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THE MUKAIYAMA ALDOL AND MUKAIYAMA–MICHAEL REACTIONS PROMOTED BY COMMERCIALLY AVAILABLE MOLECULAR SIEVES†

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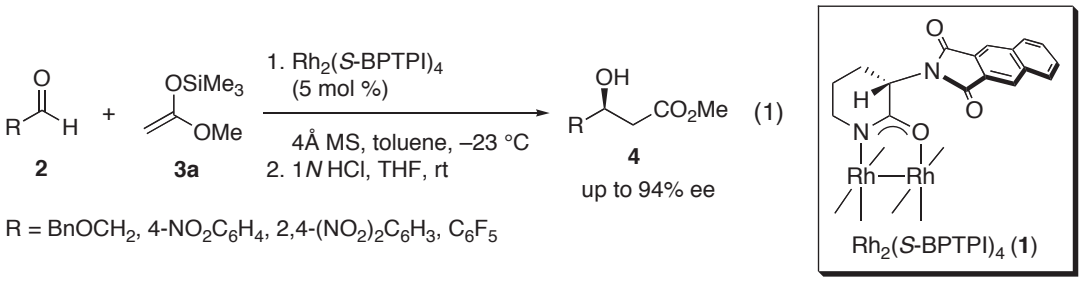
Abstract – The Mukaiyama aldol reaction of silyl ketene acetals with aldehydes has been effected by using commercially available 4Å molecular sieves (4Å MS) as a promoter. Various silyl ketene acetals and silyl enol ethers have been shown to be effective nucleophiles for this reaction. For the first time, it has been found that 4Å MS can promote the Mukaiyama–Michael addition reactions of silyl ketene acetals to α,β-enones.

The addition of silyl enol ethers and silyl ketene acetals to carbonyl compounds, commonly referred to as the Mukaiyama aldol reaction,[1] is well recognized as one of the most powerful tools for carbon–carbon bond formation. The Mukaiyama aldol reaction can be catalyzed either by Lewis acids through the activation of carbonyl compounds or by Lewis bases through the activation of silyl enol ethers and silyl ketene acetals.[2,3] It has also been shown that the Mukaiyama aldol reaction could proceed without added catalysts in some highly polar solvents such as DMF, DMSO, ionic liquids, water, and 1,8-diazabicyclo[5.4.0]undec-7-ene.[4]

Recently, we reported a catalytic enantioselective Mukaiyama aldol reaction of aldehydes (**2**) and methyl acetate-derived trimethylsilyl ketene acetal (**3a**) with the use of Rh_2(*S*-BPTPI)$_4$ (**1**), a dirhodium(II) carboxamidate complex that incorporates (*S*)-3-benzene-fused phthalimido-2-piperidinonate as chiral bridging ligands, as a chiral Lewis acid in the presence of 4Å molecular sieves (4Å MS) [eqn. (1)].[5] Although high yields and enantioselectivities of up to 94% ee were observed with specific aldehydes such as benzyloxyacetaldehyde and electron-poor aromatic aldehydes, the use of most aldehydes such as benzaldehyde resulted in the production of racemic aldol adducts. Surprisingly, further studies to improve the scope and generality of this reaction revealed that 4Å MS could accelerate the Mukaiyama aldol reaction of silyl ketene acetal and benzaldehyde even more effectively than could dirhodium(II) catalyst

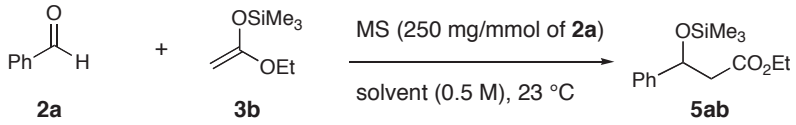
† Dedicated to Professor Emeritus Akira Suzuki on the occasion of his 80th birthday.

(**1**) at room temperature. Although a number of examples of the Mukaiyama aldol reaction accelerated by zeolite-type mesoporous silica have been reported,[6-8] there is only one example of the Mukaiyama aldol reaction promoted by *commercially available* molecular sieves. Scettri and co-workers reported that the solvent-free Mukaiyama aldol reaction of *O*-silyl dienolates derived from 2,2-dimethyl-1,3-dioxin-4-ones with aromatic aldehydes in the presence of 3Å MS (pellets, purchased from Aldrich) gave the corresponding aldol adducts, albeit in moderate yields.[9] In this paper, we report that the Mukaiyama aldol and Mukaiyama–Michael reactions can proceed smoothly in the presence of *commercially available* molecular sieves to afford the corresponding products in good to high yields.



At the outset of this work, the aldol reaction of benzaldehyde (**2a**) and ethyl acetate-derived trimethylsilyl ketene acetal (**3b**) in the presence of commercially available pulverized 4Å MS (Junsei, 250 mg/mmol of **2a**) was explored. The reaction in toluene proceeded smoothly at 23 °C to complete in less than 10 min, providing a silylated aldol adduct (**5ab**) in 97% yield (Table 1, Entry 1).[10,11] We next evaluated the

Table 1. The Mukaiyama Aldol Reaction of Benzaldehyde (**2a**) with Silyl Ketene Acetal (**3b**) Promoted by Molecular Sieves[a)]



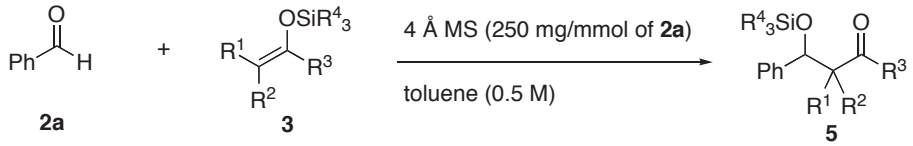
				β-Siloxy Ester **5ab**
Entry	Molecular sieves	Solvent	Time (h)	Yield (%)[b)]
1	4Å MS (pulverized)	toluene	0.5	97
2	5Å MS (pulverized)	toluene	0.5	96
3	AW 300 MS (pulverized)	toluene	0.5	96
4	3Å MS (pulverized)	toluene	2	12
5	13X MS (pulverized)	toluene	2	45
6	4Å MS (powdered)	toluene	24	no reaction
7	4Å MS (pulverized)	benzene	0.5	96
8	4Å MS (pulverized)	CH_2Cl_2	0.5	96
9	4Å MS (pulverized)	$(CH_2Cl)_2$	0.5	97
10	4Å MS (pulverized)	Et_2O	1	95
11	4Å MS (pulverized)	no solvent	0.5	96

[a)] All reactions were performed on a 0.2 mmol scale (0.5 M) using 1.5 equiv. of silyl ketene acetal. [b)] Isolated yield.

performance of other commercially available molecular sieves. While 5Å MS (Junsei) and AW 300 MS (Aldrich) were as effective as 4Å MS (Entries 2 and 3), 3Å MS (Junsei) and 13X MS (Aldrich) were less effective than 4Å MS (Entries 4 and 5). Surprisingly, no reaction took place when powdered 4Å MS (purchased from Junsei, Aldrich, Merck, and Nacalai) was used (Entry 6). A solvent survey revealed that benzene, dichloromethane, and 1,2-dichloroethane were also suitable solvents for the present aldol reaction (Entries 7–9). The use of ether required a longer reaction time than that with toluene (Entry 10). Interestingly, the aldol reaction proceeded smoothly without a solvent, providing **5ab** in high yield (Entry 11).

Using pulverized 4Å MS as a promoter and toluene as a solvent, the scope of the reaction with regard to silyl ketene acetals and silyl enol ethers was explored. Trimethylsilyl ketene acetal (**3a**) derived from methyl acetate and *tert*-butyldimethylsilyl ketene acetal (**3c**) derived from ethyl acetate each reacted with benzaldehyde smoothly at 23 °C to give the corresponding aldol adducts (**5aa,ac**) in high yields (Table 2, Entries 2 and 3). The use of pulverized 4Å MS was effective even for the sterically demanding silyl ketene acetal (**3d**) derived from methyl isobutyrate to afford *O*-silylated aldol product (**5ad**) in 87% yield (Entry 4). Trimethylsilyl ketene acetals (**3e**,**f**) derived from thioester and silyl enol ether (**3g**) could also be employed, though these reactions required heating at reflux for smooth conversion (Entries 5–7). The reaction with 1-trimethylsiloxycyclohexene (**3h**) proceeded at reflux to provide *O*-silylated aldol adduct (**5ah**) in good yield with no *syn*/*anti* selectivity (Entry 8).

Table 2. The Mukaiyama Aldol Reaction of Benzaldehyde (**2a**) with Silyl Ketene Acetals (**3a-f**) and Silyl Enol Ethers (**3g,h**) Promoted by Molecular Sieves 4 Å[a)]

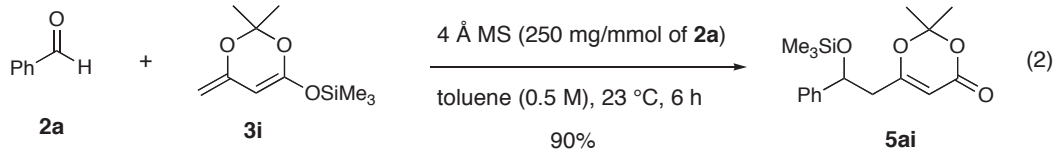


	Substrate							β-Siloxy Ester	
Entry		R^1	R^2	R^3	SiR^4_3	Temp (°C)	Time (h)		Yield (%)[b)]
1	**3b**	H	H	OEt	$SiMe_3$	23	0.5	**5ab**	97
2	**3a**	H	H	OMe	$SiMe_3$	23	0.5	**5aa**	95
3	**3c**	H	H	OEt	$SiMe_2{}^tBu$	23	1	**5ac**	95
4	**3d**	Me	Me	OMe	$SiMe_3$	23	2	**5ad**	87
5	**3e**	H	H	SEt	$SiMe_3$	reflux	2	**5ae**	96
6	**3f**	H	H	S^{t}Bu	$SiMe_3$	reflux	2	**5af**	94
7	**3g**	H	H	C_6H_5	$SiMe_3$	reflux	6	**5ag**	93
8	**3h**	H	–$(CH_2)_4$–		$SiMe_3$	reflux	10	**5ah**	70[c)]

[a)] All reactions were performed on a 0.2 mmol scale (0.5 M) using 1.5 equiv. of substrate. [b)] Isolated yield. [c)] *syn*/*anti* = 1:1.4.

The reaction of *O*-silyl dienolates (**3i**) derived from 2,2-dimethyl-1,3-dioxin-4-one with benzaldehyde proceeded at 23 °C to give the corresponding adduct (**5ai**) in 90% yield [eqn. (2)]. It is noteworthy that

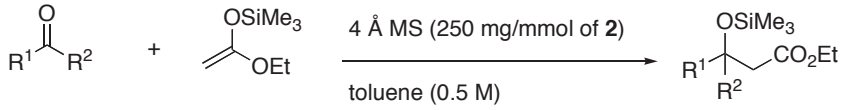
the yield of the reaction is very good, compared with a previous description of this type of reaction (reaction of **3i** with *p*-anisaldehyde or *p*-tolualdehyde in the presence of 3Å MS) resulting in 45–50% yield.[9]



2a **3i** **5ai**

Using silyl ketene acetal **3b**, the reaction scope with regard to the electrophilic component was next investigated (Table 3). *p*-Anisaldehyde (**2b**) led to the desired aldol adduct (**5bb**) in 94% yield (Entry 2). Aromatic aldehydes (**2c,d**) bearing electron-withdrawing groups at the *para* position on the benzene ring provided the aldol adducts (**5cb,db**) in high yields, but reaction times were significantly longer than those with **2a** or **2b** (Entries 3 and 4), though the mechanistic profile is unclear at this time. The present method was applicable to α,β-unsaturated aldehydes (**2e,f**), providing the corresponding aldol adducts (**5eb**,**fb**) in high yields (Entries 5 and 6). No evidence of the conjugate addition, commonly known as the Mukaiyama–Michael reaction, was observed.[12] The reaction with aliphatic aldehydes (**2g,h**) proceeded uneventfully to give aldol adducts (**5gb,hb**) in high yields (Entries 7 and 8). Aside from aldehydes, acetophenone (**2i**) reacted with **3b** in toluene under reflux to give the corresponding aldol adduct (**5ib**) in high yield (Entry 9).

Table 3. The Mukaiyama Aldol Reaction of Various Carbonyl Compounds (**2**) with **3b** Promoted by Molecular Sieves 4 Å[a)]

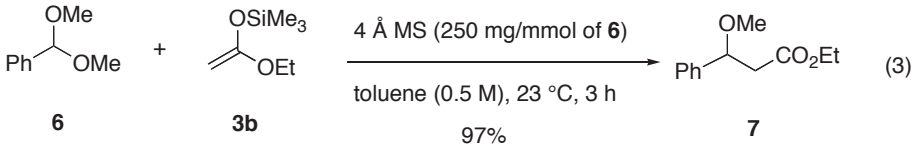


2 **3b** **5**

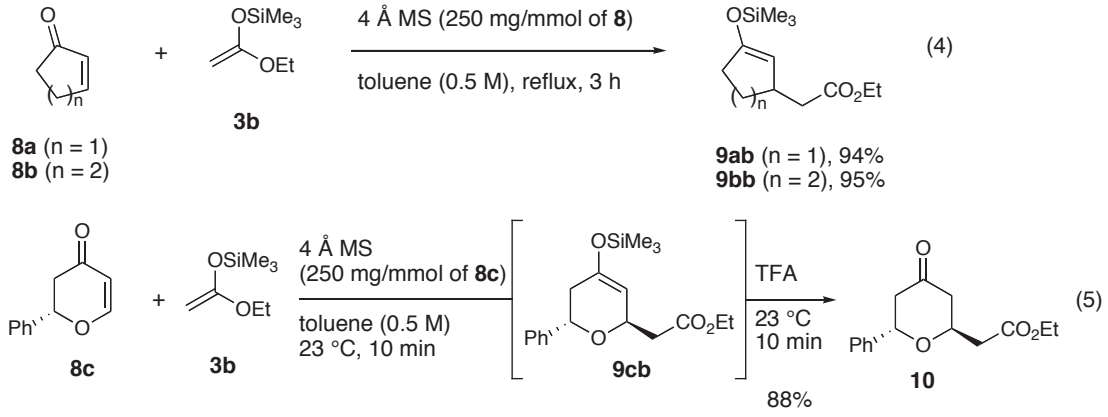
Entry	Carbonyl Compounds			Temp (°C)	Time (h)	β-Siloxy Ester	
		R^1	R^2				Yield (%)[b)]
1	**2a**	C_6H_5	H	23	0.5	**5ab**	97
2	**2b**	4-$MeOC_6H_4$	H	23	0.5	**5bb**	94
3	**2c**	4-$NO_2C_6H_4$	H	23	6	**5cb**	81
4	**2d**	4-$CF_3C_6H_4$	H	23	3	**5db**	87
5	**2e**	$C_6H_5C{\equiv}C$	H	23	0.5	**5eb**	98
6	**2f**	(*E*)-$C_6H_5CH{=}CH$	H	23	0.5	**5fb**	94
7	**2g**	$C_6H_5CH_2CH_2$	H	23	2	**5gb**	94
8	**2h**	$BnOCH_2$	H	23	2	**5hb**	92
9	**2i**	C_6H_5	CH_3	reflux	6	**5ib**	87

[a)] All reactions were performed on a 0.2 mmol scale (0.5 M) using 1.5 equiv. of silyl ketene acetal. [b)] Isolated yield.

As might be expected, the reaction of benzaldehyde dimethyl acetal (**6**) and **3b** under the standard conditions proceeded cleanly to provide β-methoxy ester (**7**) in 97% yield [eqn. (3)].



Armed with these positive results, we then explored the 4Å MS-promoted Mukaiyama–Michael addition reaction.[12,13] The addition of silyl ketene acetal (**3b**) to α,β-enones (**8a,b**) in the presence of 4Å MS in toluene proceeded at reflux to provide the corresponding silyl enol ethers (**9ab,bb**) in high yields [eqn. (4)]. Somewhat surprisingly, when 2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**8c**) of 95% ee, prepared by the catalytic enantioselective hetero-Diels-Alder reaction employing Rh_2(*S*-BPTPI)$_4$ (**1**),[5b] was used as a Michael acceptor, the reaction with **3b** proceeded smoothly at 23 °C to completion in less than 10 min and, after treatment with trifluoroacetic acid, gave 2,6-*trans*-disubstituted tetrahydropyran-4-one (**10**) as the sole product in 88% yield [eqn. (5)].[14] This protocol represents the first example of the Mukaiyama–Michael reaction promoted by commercially available molecular sieves.



In summary, we have demonstrated that the Mukaiyama aldol reactions of aldehydes with silyl ketene acetals or silyl enol ethers can proceed smoothly in the presence of pulverized commercially available 4Å MS. This method is applicable to a wide range of aldehydes, benzaldehyde dimethyl acetal, and acetophenone, providing the corresponding aldol adducts in good to high yields. It has also been found that 4Å MS can promote the Mukaiyama–Michael addition reactions of silyl ketene acetals to α,β-enones. The present protocol based on commercially available 4Å MS offers several advantages including mild reaction conditions as well as operational simplicity and practical value. Further studies on the scope and utility of 4Å MS-promoted reactions are currently in progress.

EXPERIMENTAL

General. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^{1}H NMR spectra were recorded on a JEOL JNM-EX 270 (270 MHz) or

JEOL JNM-AL 400 (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane; δ_H 0.00, $CDCl_3$; δ_H 7.26 or C_6D_6; δ_H 7.20). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded on a JEOL JNM-AL 400 (100 MHz) spectrometer. The following internal references were used ($CDCl_3$; δ 77.0). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). EI-MS spetra were obtained on a JEOL JMS-T100GC spectrometer, operating with ionization energy of 70 eV. ESI-MS spectra were obtained on a Thermo Scientific Exactive spectrometer. Column chromatography was carried out on Kanto silica gel 60 N (63–210 mesh) or Wakogel® C-200 (75–150 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by UV light, anisaldehyde stain solution or phosphomolybdic acid stain solution.

All non-aqueous reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated stabilizer-free CH_2Cl_2, toluene and THF were purchased from Kanto Chemical Co., Inc. Diisopropylamine and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride prior to use. *O*-Methyl-*O*-trimethylsilyl ketene acetal (**3a**) was prepared from methyl acetate according to the procedure of Shibasaki.[15] Silyl ketene acetals (**3b-d**) were prepared from corresponding esters according to the literature procedure.[16] Trimethylsilyl ketene acetals derived from thioester (**3f**,**g**) were prepared according to the procedure of Evans.[17] Silyl enol ethers (**3g,h**) were prepared from corresponding ketones according to the literature procedure.[18] 2,2-Dimethyl-6-methylene-4-trimethylsiloxy-6*H*-1,3-dioxine (**3i**) was prepared from 2,2,6-trimethyl-1,3-dioxin-4-one according to the procedure of Grunwell.[19] (*S*)-2-Phenyl-2,3-dihydro-4*H*-pyran-4-one (**8c**) (95% ee) was prepared according to literature procedure.[5b] All molecular sieves were used after finely ground in mortar and activated by heating *in vacuo* at 220 °C for 12 h.

General procedure for the Mukaiyama aldol reaction (Table 1, Entry 1): Ethyl 3-phenyl-3-trimethylsiloxypropanoate (5ab).[20] To an oven-dried flask equipped with a Teflon-coated magnetic stirring bar were added pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**), and a solution of benzaldehyde (**2a**) (21.2 mg, 0.20 mmol) in toluene (0.2 mL). A solution of **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.) in toluene (0.2 mL) was added to the mixture at 23 °C. After 2 h of stirring at this temperature, the reaction mixture was then filtered through a plug of Celite and the residue was washed with EtOAc (10 mL). Concentration of the combined filtrates *in vacuo* followed by column chromatography (silica gel, 19:1 hexane/EtOAc) provided **5ab** (52.2 mg, 98%) as a colorless oil; R_f = 0.29 (19:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H, $SiCH_3$), 1.25 (t, J = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.57 (dd, J = 4.0,

14.5 Hz, 1H, C2-*H*), 2.72 (dd, *J* = 9.2, 14.5 Hz, 1H, C2-*H*), 4.12 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 5.16 (dd, *J* = 4.0, 9.2 Hz, 1H, C3-*H*), 7.22-7.36 (m, 5H, *Ar*).

Methyl 3-phenyl-3-trimethylsiloxypropanoate (5aa).[21] According to the general procedure for the Mukaiyama aldol reaction, **5aa** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3a** (43.9 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5aa** (49.3 mg, 95%) as a colorless oil; R_f = 0.27 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 9H, $SiCH_3$), 2.59 (dd, *J* = 4.0, 15.1 Hz, 1H, C2-*H*), 2.73 (dd, *J* = 9.2, 15.1 Hz, 1H, C2-*H*), 3.69 (s, 3H, CO_2CH_3), 5.16 (dd, *J* = 4.0, 9.2 Hz, 1H, C3-*H*), 7.31-7.34 (m, 5H, *Ar*).

Ethyl 3-*tert*-butyldimethylsiloxy-3-phenylpropanoate (5ac).[22] According to the general procedure for the Mukaiyama aldol reaction, **5ac** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3c** (60.7 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5ac** (58.6 mg, 95%) as a colorless oil; R_f = 0.31 (19:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.18 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 1.25 (t, *J* = 6.8 Hz, 3H, $CO_2CH_2CH_3$), 2.53 (dd, *J* = 3.6, 14.5 Hz, 1H, C2-*H*), 2.72 (dd, *J* = 9.1, 14.5 Hz, 1H, C2-*H*), 4.13 (q, *J* = 6.8 Hz, 2H, $CO_2CH_2CH_3$), 5.14 (dd, *J* = 3.6, 9.1 Hz, 1H, C3-*H*), 7.23-7.35 (m, 5H, *Ar*).

Methyl 2,2-dimethyl-3-phenyl-3-trimethylsiloxypropanoate (5ad).[23] According to the general procedure for the Mukaiyama aldol reaction, **5ad** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3d** (52.3 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5ad** (48.8 mg, 87%) as a colorless oil; R_f = 0.29 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.03 (s, 9H, $SiCH_3$), 0.99 (s, 3H, C2-CH_3), 1.12 (s, 3H, C2-CH_3), 3.67 (s, 3H, CO_2CH_3), 4.97 (s, 1H, C3-*H*), 7.21-7.29 (m, 5H, *Ar*).

***S*-Ethyl 3-phenyl-3-trimethylsiloxypropanethioate (5ae).**[24] According to the general procedure for the Mukaiyama aldol reaction, **5ae** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3e** (52.9 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5ae** (54.2 mg, 96%) as a colorless oil; R_f = 0.34 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 9H, $SiCH_3$), 1.25 (t, *J* = 7.3 Hz, 3H, SCH_2CH_3), 2.74 (dd, *J* = 4.0, 14.5 Hz, 1H, C2-*H*), 2.89 (q, *J* = 7.3 Hz, 2H, SCH_2CH_3),

2.97 (dd, *J* = 9.2, 14.5 Hz, 1H, C2-*H*), 5.19 (dd, *J* = 4.0, 9.2 Hz, 1H, C3-*H*), 7.24-7.33 (m, 5H, *Ar*).

***S-tert*-Butyl 3-phenyl-3-trimethylsiloxypropanethioate (5af).**[24] According to the general procedure for the Mukaiyama aldol reaction, **5af** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3f** (61.3 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5af** (58.4 mg, 94%) as a colorless oil; R_f = 0.43 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6H, SiCH_3), 1.46 (s, 9H, SC(CH_3)$_3$), 2.63 (dd, *J* = 4.0, 14.5 Hz, 1H, C2-*H*), 2.87 (dd, *J* = 9.2, 14.5 Hz, 1H, C2-*H*), 5.17 (dd, *J* = 4.0, 9.2 Hz, 1H, C3-*H*), 7.20-7.32 (m, 5H, *Ar*).

3-Trimethylsiloxy-1,3-diphenylpropan-1-one (5ag).[25] According to the general procedure for the Mukaiyama aldol reaction, **5ag** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3g** (57.7 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5ag** (52.2 mg, 93%) as a colorless oil; R_f = 0.36 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ –0.05 (s, 9H, SiCH_3), 3.02 (dd, *J* = 4.0, 15.8 Hz, 1H, C2-*H*), 3.57 (dd, *J* = 8.6, 15.8 Hz, 1H, C2-*H*), 5.37 (dd, *J* = 4.0, 8.6 Hz, 1H, C3-*H*), 7.22-7.58 (m, 8H, *Ar*), 7.94-7.97 (m, 2H, *Ar*).

2-[Phenyl(trimethylsiloxy)methyl]cyclohexanone (5ah).[1b] According to the general procedure for the Mukaiyama aldol reaction, **5ah** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3h** (51.1 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 1:2 hexane/toluene) to provide *syn*-**5ah** (16.1 mg, 29%) as a colorless oil and *anti*-**5ah** (22.6 mg, 41%) as a colorless oil; *syn*-**5ah**: R_f = 0.32 (1:3 hexane/toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H, SiCH_3), 1.48–1.96 (m, 6H, C3-*H*, C4-*H* and C5-*H*), 2.25 (m, 1H, C6-*H*), 2.37-2.46 (m, 2H, C2-*H* and C6-*H*), 5.31 (d, *J* = 4.1 Hz, 1H, C1'-*H*), 7.24-7.30 (m, 5H, *Ar*); *anti*-**5ah**: R_f = 0.18 (1:3 hexane/toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.03 (s, 9H, SiCH_3), 1.21 (m, 1H, C3-*H*), 1.51-1.62 (m, 2H, C3-*H* and C4-*H*), 1.68-1.78 (m, 2H, C4-*H* and C5-*H*), 1.95 (m, 1H, C5-*H*), 2.35-2.44 (m, 2H, C6-*H*), 2.70 (m, 1H, C2-*H*), 5.04 (d, *J* = 8.2 Hz, 1H, C1'-*H*), 7.24-7.40 (m, 5H, *Ar*).

6-(2-Phenyl-2-trimethylsiloxyethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (5ai).[26] According to the general procedure for the Mukaiyama aldol reaction, **5ai** was prepared from benzaldehyde (**2a**) (21.2 mg, 0.20 mmol), **3i** (64.3 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2a**). The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide **5ai** (57.7 mg, 90%) as a colorless oil; R_f = 0.29 (2:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s,

9H, SiC*H*$_3$), 1.64 (s, 3H, CC*H*$_3$), 1.67 (s, 3H, CC*H*$_3$), 2.50 (dd, *J* = 4.6, 13.8 Hz, 1H, C4-*H*), 2.63 (dd, *J* = 7.9, 13.8 Hz, 1H, C4-*H*), 4.92 (q, *J* = 4.6, 7.9 Hz, 2H, C5-*H*), 5.23 (s, 1H, C2-*H*), 7.24-7.36 (m, 5H, *Ar*).

Ethyl 3-(4-methoxyphenyl)-3-trimethylsiloxypropanoate (5bb).[27] According to the general procedure for the Mukaiyama aldol reaction, **5bb** was prepared from *p*-anisaldehyde (**2b**) (27.2 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2b**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5bb** (55.7 mg, 94%) as a colorless oil; R_f = 0.41 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 9H, SiC*H*$_3$), 1.27 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.57 (dd, *J* = 4.6, 14.5 Hz, 1H, C2-*H*), 2.73 (dd, *J* = 9.2, 14.5 Hz, 1H, C2-*H*), 3.81 (s, 3H, ArO-C*H*$_3$), 4.15 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 5.12 (dd, *J* = 4.6, 9.2 Hz, 1H, C3-*H*), 6.83-6.89 (m, 2H, *Ar*), 7.25-7.29 (m, 2H, *Ar*).

Ethyl 3-(4-nitrophenyl)-3-trimethylsiloxypropanoate (5cb).[5a] According to the general procedure for the Mukaiyama aldol reaction, **5cb** was prepared from *p*-nitrobenzaldehyde (**2c**) (30.2 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2c**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5cb** (50.4 mg, 81%) as a colorless oil; R_f = 0.25 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 9H, SiC*H*$_3$), 1.25 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.58 (dd, *J* = 4.6, 14.5 Hz, 1H, C2-*H*), 2.71 (dd, *J* = 8.6, 14.5 Hz, 1H, C2-*H*), 4.15 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 5.25 (dd, *J* = 4.6, 8.6 Hz, 1H, C3-*H*), 7.53 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.19 (d, *J* = 8.6 Hz, 2H, *Ar*).

Ethyl 3-[(4-trifluoromethyl)phenyl]-3-trimethylsiloxypropanoate (5db). According to the general procedure for the Mukaiyama aldol reaction, **5db** was prepared from *p*-trifluoromethylbenzaldehyde (**2d**) (34.8 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2d**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5db** (58.2 mg, 87%) as a colorless oil; TLC R_f = 0.47 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 9H, SiC*H*$_3$), 1.25 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.56 (dd, *J* = 4.0, 14.5 Hz, 1H, C2-*H*), 2.70 (dd, *J* = 8.6, 14.5 Hz, 1H, C2-*H*), 4.12 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 5.21 (dd, *J* = 4.0, 8.6 Hz, 1H, C3-*H*), 7.47 (d, *J* = 7.9 Hz, 2H, *Ar*), 7.59 (d, J = 7.9 Hz, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.11 (CH_3), 14.2 (CH_3), 46.0 (CH_2), 60.6 (CH_2), 71.3 (CH), 124.1 (q, *J* = 271 Hz, CF_3), 125.3 (q, *J* = 3.8 Hz, CH), 129.6 (C), 130.0 (q, *J* = 12.5 Hz, C), 148.0 (C), 170.7 (C); EI-HRMS *m/z* calcd for $C_{15}H_{21}F_3O_2Si$ (M^+) 334.12120, found 334.12083.

Ethyl 5-phenyl-3-trimethylsiloxypent-4-ynoate (5eb). According to the general procedure for the Mukaiyama aldol reaction, **5eb** was prepared from phenylpropargylaldehyde (**2e**) (26.0 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2e**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5eb** (56.9 mg, 98%) as a colorless oil; R_f = 0.47 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.15 (s, 9H, SiC*H*$_3$), 1.22 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.69 (dd, *J* = 5.9, 15.2 Hz, 1H, C2-*H*), 2.78 (dd, *J* = 8.6, 15.2Hz, 1H, C2-*H*), 4.15 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 4.99 (dd, *J* = 4.6, 9.2 Hz, 1H, C3-*H*), 7.20-7.28 (m, 3H, *Ar*), 7.31-7.37 (m, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.04 (CH_3), 14.2 (CH_3), 43.9 (CH_2), 59.8 (CH), 60.6 (CH_2), 84.7 (C), 89.1 (C), 122.5 (C), 128.2 (CH), 128.3 (CH), 131.5 (CH), 170.1 (C); ESI-HRMS *m/z* calcd for $C_{16}H_{22}O_3NaSi$ (M^++Na) 313.12303, found 313.12304.

Ethyl *trans*-5-phenyl-3-trimethylsiloxypent-4-enoate (5fb).[20] According to the general procedure for the Mukaiyama aldol reaction, **5fb** was prepared from *trans*-cinnamaldehyde (**2f**) (26.4 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2f**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5fb** (55.0 mg, 94%) as a colorless oil; R_f = 0.40 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.14 (s, 9H, SiC*H*$_3$), 1.26 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.53 (dd, *J* = 5.3, 14.5 Hz, 1H, C2-*H*), 2.62 (dd, *J* = 7.9, 14.5 Hz, 1H, C2-*H*), 4.15 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 6.19 (dd, *J* = 6.6, 15.8 Hz, 1H, C4-*H*), 6.57 (d, *J* = 15.8 Hz, 1H C5-*H*), 7.20-7.39 (m, 5H, *Ar*).

Ethyl 5-phenyl-3-trimethylsiloxypentanoate (5gb).[20] According to the general procedure for the Mukaiyama aldol reaction, **5gb** was prepared from 3-phenylpropanal (**2g**) (26.8 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2g**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5gb** (55.4 mg, 94%) as a colorless oil; R_f = 0.27 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.12 (s, 9H, SiC*H*$_3$), 1.26 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.76-1.85 (m, 2H, C4-*H*), 2.47-2.77 (m, 4H, C2-*H* and C5-*H*), 4.10-4.24 (m, 3H, $CO_2CH_2CH_3$ and C3-*H*), 7.16-7.31 (m, 5H, *Ar*).

Ethyl 4-benzyloxy-3-trimethylsiloxybutanoate (5hb).[5a] According to the general procedure for the Mukaiyama aldol reaction, **5hb** was prepared from benzyloxyacetaldehyde (**2h**) (30.0 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2h**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5hb** (57.1 mg, 92%) as a colorless oil; R_f = 0.36 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 9H, SiC*H*$_3$), 1.25 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.44 (dd, *J* = 8.6, 15.1 Hz, 1H, C2-*H*), 2.60 (dd, *J* = 4.6,

15.1 Hz, 1H, C2-*H*), 3.38 (dd, *J* = 5.3, 9.3 Hz, 1H, C4-*H*), 3.45 (dd, *J* = 5.3, 9.2 Hz, 1H, C4-*H*), 4.13 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 4.31 (m, 1H, C3-*H*) 4.53 (s, *2*H, $PhCH_2$), 7.26-7.37 (m, 5H, *Ar*).

Ethyl 3-phenyl-3-trimethylsiloxybutanoate (5ib).[28] According to the general procedure for the Mukaiyama aldol reaction, **5ib** was prepared from acetophenone (**2i**) (24.0 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **2i**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **5ib** (48.8 mg, 87%) as a colorless oil; R_f = 0.42 (19:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 9H, $SiCH_3$), 1.10 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.82 (s, 3H, C4-*H*), 2.74 (dd, *J* = 5.9, 7.2 Hz, 1H, C2-*H*), 3.98 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 7.19-7.33 (m, 3H, *Ar*), 7.40-7.44 (m, 2H, *Ar*).

Ethyl 3-methoxy-3-phenylpropanoate (7).[29] According to the general procedure for the Mukaiyama aldol reaction, **7** was prepared from benzaldehyde dimethyl acetal (**6**) (30.4 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **6**). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **7** (40.4 mg, 81%) as a colorless oil; R_f = 0.39 (9:1 hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, *J* = 6.6 Hz, 3H, $CO_2CH_2CH_3$), 2.55 (dd, *J* = 4.6, 15.1 Hz, 1H, C2-*H*), 2.80 (dd, *J* = 9.2, 15.1 Hz, 1H, C2-*H*), 3.23 (s, 3H, OCH_3), 4.12 (q, *J* = 6.6 Hz, 2H, $CO_2CH_2CH_3$), 4.63 (dd, *J* = 4.6, 9.2 Hz, 1 H, C3-*H*), 7.27-7.39 (m, 5H, *Ar*).

General procedure for the Mukaiyama-Michael reaction [eqn. (4)]: Ethyl 2-(3-trimethylsiloxycyclopent-2-enyl)acetate (9ab).[30] To an oven-dried flask equipped with a Teflon-coated magnetic stirring bar were added pulverized 4Å MS (50 mg, 250 mg/mmol of **8a**), 2-cyclopentenone (**8a**) (16.4 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.) and toluene (0.4 mL). The mixture was refluxed for 3 h and filtered through a plug of Celite, and the residue was washed with EtOAc (10 mL). Concentration of the combined filtrates *in vacuo* followed by column chromatography (Wakogel C-200, 1% Et_3N in hexane) provided **9ab** (45.5 mg, 94%) as a colorless oil; TLC R_f = 0.31 (2:1 hexane/EtOAc); ^{1}H NMR (270 MHz, C_6D_6) δ 0.19 (s, 9H, $SiCH_3$), 1.01 (t, *J* = 7.2 Hz, 3H, CO_2CH_2-CH_3), 1.44 (m, 1H, C5'-*H*), 2.04 (m, 1H, C5'-*H*), 2.24–2.35 (m, 4H, C1-*H*, C4'-*H* and C1-H_2), 3.19 (m, 1H, C4'-*H*), 4.03 (q, *J* = 7.2 Hz, 2H, CO_2-CH_2), 4.80 (m, 1H, C2'-*H*).

Ethyl 2-(3-trimethylsiloxycyclohex-2-enyl)acetate (9bb).[30] According to the general procedure for the Mukaiyama-Michael reaction, **9bb** was prepared from 2-cyclohexenone (**8b**) (19.2 mg, 0.20 mmol), **3b** (48.0 mg, 0.30 mmol, 1.5 equiv.), and pulverized 4Å MS (50 mg, 250 mg/mmol of **8b**). The crude

product was purified by column chromatography (Wakogel C-200, 1% Et_3N in hexane) to provide **9bb** (48.7 mg, 95%) as a colorless oil; R_f = 0.33 (2:1 hexane/EtOAc); ^{1}H NMR (270 MHz, C_6D_6) δ 0.16 (s, 9H, SiC*H*$_3$), 1.15 (m, 1H, C5-*H*), 1.24 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.59 (m, 1H, C6-*H*), 1.72-1.77 (m, 2H, C5-*H* and C6-*H*), 1.94-2.00 (m, 2H, C1-*H* and C4-*H*), 2.22 (m, 2H, EtOCOC*H*$_2$), 2.64 (m, 1H, C4-*H*), 4.12 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.75 (m, 1H, C2-*H*).

Ethyl 2-[(2S,6S)-4-oxo-6-phenyltetrahydro-2*H*-pyran-2-yl]acetate (10). A solution of **3b** (24.1 mg, 0.15 mmol) in toluene (0.1 mL) was added to the mixture of (*S*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**8c**) (95% ee, 17.4 mg, 0.10 mmol) and 4Å MS (50 mg, 250 mg/mmol of **8c**) in toluene (0.1 mL) at 23 °C. After stirring for 10 min, the reaction mixture was filtered through a plug of Celite and the residue was washed with CH_2Cl_2 (10 mL). A 10% solution of trifluoroacetic acid in CH_2Cl_2 (0.1 mL) was added to the combined filtrate, and the mixture was stirred for 10 min and poured into saturated aq. $NaHCO_3$ solution (3 mL). The whole mixture was extracted with EtOAc (2 x 10 mL), and the combined organic layers were washed with water (3 mL) and brine (2 x 3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by column chromatography (silica gel, 4:1 hexane/EtOAc) to provide **10** (46.4 mg, 88%) as a colorless oil; R_f = 0.28 (4:1 hexane/EtOAc); $[\alpha]_D^{23}$ +37.6° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.44 (ddd, *J* = 1.4, 7.0, 15.0 Hz, 1H, C5-*H*), 2.50 (dd, *J* = 5.4, 14.9 Hz, 1H, C6-C*H*), 2.60 (ddd, *J* = 1.4, 4.5, 15.0 Hz, 1H, C5-*H*), 2.69 (dd, *J* = 8.2, 14.9 Hz, 1H, C6-C*H*), 2.83 (ddd, *J* = 1.4, 5.9, 14.5 Hz, 1H, C3-*H*), 2.92 (ddd, *J* = 1.4, 5.9, 14.5 Hz, 1H, C3-*H*), 4.15 (q, *J* = 7.0 Hz, 1H, $CO_2CH_2CH_3$), 4.38 (m, 1H, C6-*H*), 5.32 (t, *J* = 5.9 Hz, 1H, C2-*H*), 7.31-7.38 (m, 5H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 40.2 (CH_2), 45.4 (CH_2), 46.4 (CH_2), 60.8 (CH_2), 68.6 (CH), 74.1 (CH), 126.9 (CH), 128.2 (CH), 128.6 (CH), 139.2 (C), 170.0 (C), 206.2 (C); ESI-HRMS *m/z* calcd for $C_{15}H_{18}O_4$ (M^+) 263.12757, found 263.12779.

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