl)-2,2,4,4-tetramethyl-3,5-dioxopentanoate (**4n**).* Starting with **3k** (0.6 g, 2.12 mmol) dissolved in a suspension of K_2CO_3 (1.46 g, 10.59 mmol) in DMSO (1.3 mL) and iodomethane (0.7 mL, 10.59 mmol), **4n** was isolated as a colourless solid (0.08 g, 11%); mp 74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.47 (s, 6H, CH_3), 1.58 (s, 6H, CH_3), 3.73 (s, 3H, OCH_3), 7.21–7.41 (m, 2H, Ar), 8.19–8.23 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.4, 23.7 (CH_3), 52.4 (OCH_3), 55.6, 63.1 (C), 115.6 (d, ^2J=26.2 Hz, CH_{Ar}), 116.8 (d, ^2J=23.5 Hz, CH_{Ar}), 127.3 (d, ^3J=9.9 Hz, CH_{Ar}), 140.1 (d, ^3J=8.4 Hz, C_{Ar}), 141.8 (C_{Ar}), 165.3 (d, ^1J=261 Hz, CF), 173.6, 201.7, 208.7 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−99.97 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3114 (w), 3082 (w), 2993 (w), 2952 (w), 1744 (m), 1719 (m), 1688 (s), 1621 (w), 1585 (m), 1529 (s), 1474 (m), 1437 (m), 1406 (w), 1388 (w), 1346 (s), 1314 (w), 1272 (s), 1215 (m), 1194 (m), 1150 (s), 1086 (w), 1034 (m), 979 (m), 901 (w), 870 (s), 840 (s), 760 (m). HRMS (ESI): calcd for $NaC_{16}H_{18}FNO_6$ ($[M+Na]^+$) 362.10104, found 362.10084. Anal. Calcd for $C_{16}H_{18}FNO_6$ (339.32): C, 56.63; H, 5.35; N, 4.13. Found: C, 56.55; H, 5.25; N, 4.07.

*3.6.3. Methyl 5-(2-nitrophenyl)-2,4,4-trimethyl-3,5-dioxopentanoate (**6**).* Starting with **3m** (0.34 g, 1.28 mmol) dissolved in a suspension of K_2CO_3 (0.89 g, 6.41 mmol) in DMSO (0.8 mL) and iodomethane (0.40 mL, 6.41 mmol), **6** was isolated as a colourless oil (0.13 g, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 (d, ^3J=7.0 Hz, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.35 (q, ^3J=7.0 Hz, 1H, CH), 7.37 (dd, ^3J=7.6 Hz, ^4J=1.5 Hz, 1H, Ar), 7.60 (ddd, ^3J=8.3, 7.5 Hz, ^4J=1.5 Hz, 1H, Ar), 7.73 (ddd, ^3J=7.6, 7.5 Hz, ^4J=1.2 Hz, 1H, Ar), 8.18 (dd, ^3J=8.3 Hz, ^4J=1.2 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.1, 21.9, 23.2 (CH_3), 46.9 (CH), 52.5 (CH_3), 63.4 (C), 124.5, 127.0, 130.1, 134.4 (CH_{Ar}), 136.8, 145.3 (C_{Ar}), 170.9, 203.0, 205.9 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2990 (w), 2950 (w), 1744 (m), 1716 (m), 1693 (s), 1573 (w), 1527 (s), 1458 (m), 1346 (s), 1304 (m), 1208 (m), 1081 (m), 1031 (m), 994 (m), 952 (s), 915 (w), 954 (m), 791 (m). HRMS (ESI): calcd for $NaC_{15}H_{17}NO_6$ ($[M+Na]^+$) 330.0948, found 330.0946. Anal. Calcd for $C_{15}H_{17}NO_6$ (307.30): C, 58.63; H, 5.58, N, 4.56. Found: C, 58.71; H, 5.64, N, 4.52.

3.7. General procedure for the synthesis of quinolines 5 and 7

A MeOH solution of starting material and of Pd/C was stirred under a hydrogen atmosphere for 24 h at 20 °C. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was purified by crystallization of EtOAc/heptanes-mixtures.

*3.7.1. Methyl 2-methyl-2-(3,3,8-trimethyl-4-oxo-1,2,3,4-tetrahydroquinolin-2-yl)propanoate (**5**).* Starting with **4k** (0.10 g, 0.30 mmol) dissolved in a suspension of Pd/C (10%) in MeOH (1.2 mL) under H_2-atmosphere, **5** was isolated as a yellow solid (0.05 g, 58%); mp 144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.01 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.57 (d, ^3J=3.3 Hz, 1H, CH), 2.17 (s, 3H, CH_3), 4.56 (d, ^3J=3.9 Hz, 1H, NH), 6.59 (m, 1H, Ar), 7.15 (m, 1H, Ar), 7.66 (m, 1H, Ar) (one signal not found). ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.7, 19.3, 19.8, 26.2, 28.3 (CH_3), 44.6, 47.5 (C), 52.7 (CH), 66.2 (OCH_3), 116.3 (CH_{Ar}), 120.8 (C_{Ar}), 125.5, 135.6 (CH_{Ar}), 146.9 (C_{Ar}), 177.8, 198.7 (CO) (one signal not found). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3385 (m), 2981 (m), 2951 (w), 1730 (s), 1655 (s), 1605 (s), 1587 (m), 1524 (m), 1469 (m), 1455 (m), 1436 (m), 1367 (w), 1357 (w), 1330 (m), 1265 (m), 1232 (m), 1203 (m), 1190 (m), 1139 (s), 1116 (m), 1097 (m), 1037 (m), 989 (m), 971 (m), 945 (w), 927 (w), 882 (w), 854 (m), 830 (m), 803 (w), 786 (w), 764 (w), 752 (s). MS (EI, 70 eV) *m*/*z*=289 (M^+, 22.9), 271 (21.1), 256 (60.4), 212 (100), 188 (86.9), 172 (23.7), 160 (74.6), 146 (27.7), 128 (10.9), 115 (10.4), 91 (21.9), 77 (8.6). Anal. Calcd for $C_{17}H_{23}NO_3$ (289.37): C, 70.56; H, 8.01, N, 4.84. Found: C, 70.44; H, 7.93, N, 4.69.

*3.7.2. 2-Ethyl-3,3-dimethyl-2,3-dihydroquinolin-4(1H)-one (**7**).* Starting with **6** (0.23 g, 0.75 mmol) dissolved in a suspension of Pd/C

(10%) in MeOH (3.0 mL) under H_2-atmosphere, **7** was isolated as a yellow solid (0.08 g, 53%); mp 94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00–1.05 (m, 6H, CH_3), 1.23 (s, 3H, CH_3), 1.48–1.73 (m, 2H, CH_2), 3.10 (m, 1H, CH), 4.52 (s, 1H, NH), 6.66 (m, 1H, Ar), 6.71 (m, 1H, Ar), 7.29 (m, 1H, Ar), 7.83 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.2, 18.1, 21.2 (CH_3), 21.6 (CH_2), 45.1 (C), 63.0 (CH), 115.4 (CH_{Ar}), 117.l (C_{Ar}), 117.6, 128.3, 134.7 (CH_{Ar}), 149.7 (C_{Ar}), 199.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3381 (w), 3337 (m), 2968 (w), 2928 (w), 1646 (s), 1607 (s), 1581 (m), 1505 (s), 1482 (s), 1438 (m), 1378 (m), 1335 (s), 1307 (m), 1281 (m), 1262 (m), 1247 (m), 1230 (m), 1174 (m), 1155 (m), 1118 (m), 1094 (m), 1030 (m), 1006 (m), 976 (s), 952 (m), 908 (w), 883 (w), 857 (w), 837 (w), 789 (m). MS (EI, 70 eV) m/z=203 (M^+, 27.5), 174 (100), 160 (7.6), 146 (11.3), 132 (17.5). Anal. Calcd for $C_{13}H_{17}NO$ (203.28): C, 76.81; H, 8.43, N, 6.89. Found: C, 76.88; H, 8.37, N, 6.87.

3.8. Computational part

All calculations were carried out by using the Gaussian 03 program on the B3LYP/6-311+G** level of theory. All structures were first optimized at the B3LYP/6-31G* level of theory and characterized as either energy minimum without imaginary frequencies or transition state with only one imaginary frequency on the potential energy surface. The optimized structures were refined at the B3LYP/6-311+G** level. For discussion and comparison, the structural and energetic parameters at B3LYP/6-311+G** were used. See also Supplementary data.

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Supplementary data

Details of the computational studies. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.065.

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9. CCDC-812646 and 812647 contain all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk.
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