Michael Addition of Ketone Enolates to α,β-Unsaturated Esters or Amides in a One-Pot Procedure: Highly Efficient Effect of Lithium Salt Generated in situ on Organotin Enolate

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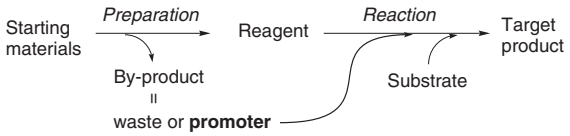
Abstract: Michael addition of a metal ketone enolate to an α,β-unsaturated ester is thermodynamically disfavored, and thus, isolated metal enolates with an equimolar amount of Lewis acids or additives are usually required. This work describes the methodology of one-pot Michael addition from the parent ketones and unsaturated esters to the products directly. The treatment of a parent ketone with *sec*-butyllithium and Bu_3SnBr gives a highly coordinated tin enolate that is complexed with LiBr generated in situ. The species is reactive and affords the Michael adducts, δ-keto esters and amides, in the reaction with α,β-unsaturated esters and amides, respectively.

Key words: tin enolates, ligand, Michael addition, unsaturated ester, high coordination

In order to produce a target compound in organic synthesis, multi-step reaction is generally required. Scheme 1 shows a typical and simplified picture, which involves the preparation of a reagent and its reaction toward the target product. The preparation of a reagent from starting materials involves two aspects that include production of a highly potential reagent and a low-energetic by-product (such as salts). The formed by-product is separated as waste, and the reaction of the isolated reagent with a substrate takes place in the presence of an appropriate promoter and/or catalyst. In this context, we thought that the total reaction from the original starting materials to the target molecule could be ideal and really practical if the formed by-product is not discarded as waste but can work as a promoter. In this case, the starting materials should be carefully chosen with consideration of the by-product as well as efficiency of the reaction pathway. We now report a Michael addition of metal ketone enolates to α,β-unsaturated esters or amides *based on the by-product/promoter concept* and show a significantly practical and efficient reaction pathway from the overall picture of the synthetic plan.



Scheme 1 Can a by-product be not a waste but a promoter?

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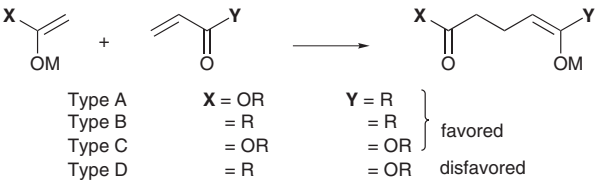
One-Pot Michael Addition of Ketone Enolates to α,β-Unsaturated Esters

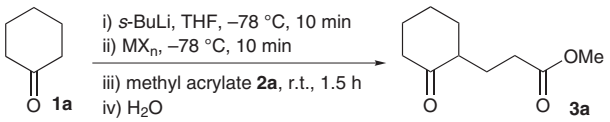
The Michael addition of metal enolates[1] (ketone or ester enolate) to α,β-unsaturated carbonyl compounds (enone or enoate) can be classified as four types A–D as shown in Scheme 2. As we have already discussed by theoretical calculations, only type D of the four types is thermodynamically disfavored while the other three types are favored.[2,3] In fact, the reactions using lithium enolates, which are fundamental metal enolates and have high nucleophilicity, were reported for types A–C.[4] However, type D has been hardly reported except for a few examples.[5] We actually tried the reaction of the lithium enolate derived from cyclohexanone (**1a**) with methyl acrylate (**2a**), and obtained a very low yield of the Michael adduct **3a** (Table 1, entry 1).[2,6] To overcome this serious problem for type D, reactions using silyl enolates in the presence of an equimolar or more amount of Lewis acids are often employed.[7] We recently reported a catalytic system for type D using tin enolates.[2,8] In any case, the metal enolates should be isolated and separated from the by-product before employing the Michael addition for type D, and a promoter or catalyst is required.



Scheme 2 Classification of Michael addition of metal enolates with α,β-unsaturated carbonyl compounds

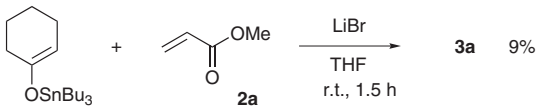
We examined the reaction system using lithium enolate with several metal halides (MtX_n) to prepare metal enolates in situ by considering the by-product metal salts (LiX) (Table 1). The use of $MgCl_2$, $ZnCl_2$, and $SnCl_2$ resulted in very low yields (entries 2-4) in the reaction with **2a**. Although the silyl enolate, which is used for the Mukaiyama Michael reaction,[7] would be generated in situ in entry 5, the product **3a** was not formed owing to low Lewis acidity of the by-product (LiCl).[9] Gratifyingly, the loading of tributyltin halides to the lithium enolate gave a high yield of the desired product (entries 6–10). Among the tin species examined, Bu_3SnBr was the best choice to

Table 1 Michael Addition of Ketone Enolate to Methyl Acrylate (**2a**)



Entry	Metal Halide (MX_n)	Yield (%)
1	none	9
2	$MgCl_2$	0
3	$ZnCl_2$	29
4	$SnCl_2$	0
5	Me_3SiCl	0
6	Et_3GeCl	23
7	Bu_3SnCl	51
8	Bu_3SnBr	72
9	Bu_3SnI	39
10	Bu_3SnOTf	62

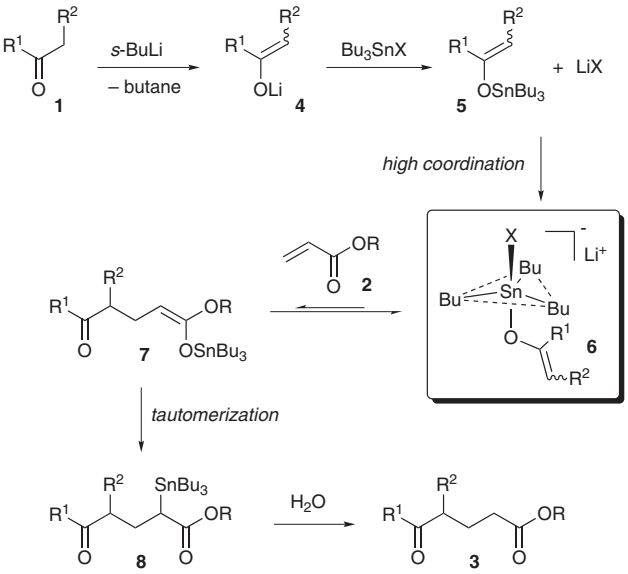
give **3a** in 72% yield (entry 8) in which the corresponding tin enolate and LiBr are generated in situ. It was surprising that only 9% of the product **3a** was formed in the reaction of isolated tin enolate from cyclohexanone with **2a** in the presence of LiBr (Scheme 3). We assume that the higher yield in the one-pot system would be ascribed to the in situ generated LiBr, which could have a different association state from the chemical grade LiBr. This result shows a very interesting and advantageous point and prompted us to investigate this one-pot methodology.



Scheme 3

Reaction Mechanism

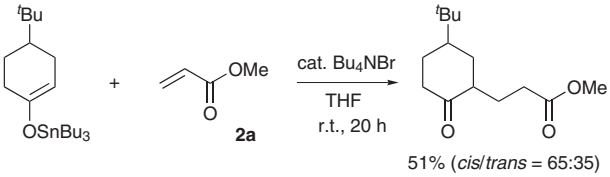
A plausible reaction mechanism is shown in Scheme 4. The treatment of parent ketone **1** with *s*-BuLi followed by the addition of Bu_3SnX gives tin enolate **5** and lithium halide (LiX). Because a tin enolate itself without additives does not react with enoates,[2,8] an interaction between **5** with the co-generated LiX should be included. The halide ion X^- coordinates to **5** to afford highly coordinated tin species **6**[10] that would have high reactivity toward the Michael acceptor **2** because of increment of the HOMO lobe at vinylic moiety and the increase of energy level of HOMO.[2] The transformation of the Michael adduct **7** into **8** by tautomerization contributes to the thermodynamic stabilization.[2] This type of tautomerization is a general feature of the tin species,[11] and thus, tin compounds are indispensable for this methodology. Hydrolysis of **8** gives δ-dicarbonyl compound **3**. Scheme 4 also explains the high dependency of the product yield on X because the halide ion directly activates the tin enolate as a ligand.



Scheme 4 Plausible reaction course

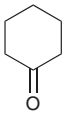
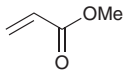
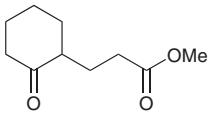
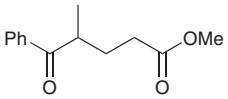
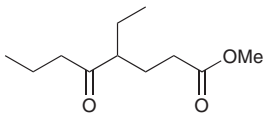
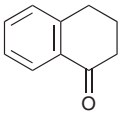
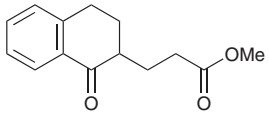
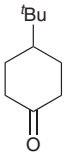
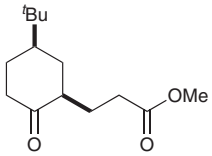
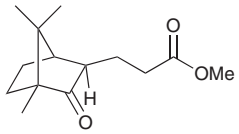
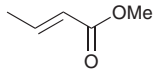
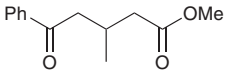
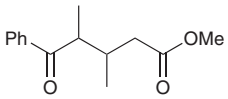
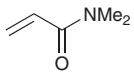
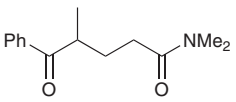
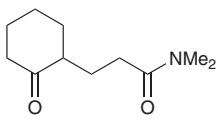
Synthesis of δ-Dicarbonyl Compounds

Table 2 shows the reactions of various ketones **1** and unsaturated carbonyls **2** mediated by *s*-BuLi and Bu_3SnBr. The corresponding δ-dicarbonyl compounds **3** were obtained in moderate to high yields. The loading of Bu_3SnBr was essential to accelerate the Michael addition because the treatment without tin compounds, in which the lithium enolate acts as an actual species, resulted in almost no reaction. Aromatic, aliphatic, and cyclic ketones are applicable to this system. The reaction with 4-*tert*-butylcyclohexanone (**1e**) gave the product **3e** as a single isomer. This selectivity is quite interesting because the corresponding reaction system using isolated tin enolate gave a mixture of diastereomers (Scheme 5).[2,12] When camphor (**1f**), whose tin enolate is difficult to be isolated pure because of high molecular weight, was used as the parent ketone, the product **3f** was obtained as a single isomer (entry 6). The α,β-unsaturated amide **2c** can be also used as a Michael acceptor to give δ-keto amides **3i** and **3j** in high yields (entries 9 and 10).



Scheme 5

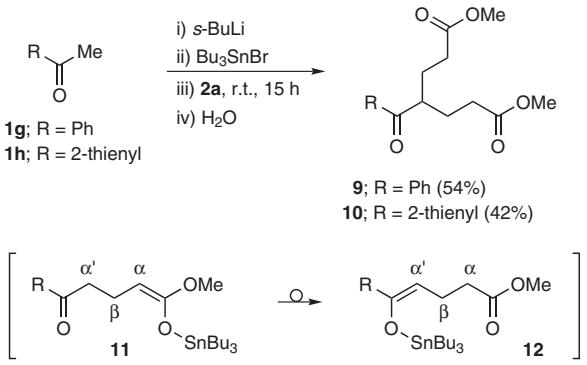
Table 2 Michael Addition of α,β-Unsaturated Esters or Amides Mediated by *s*-BuLi/Bu_3SnBr

Entry	Ketone	2	Time (h)	Product	Yield (%)[a]
1	 **1a**	 **2a**	1.5	 **3a**	72 (9)
2	 **1b**	**2a**	1	 **3b**	71 (0)
3	 **1c**	**2a**	13	 **3c**	28 (0)
4	 **1d**	**2a**	15	 **3d**	68 (0)
5	 **1e**	**2a**	16	 **3e**	76[b]
6	 **1f**	**2a**	16	 **3f**	23[b]
7	 **1g**	 **2b**	18	 **3g**	16
8	**1b**	**2b**	18	 **3h**	36[c]
9[d]	**1b**	 **2c**	28	 **3i**	73 (0)
10	**1a**	**2c**	23	 **3j**	83 (1)

[a] The values in parentheses show the yields from the reaction without Bu_3SnBr.
[b] Obtained as a single isomer.
[c] Obtained as a diastereomeric mixture (7:3).
[d] Reaction temperature 60 °C.

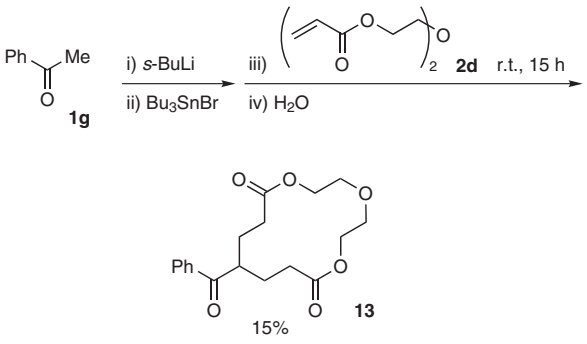
Application to Synthesis of Macrocycles

When acetophenone (**1g**) was used as the parent ketone in the reaction with **2a**, double introduction of **2a** unexpectedly took place to give the tricarbonyl compound **9** (Scheme 6), although the normal adduct was obtained in the case of substituted unsaturated ester **2b** (Table 2, entry 7). The same type of compound **10** was also formed from methyl thienyl ketone (**1h**). The initially formed Michael adduct **11** readily rearranges to **12** prior to tautomerization and it accepts the second enoate to give tricarbonyls. In all cases in Table 2, the initial adducts have substituents at the α′ or β-positions that suppress the rearrangement probably because of steric or conformational effect.



Scheme 6

We applied this system to the synthesis of macrocycles by using bis-unsaturated enoate **2d** and obtained the 14-membered lactone **13** in a one-pot reaction (Scheme 7). The results in Schemes 6 and 7 are in striking contrast to the reactions using isolated tin enolates that give normal alkylated products.[2]



Scheme 7

We have demonstrated a Michael addition of ketone enolates to α,β-unsaturated esters or amides to give δ-dicarbonyl compounds as a straightforward method which avoids production of waste. This method is now the most practical method for this type of Michael addition. It gives high yields of the products based on the whole reaction course. Highly coordinated tin enolates are included in the reaction course by a ketone/*s*-BuLi/Bu_3SnBr system, in which active lithium salt generated in situ plays an important role. Macrocycle synthesis was accomplished by this methodology using a bis-functional acceptor.

IR spectra were recorded as thin films. ^1H and ^{13}C NMR spectra were obtained with TMS as internal standard. Carbon resonance assignments were made by off-resonance or DEPT 135 spectral analyses. Mass spectra were recorded on a JEOL JMS-DS303. GLC analyses were performed on a Shimadzu GC-8A with FID using a 2 m × 3 mm column packed with SE-52 or OV-1. Column chromatography was performed on silica gel (Fuji Silysia BW-200). Bulb-to-bulb distillation (Kugelrohr) was accomplished in a Sibata GTO-250RS at the oven temperature and pressure indicated. Yields were determined by GC or ^1H NMR using internal standards.

THF was distilled from sodium and benzophenone. The ketones **1**, unsaturated esters **2**, *s*-BuLi (1 M in cyclohexane–hexane; 95:5, Aldrich) and metal halides used in text were commercially available. Tin enolates were prepared by the known method from enol acetate and tributyltin methoxide.[13]

δ-Dicarbonyl Compounds 3; General Procedure

s-BuLi (1 M in cyclohexane–hexane, 95:5, 2.0 mL, 2 mmol) was added to a solution of ketone **1** (2 mmol) in anhyd THF (5 mL) at –78 °C. After stirring for 10 min at the same temperature, Bu_3SnBr (739 mg, 2 mmol) was added to the mixture, which was stirred for 10 min. α,β-Unsaturated carbonyl compound **2** (2 mmol) was added at –78 °C, and the mixture was gradually warmed to r.t. during the time given in Table 2. Aq NH_4F (30%, 50 mL) and EtOAc (30 mL) were added, and the heterogeneous mixture was vigorously stirred for 20 min. The generated white precipitate of Bu_3SnF was removed by filtration. The filtrate was extracted with EtOAc, and the organic layer was dried ($MgSO_4$), and evaporated to give the crude product. Column chromatography of the resultant residue on silica gel followed by distillation or recrystallization gave the pure product.

Reaction of Tin Enolate Derived from 1a with 2a in the Presence of LiBr (Scheme 3)

The reaction of the tin enolate (1.0 mmol) with methyl acrylate (**2a**; 1.0 mmol) in the presence of LiBr (1.0 mmol; Aldrich, Lot No. 07513PY) in THF (5 mL) was carried out at r.t. for 1.5 h.

Bu_4NBr-Catalyzed Reaction of Isolated Tin Enolate Derived from 1e with 2a (Scheme 5)

The reaction of the tin enolate (1.0 mmol) with methyl acrylate (**2a**; 1.0 mmol) in the presence of Bu_4NBr (0.1 mmol) in THF (5 mL) was carried out at r.t. for 20 h.

Product Data

The spectral data of products **3a, 3b, 3i**, and **3j** were previously reported by us.[2,8a]

Methyl 4-Ethyl-5-oxooctanoate (3c)

According to the general procedure, this compound was prepared from **1c** and **2a** to give the product as a colorless liquid after chromatography (hexane–EtOAc, 7:3). Further purification was done by distillation; bp 60 °C/0.08 mmHg.

IR (neat): 1743, 1712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, OCH_3), 2.50–2.41 (m, 1 H, 4-H), 2.41 (t, *J* = 7.3 Hz, 2 H, 6-CH_2), 2.34–2.17 (m, 2 H, 2-CH_2), 1.98–1.88 (m, 1 H, 3-H^A), 1.78–1.54 (m, 4 H, 3-H^B, 4-CH^A, and 7-CH_2), 1.52–1.44 (m, 1 H, 4-CH^B), 0.91 (t, *J* = 7.4 Hz, 3 H, 8-CH_3), 0.87 (t, *J* = 7.4 Hz, 3 H, 4-CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.76 (C-5), 173.65 (C-1), 52.44 (C-4, +), 51.58 (OCH_3, +), 44.35 (C-6, –), 31.71 (C-2, –), 25.70 (C-3, –), 24.49 (4-CH_2CH_3, –), 16.93 (C-7, –), 13.80 (C-8, +), 11.57 (4-CH_2CH_3, +).

MS (EI, 70 eV): *m/z* (%) = 200 (M^+, 15), 169 (M^+ – OMe, 22), 141 (M^+ – CO_2Me, 11), 129 (41), 97 (42), 71 (100), 43 (47).

HRMS (EI, 70 eV): *m/z* calcd for $C_{11}H_{20}O_3$: 200.1412; found: 200.1426 (M^+).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.80; H, 9.79.

Methyl 3-(1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propionate (3d)

According to the general procedure, this compound was prepared from **1d** and **2a** to give the product as a colorless liquid after chromatography (hexane–EtOAc, 7:3). Further purification was accomplished by distillation; bp 130 °C/0.030 mmHg.

IR (neat): 1735, 1681 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.83 Hz, 1 H_{arom}), 7.48–7.43 (m, 1 H_{arom}), 7.33–7.20 (m, 2 H_{arom}), 3.68 (s, 3 H, OCH_3), 3.02 (dd, 2 H, 4′-CH_2), 2.61–2.47 (m, 1 H, 2′-H), 2.51 (t, *J* = 7.56 Hz, 2 H, 2-CH_2), 2.33–2.17 (m, 2 H, 3-H^A and 3′-H^A), 1.99–1.79 (m, 2 H, 3-H^B and 3′-H^B).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 199.46 (s, C=O), 173.83 (s, COO), 143.67 (s, Ar), 133.15 (d, Ar), 132.31 (s, Ar), 128.59 (d, Ar), 127.31 (d, Ar), 126.52 (d, Ar), 51.56 (q, OCH_3), 46.69 (d, C-2′), 31.63 (t, C-2), 28.74 (t), 28.59 (t, C-4′), 25.13 (t).

MS (EI, 70 eV): *m/z* (%) = 232 (M^+, 30), 200 (51), 146 (100), 118 (54), 90 (44).

HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{16}O_3$: 232.1099; found: 232.1078, 232.1106, 232.1098 (M^+).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.27; H, 6.79.

(2*R,4*R**)-4-*tert*-Butyl-2-(3-methoxy-3-oxopropyl)cyclohexanone (3e)**

According to the general procedure, this compound was prepared from **1e** and **2a** to give the product as a colorless liquid after chromatography (hexane–Et_2O, 3:1). Further purification was accomplished by distillation; bp 135 °C/0.014 mmHg.

IR (neat): 1739, 1716 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, OCH_3), 2.46–2.23 (m, 5 H, 6-CH_2, 2-H_{ax}, and 2-CH_2CH_2), 2.13–2.02 (m, 3 H, 3-H_{eq}, 5-H_{eq}, 2-$CH^A H^B CH_2$), 1.60 (dddd, 1 H, *J* = 12.6, 12.6, 3.0, 3.0 Hz, 4-H_{ax}), 1.55–1.49 (m, 1 H, 2-$CH^A H^B CH_2$), 1.43 (dddd, 1 H, *J* = 12.6, 12.6, 12.6, 4.8 Hz, 5-H_{ax}), 1.17 (ddd, 1 H, *J* = 12.6, 12.6, 12.6 Hz, 3-H_{ax}), 0.93 (s, 9 H, *t*-C_4H_9). The signal for 4-H at 1.60 (dddd, *J* = 12.6, 12.6, 3.0, 3.0 Hz) suggests that it is located at the axial position. The coupling constant between 2-H and 3-H_{ax} is 12.6 Hz because of the multiplicity of 3-H and decoupling NMR experiment. This large value suggests that 2-H is located at the axial position.

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 212.82 (s, C-1), 174.08 (s, COO), 51.47 (q, OCH_3), 48.69 (d, C-2), 47.00 (d, C-4), 41.64 (t, C-6), 35.30 (t, C-3), 32.38 (s, CMe_3), 31.63 (t, 2-$CH_2CH_2CO_2Me$), 28.75 (t, C-5), 27.59 [q, $C(CH_3)_3$], 24.87 (t, 2-$CH_2CH_2CO_2Me$).

MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 43), 208 (100), 124 (68), 57 (78).

HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{24}O_3$ 240.1725; found: 240.1738, 240.1725, 240.1726 (M^+).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.79; H, 10.28.

***trans*-3e**

This compound was a minor product in Scheme 5 and was not isolated pure. The selected signal in the crude mixture:

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 51.39 (OCH_3).

(1*R*,3*R*)-3-(3-Methoxy-3-oxopropyl)camphor (3f)

According to the general procedure, this compound was prepared from **1f** and **2a** to give the product as a colorless liquid after chromatography (hexane–EtOAc, 7:3). Further purification was accomplished by distillation; bp 150 °C/0.08 mmHg.

IR (neat): 1735 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, OCH_3), 2.54–2.43 (m, 2 H, 3-CH_2CH_2), 2.14–2.07 (m, 1 H, 3-CH^A), 2.06–1.97 (m, 1 H, 5-H_x), 1.92 (d, *J* = 3.9 Hz, 1 H, 4-H), 1.81 (dd, *J* = 8.1, 5.6 Hz, 1 H, 3-H), 1.75–1.67 (m, 1 H, 3-CH^B), 1.64 (ddd, *J* = 14.1, 11.1, 3.6 Hz, 1 H, 6-H_x), 1.47 (ddd, *J* = 14.1, 9.0, 5.0 Hz, 1 H, 6-H_n), 1.34 (ddd, *J* = 12.3, 9.0, 3.6 Hz, 1 H, 5-H_n), 0.93 (s, 3 H, 7-CH_3^A), 0.90 (s, 3 H, 1-CH_3), 0.85 (s, 3 H, 7-CH_3^B) (x = *exo*, n = *endo*). The decoupling NMR experiment shows that the coupling constant between 3-H and 4-H is less than 1 Hz (ca. 0 Hz). The double doublet signal at 3-H is caused by 3-CH_2. This small value suggests that 3-H is located at *endo* position.

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 221.00 (C-2), 173.71 (COO), 57.63 (C-1), 54.05 (C-3, +), 51.58 (OCH_3, +), 47.63 (C-4, +), 46.74 (C-7), 33.86 (3-CH_2CH_2, –), 29.32 (C-6, –), 29.22 (C-5, –), 27.03 (3-CH_2, –), 21.71 (7-CH_3^A, +), 20.45 (7-CH_3^B, +), 9.39 (1-Me, +).

MS (EI, 70 eV): *m/z* (%) = 238 (M^+, 36), 210 (100), 178 (75), 95 (89).

HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{22}O_3$: 238.1569; found: 238.1598, 238.1577 (M^+).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.35; H, 9.38.

Methyl 3-Methyl-5-oxo-5-phenylpentanoate (3g)

According to the general procedure, this compound was prepared from **1g** and **2b** to give the product as a colorless liquid after chromatography (hexane–Et_2O, 5:1). Further purification was accomplished by distillation; bp 130 °C/2 mmHg.

IR (neat): 1730, 1690 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.99–7.95 (m, 2 H_{arom}), 7.60–7.43 (m, 3 H_{arom}), 3.67 (s, 3 H, OCH_3), 3.12 (dd, *J* = 16.1, 5.9 Hz, 1 H, 4-H^A), 2.86 (dd, *J* = 16.1, 7.3 Hz, 1 H, 4-H^B), 2.68 (m, 1 H, 3-H), 2.46 (dd, *J* = 15.1, 6.4 Hz, 1 H, 2-H^A), 2.33 (dd, *J* = 15.1, 6.8 Hz, 1 H, 2-H^B), 1.05 (d, *J* = 6.8 Hz, 3 H, 3-CH_3).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 199.16 (s, C-5), 172.96 (s, C-1), 137.07 (s, *ipso*-C_{arom}), 133.00 (d, *p*-CH_{arom}), 128.55 (d, Ar), 128.08 (d, Ar), 51.42 (q, OCH_3), 44.81 (t, C-4), 40.86 (t, C-2), 26.82 (d, C-3), 20.08 (q, 3-CH_3).

MS (EI, 70 eV): *m/z* (%) = 220 (M^+, 0.6), 189 (M^+ – OCH_3, 5), 161 (M^+ – CO_2Me, 1.7), 147 (6), 120 (30), 105 (100), 77 (41).

HRMS (EI, 70 eV): *m/z* calcd for $C_{13}H_{16}O_3$: 220.1110; found: 220.1081, 220.1136, 220.1116 (M^+).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.84; H, 7.46.

Methyl 3,4-Dimethyl-5-oxo-5-phenylpentanoate (3h)

According to the general procedure, this compound was prepared from **1b** and **2b** to give the product (diastereomeric mixture, 70:30) as a colorless liquid after chromatography (hexane–Et_2O, 5:1). Further purification was done by distillation; bp 120 °C/2 mmHg.

IR (neat): 1735, 1682 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 234 (M^+, 8), 203 (M^+ – OCH_3, 8), 175 (M^+ – CO_2Me, 2), 161 (M^+ – CH_2CO_2Me, 12), 133 (4), 105 (100), 77 (21).

HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1251, 234.1237 (M^+).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.85; H, 7.54.

3h (Major)

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.10–7.40 (m, 5 H_{arom}), 3.68 (s, 3 H, OCH_3), 3.58 (qd, *J* = 7.3, 5.4 Hz, 1 H, 4-H), 2.57–2.39 (m, 1 H, 3-H), 2.44 (dd, *J* = 15.1, 6.8 Hz, 1 H, 2-H^A), 2.27 (dd, *J* = 15.1, 7.3 Hz, 1 H, 2-H^B), 1.13 (d, *J* = 7.3 Hz, 3 H, 4-CH_3), 0.90 (d, 3 H, 3-CH_3).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 203.49 (s, Ph*C*O), 173.08 (s, C-1), 136.56 (s, *ipso*-C_{arom}), 132.88 (d, *p*-CH_{arom}), 128.60 (d, Ar), 128.34 (d, Ar), 51.44 (q, OCH_3), 43.80 (d, C-4), 39.24 (t, C-2), 31.97 (d, C-3), 15.51 (q, 4-CH_3), 11.86 (q, 3-CH_3).

3h (Minor)

Selected signals.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.10–7.40 (m, 5 H_{arom}), 3.64 (s, 3 H, OCH_3), 3.58 (qd, *J* = 7.3, 5.9 Hz, 1 H, 4-H), 2.57–2.39 (m, 1 H, 3-H), 2.15 (dd, *J* = 16.1, 6.8 Hz, 1 H, 2-H^B), 1.02 (d, *J* = 6.8, 3 H, 3-CH_3).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 203.68 (s, Ph*C*O), 173.20 (s, C-1), 136.91 (s, *ipso*-C_{arom}), 132.88 (d, *p*-CH_{arom}), 128.34 (d, Ar), 128.19 (d, Ar), 51.44 (q, OCH_3), 44.67 (d, C-4), 37.36 (t, C-2), 32.64 (d, C-3), 18.54 (q, 4-CH_3), 13.71 (q, 3-CH_3).

Dimethyl 4-Benzoylheptanedioate (9)

s-BuLi (0.99 M in cyclohexane–hexane 95:5, 10.1 mL, 10 mmol) was added to a stirred and cooled (–78 °C) solution of acetophenone (1.2 g, 10 mmol) in anhyd THF (15 mL). The mixture was stirred at –78 °C for 10 min, and then Bu_3SnBr (3.7 g, 10 mmol) was added at –78 °C. After stirring for 10 min, methyl acrylate (1..72 g, 20 mmol) was added at –78 °C, then the mixture was gradually warmed to r.t. After stirring for 15 h, 30% aq NH_4F (150 mL) and EtOAc (30 mL) were added, and the heterogeneous mixture was vigorously stirred for 20 min. The generated Bu_3SnF was removed by filtration. Organic layer was extracted with EtOAc, dried ($MgSO_4$) and evaporated to give the crude product. Column chromatography (hexane–EtOAc, 7:4) of the residue over silica gel was followed by further purification by distillation; bp 150 °C/0.030 mmHg.

IR (neat): 1735, 1681 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.64 Hz, 2 H_{arom}), 7.62–7.55 (m, 1 H_{arom}), 7.53–7.42 (m, 2 H_{arom}), 3.69–3.64 (m, 1 H, 4-H), 3.64 (s, 6 H, OCH_3), 2.45–2.04 (m, 6 H, 2-CH_2, 6-CH_2, 3-H^A and 5-H^A), 1.92–1.76 (m, 2 H, 3-H^B and 5-H^B).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 202.60 (s, PhCO), 173.32 (s, C-1 and C-7), 136.69 (s, Ar), 133.25 (d, Ar), 128.68 (d, Ar), 128.25 (d, Ar), 51.57 (q, OCH_3), 43.69 (d, C-4), 31.27 (t, C-2 and C-6), 26.69 (t, C-3 and C-5).

MS (EI, 70 eV): *m*/*z* (%) = 292 (M^+, 8), 261 (M^+ – OMe, 18), 105 (100), 77 (24).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{16}H_{20}O_5$: 292.1311; found: 292.1313, 292.1315 (M^+). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.72; H, 6.98.

Dimethyl 4-(2-Thienylcarbonyl)heptanedioate (10)

According to the procedure for the synthesis of **9**, this compound was prepared from acetylthiophene (**1h**; 1.25 g, 10 mmol) and methyl acrylate (**2a**; 1.72 g, 20 mmol) to give the product as a colorless liquid after chromatography (hexane–EtOAc, 7:3). Further purification was done by distillation; bp 150 °C/0.008 mmHg.

IR (neat): 1735, 1658 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 4.1 Hz, 1 H_{arom}), 7.68 (d, *J* = 4.9 Hz, 1 H_{arom}), 7.16 (dd, *J* = 4.9, 4.1 Hz, 1 H_{arom}), 3.65 (s, 6 H, OCH_3), 3.41–3.48 (m, 1 H, 4-H), 2.46–2.22 (m, 4 H, 2-CH_2 and 6-CH_2), 2.19–2.03 (m, 2 H, 3-H^A and 5-H^A), 1.94–1.79 (m, 2 H, 3-H^B and 5-H^B).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 195.56 (s, C=O), 173.23 (s, C-1 and C-7), 144.59 (s, Ar), 134.52 (d, Ar), 132.38 (d, Ar), 128.32 (d, Ar), 51.56 (q, OCH_3), 45.70 (d, C-4), 31.26 (t, C-2 and C-6), 27.10 (t, C-3 and C-5).

MS (EI, 70 eV): *m*/*z* (%) = 298 (M^+, 35), 267 (M^+ – OCH_3, 23), 111 (C_4H_3SCO, 100).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{14}H_{18}O_5S$: 298.0875; found: 298.0808, 298.0866 (M^+).

Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.65; H, 6.18.

11-Benzoyl-1,4,7-trioxacyclotetradecan-8,14-dione (13)

According to the procedure for synthesis of **9**, this compound was prepared from acetophenone (**1g**; 1.2 g, 10 mmol) and ethyleneglycol diacrylate (**2d**; 2.14 g, 10 mmol) to give the product as a colorless liquid after chromatography (EtOAc). Further purification was done by distillation; bp 166 °C/0.011 mmHg.

IR (neat): 1736, 1674 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.1 Hz, 2 H_{arom}), 7.58 (t, *J* = 6.8 Hz, 1 H_{arom}), 7.48 (t, *J* = 7.6 Hz, 2 H_{arom}), 4.46 (dt, *J* = 12.2, 5.1 Hz, 2 H, 2-H^A and 6-H^A), 4.26 (dt, *J* = 12.2, 3.9 Hz, 2 H, 2-H^B and 6-H^B), 4.01–3.89 (m, 1 H, 11-H), 3.80–3.68 (m, 4 H, 3-CH_2 and 5-CH_2), 2.51 (ddd, *J* = 15.5, 8.2, 3.5 Hz, 2 H, 9-H^A and 13-H^A), 2.25 (ddd, *J* = 15.5, 10.5, 3.2 Hz, 2 H, 9-H^B and 13-H^B), 2.18–2.03 (m, 2 H, 10-H^A and 12 H^A), 1.86–1.72 (m, 2 H, 10-H^B and 12-H^B).

^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 204.02 (s, C=O), 172.68 (s, C-8 and C-14), 137.02 (s, Ar), 133.35 (d, Ar), 128.70 (d, Ar), 128.62 (d, Ar), 68.31 (t, C-3 and C-5), 62.21 (t, C-2 and C-6), 42.15 (d, C-11), 32.02 (t, C-9 and C-13), 27.59 (t, C-10 and C-12).

MS (EI, 70 eV): *m*/*z* (%) = 334 (M^+, 55), 228 (10), 105 (PhCO, 100), 77 (13).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{18}H_{22}O_6$: 334.1416; found: 334.1403, 334.1420, 334.1422 (M^+).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.39; H, 6.56.

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