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The Design of Diastereoselective Mukaiyama-Michael Reaction of Ketene Silyl Acetal

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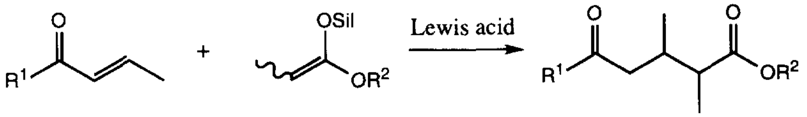
Abstract: The highly diastereoselective Mukaiyama-Michael reaction has been designed. Suppression of an electron-transfer process is crucial for this purpose and the following conditions should be satisfied. (1) $TiCl_4$ is employed as a Lewis acid. (2) Ketene silyl acetals have bulky siloxy and/or alkoxy group(s). (3) α-Enones have a bulky acyl group. The excellent *syn*-selectivity up to a 99:1 ratio is attained under these conditions. The selectivity is reversed to the *anti*-preference upon decreasing the size of the alkoxy group. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

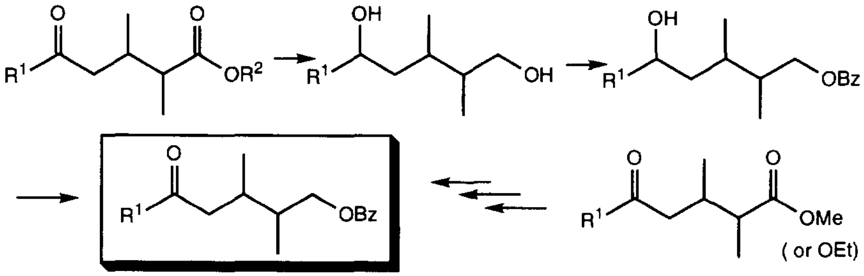
Despite its synthetic versatility,[1] Mukaiyama-Michael reaction of ketene silyl acetals still remains to be more stereoselective. For example, no diastereoselectivity is usually attained between the prochiral centers in eq. 1.[2] We suggested that such nonstereoselective propensity could be partly ascribed to a radical reaction mechanism initiated by electron transfer from ketene silyl acetal to Lewis acid.[3] In this process, the C-C double bond of ketene silyl acetal is twisted upon the radical cation formation. The rotation of the C-C double bond of α-enone also occurs when this substrate undergoes the 1,4-addition by a reduced metal radical that is generated by spontaneous fragmentation of the Lewis acid radical anion. Consequently, the Michael adducts are not reminiscent of the original stereochemistries of ketene silyl acetal and α-enone, giving rise to the thermodynamically controlled stereorandom outcome. In other words, if the electron transfer is avoided, the reaction could proceed through an alternative nucleophilic path and, hence, the high diastereocontrol would possibly be attained. This is indeed the case. Herein we report a full account of designing the stereochemical reaction based on this hypothesis.[4]



(1)

RESULTS

The reaction was run by employing a variety of ketene silyl acetals and α-enones in CH_2Cl_2 at -78 °C. The whole results are summarized in Table 1. In the reaction of the ketene silyl acetals derived from *tert*-butyl propionate, the Micheal adducts were obtained as a mixture of the *tert*-butyl ester and the corresponding carboxylic acid. Accordingly, the yield was determined as the methyl ester by hydrolyzing the mixture followed by treatment of the resulting carboxylic acid with CH_2N_2 (see experimental section).[2] The *syn/anti* ratios of the methyl esters were determined by ^1H NMR spectra. The ratios of ethyl ester adducts were also obtained as the methyl esters. Because of their reluctance against hydrolysis, the neopentyl (Neop) and bornyl (Born) esters were converted to keto benzoates according to the procedure shown in Scheme 1. The diastereomeric ratios were determined by HPLC. The *syn/anti* assignment of the keto benzoates were made by comparison with authentic samples derived from the well-defined methyl or ethyl esters.



Scheme 1

Our mechanistic study is basically based on the competition reaction.[3] When ketene silyl acetals involving a trimethylsilyl (TMS) or triethylsilyl (TES) group are employed, the ketene silyl acetals with more substituent(s) at the β-position react in preference to the less substituted ones, a sign of the electron-transfer initiated radical path. The opposite preference results from the use of bulky ketene silyl acetals bearing *tert*-butyldimethylsilyl (TBS) and/or *tert*-butoxy or bornyloxy groups. The nucleophilic mechanism operates in this case. It is conceivable, therefore, that the employment of bulky ketene silyl acetals gives rise to the improvement of the stereoselectivity. The alternative of these two mechanisms is also dependent on the Lewis acid. $SnCl_4$ and Et_3SiClO_4 are prone to the electron transfer while the nucleophilic path prevails with $TiCl_4$. We screened the influence of the Lewis acids first of all (entries 1-3, Table 1). As expected, $TiCl_4$ is superior to Et_3SiClO_4 and $SnCl_4$ and, hence, the Lewis acid of choice in the reactions to follow.

The dependence of the *syn*-preference on the different silyl groups of *tert*-butoxy ketene silyl acetals in the reaction with the *tert*-butyl enone (entries 1,12,19; 4,13, Table 1) is depicted in Fig. 1. Apparently, the increase of bulkiness results in the improvement of the *syn*-selectivity. The analogous trend holds qualitatively with the bornyl esters (entries 6,14,20; 7,15,21, Table 1). Fig. 2 shows the effect of the alkoxy groups in the reaction with the TBS ketene silyl acetals. The *syn*-preference increases in the order of bulkiness of the alkoxyl: Me < Et < Born < Neop < ^{t}Bu (entries 1,5,6,8,10; 4,7,9,11, Table 1).

The essentially similar results stand for the phenyl enone (entries 24-29, Table 1), yet there is a clear distinction between the mesityl enone and other enones. The characteristic features are illustrated in Fig. 3. The higher selectivity is usually attained with the *tert*-butyl enone than with the phenyl enone. Since the *tert*-butyl group is electron donating, the anisyl enone also is expected to give rise to the high selectivity. However, this is not the case (entry 30, Table 1), suggestive of the importance of bulk of the acyl group. In accordance with this view, the high *syn*-preference is attained with the sterically demanding mesityl enone (entries 31-47, Table 1), but the selectivity is much less sensitive to the change of the ketene silyl acetal geometry, a quite different behavior from those of other enones.

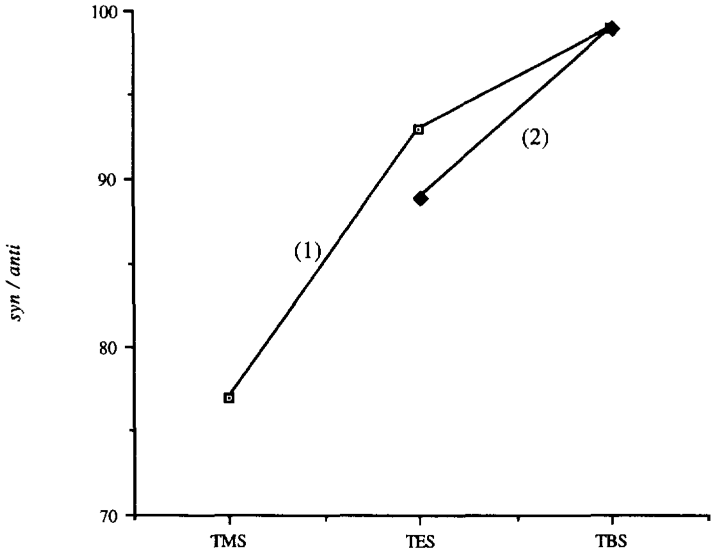


Fig. 1. Dependence of *syn/anti* ratio on the siloxy group in the reaction between *tert*-butyl enone and (1) (*E*)- and (2) (*Z*)-*tert*-butoxy ketene silyl actal.

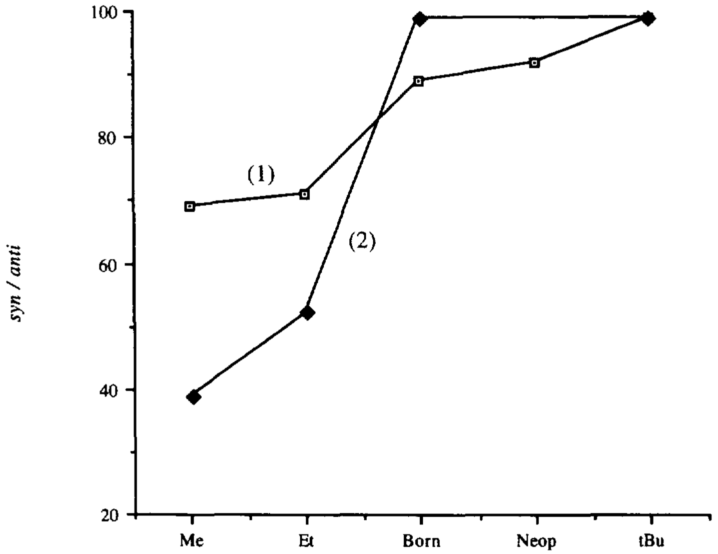


Fig. 2. Dependence of *syn/anti* ratio on the alkoxy group in the reaction between *tert*-butyl enone and (1) (*E*)- and (2) (*Z*)-TBS ketene silyl acetal.

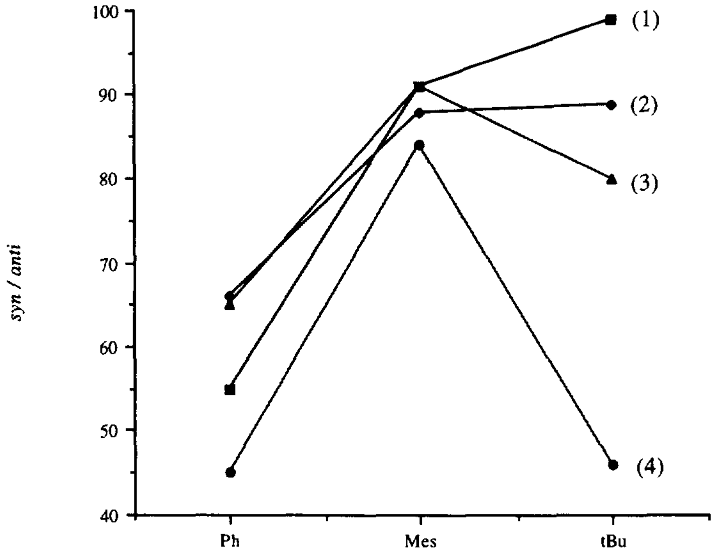


Fig. 3. Dependence of *syn*/*anti* ratio on α-enone in the reaction of (*E*)-ketene silyl acetal: (1) Sil = TBS; R^2 = ^{t}Bu (2) Sil = TBS; R^2 = Born (3) Sil = TMS; R^2 = Born (4) Sil = TMS; R^2 = Me.

Table 1. Mukaiyama-Michael Reaction of Ketene Silyl Acetals.[a)]

					Michael adduct	
entry	R^1	Sil	R^2	*E* or *Z*	yield (%)	*syn*:*anti*
1	^{t}Bu	TBS	^{t}Bu	*E*	84	99:1
2[b)]				*E*	79	92:8
3[c)]				*E*	78	90:10
4[d)]				*Z*	87	99:1
5			Neop	*E*	92	92:8
6			Born	*E*	97	89:11
7				*Z*	78	99:1
8			Et	*E*	88	71:29
9				*Z*	74	52:48
10			Me	*E*	94	69:31
11				*Z*	72	39:61
12		TES	^{t}Bu	*E*	87	93:7
13				*Z*	83	89:11
14			Born	*E*	79	91:9
15				*Z*	71	97:3

(Table 1 continued)

16			Et	*E*	78	67:33
17			Me	*E*	94	53:47
18				*Z*	67	40:60
19		TMS	^{t}Bu	*E*	88	77:23
20			Born	*E*	75	80:20
21				*Z*	80	96:4
22			Me	*E*	92	46:54
23				*Z*	59	51:49
24	Ph	TBS	^{t}Bu	*E*	61	55:45
25			Born	*E*	86	66:36
26		TMS	Born	*E*	82	65:35
27				*Z*	79	61:39
28			Me	*E*	90	45:55
29				*Z*	88	42:58
30	Anis	TBS	^{t}Bu	*E*	63	55:45
31	Mes			*E*	99	91:9
32			Neop	*E*	97	86:14
33			Born	*E*	86	88:12
34			Et	*E*	90	91:9
35				*Z*	63	91:9
36			Me	*E*	90	90:10
37				*Z*	78	93:7
38		TES	^{t}Bu	*E*	82	96:4
39				*Z*	78	94:6
40			Born	*E*	70	93:7
41				*Z*	84	91:9
42			Et	*E*	90	87:13
43			Me	*E*	82	89:11
44		TMS	^{t}Bu	*E*	84	82:18
45			Born	*E*	90	91:9
46				*Z*	74	93:7
47			Me	*E*	95	84:16

[a] Reaction conditions: α-enone:ketene silyl acetal:$TiCl_4$ = 1.0:1.3:1.0; CH_2Cl_2, -78 °C; 5 h. [b] Et_3SiClO_4 (0.1 equiv) was used. [c] $SnCl_4$ (0.1 equiv) was used. [d] Ref. 2.

DISCUSSION

It follows from the above results that the Mukaiyama-Michael reaction can be stereoselective if the following conditions are fulfilled. (1) Ketene silyl acetals involve bulky silyl and/or alkoxy group(s). These bulky groups are important for increasing the oxidation potentials of ketene silyl acetals in solution so that the electron-transfer process is suppressed.[5] Another role of the bulkiness is presumably to bias the transition state geometry in favor of the *syn*-isomer. In this regard, the alkoxy group plays more important role than the siloxy group. Namely, even if the TBS group is replaced by the TES or TMS group, not so significant drop of the *syn*-selectivity is observed with *tert*-butoxy and bornyloxy ketene silyl acetals. On the other hand, the *syn*-

selectivity sharply decreases by changing the alkoxy group from the bulky ones to methoxyl irrespective of siloxy group. Remarkably, however, the Z-bornyloxy ketene silyl acetals exhibit excellent *syn*-selectivities (more than 96:4) regardless of the siloxy group that are of great synthetic promise. As far as bulky ketene silyl acetals are concerned, no appreciable difference is observed between *E*- and *Z*-isomers though the *Z*-counterparts show slightly better selectivities in some cases. Upon decreasing the size of ketene silyl acetals, the *syn*-selectivity decreases more sharply with the *Z*-isomers than with the *E*-counterparts and the *anti*-preference appears in some extreme cases. Apparently, contribution of the *anti*-oriented transition state is enhanced under these circumstances.

(2) $TiCl_4$ is superior to $SnCl_4$ and Et_3SiClO_4. $TiCl_4$ is highly oxophilic to form a strong complex with α-enone. The tight complexation decreases the electron-accepting ability of titanium, rejecting the electron transfer from ketene silyl acetals. It may also serve to construct a rigid transition state structure.

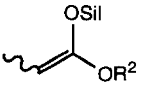
(3) The choice of the acyl group in α-enones is crucial as well. In general, the bulkier the group, the higher the *syn*-selectivity. One may suppose that the tight complexation is feasible with the bulky enones due to the strong electron-releasing character of *tert*-butyl and bornyl groups. If this is responsible for the high selectivity, the anisyl enone should exert the same effect. The experimental result is not compatible with this presumption, suggesting that the steric bulk is primarily important.6) By contrast, the behavior of the mesityl enone is totally different. Little fluctuation of the stereoselectivity occurs even by drastic change of ketene silyl acetals, considerably high levels of *syn*-preference (82:18~96:4) being constantly attained. In addition, *E*- and *Z*-ketene silyl acetals give rise to little difference. It is seen, therefore, that the mechanism of this reaction is different from those of the reactions with other enones and the stereochemistry is primarily governed by the mesityl group irrespective other variables.

In summary, the high diastereoselectivity of the Mukaiyama-Michael reaction is achievable by an appropriate synthetic design. The electron transfer should be suppressed and the transition state structure of the nucleophilic process should be sterically biased. This concept will be equally applied to develop enantioselective reaction. The study along this line is in progress in our laboratories.

EXPERIMENTAL SECTION

General. ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were measured in $CDCl_3$ solution. Mass spectra were taken on a JEOL JMS-DX 303-HF mass spectrometer using impact ionization. HPLC was measured with a Shimadzu LC-8A machine equipped with a column packed with DEVELOSIL 30-3 (4.6 x 250 mm; NOMURA CHEMICAL CO. LTD.). Elemental analyses were performed with a Perkin-Elemer 2400CHN. All reactions were run under dry nitrogen. CH_2Cl_2 and hexane were distilled from calcium hydride. THF was distilled from a benzophenone ketyl. $SnCl_4$ and $TiCl_4$ were used as received. Et_3SiClO_4 was prepared by the method of Lambert and Sun.7) The preparation of *tert*-butyl and phenyl enones was described in our previous paper.3b) The mesityl enone was prepared by the method of Heathcock et al.8)

The preparation of ketene silyl acetals (**1**-**12**) has been described.9) The *E/Z* ratios of the ketene silyl acetals employed in this study were as follows. (*E*)-**1**: *E* : *Z* = 99 : 1; (*E*)-**2**: *E* : *Z* = 85 : 15; (*E*)-**3**: *E* : *Z* = 93 : 7; (*E*)-**4**: *E* : *Z* = 84 : 16; (*E*)-**5**: *E* : *Z* = 72 : 28; (*E*)-**6**: *E* : *Z* = 99 : 1; (*E*)-**7**: *E* : *Z* = 78 : 22; (*E*)-**8**: *E* : *Z* = 91 : 9; (*E*)-**9**: *E* : *Z* = 82 : 18; (*E*)-**10**: *E* : *Z* = 99 : 1; (*E*)-**11**: *E* : *Z* = 84 : 16; (*E*)-**12**: E : Z = 87 : 13; (*Z*)-**1**: *E* : *Z* = 1 : 99; (*Z*)-**3**: *E* : *Z* = 1 : 99; (*Z*)-**4**: *E* : *Z* = 4 : 96; (*Z*)-**5**: *E* : *Z* = 1 : 99; (*Z*)-**6**: *E* : *Z* = 1 : 99; (*E*)-**7**: *E* : *Z* = 13 : 87; (*Z*)-**9**: *E* : *Z* = 1 : 99; (*Z*)-**11**: *E* : *Z* = 2:98; (*Z*)-**12**: *E* : *Z* = 4 : 96.



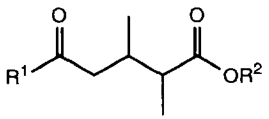
	1	2	3	4	5	6	7	8	9	10	11	12
Sil	TBS	TBS	TBS	TBS	TBS	TES	TES	TES	TES	TMS	TMS	TMS
R	^{t}Bu	Neop	Born	Et	Me	^{t}Bu	Born	Et	Me	^{t}Bu	Born	Me

***Preparation of Anisyl Enone*:** To a mixture of $AlCl_3$ (14.27 g, 107 mmol) and anisol (10.81 g, 100 mmol) in dry CH_2Cl_2 (100 mL) was added *trans*-crotonoyl chloride (10.45 g, 9.58 mL, 100 mmol) at 0 °C over a 5 min period. The reaction mixture was stirred for 30 min at room temperature. The reaction mixture was poured into 2N-HCl (150 mL), and the mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography on silica gel to give 11.62 g (66 %) of the desired enone as a colorless oil: ^{1}H NMR δ 1.98 (d, 3H, J = 6.59Hz), 3.85 (s, 3H), 6.89-7.96 (m, 1H), 6.94 (d, 2H, J=8.79Hz), 7.06 (dq, 1H, J =15.20Hz, 6.65Hz), 7.95 (d, 2H, J = 8.79Hz); ^{13}C NMR δ 18.23, 55.08, 113.39, 126.68, 130.29, 130.44, 143.58, 162.94, 188.41; MS (m/z) 176 (M^+); HRMS calcd for $C_{11}H_{12}O$ (M^+) 176.0837, found 176.0836.

Reaction of Ketene Silyl Acetal with α-Enone (General Procedure). To a solution of Lewis acid (1.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise α-enone (1.0 mmol) at -78 °C. Ketene silyl acetal (1.3 mmol) was added to this solution over a 2 min period. The mixture was stirred for 3 h at this temperature and then H_2O (0.5 mL) was added. The mixture was diluted with EtOAc (60 mL) and washed with H_2O (20 mL). The organic layer was dried over Na_2SO_4, and evaporated. The pure Michael adduct (methyl ester) was isolated by column chromatography on silica gel.

The ethyl ester Michael adduct was converted to the methyl esters as follows. To a solution of the crude Michael adduct and MeOH (3 mL) was added 2N-NaOH (3 mL) at room temperature. The solution was stirred for 18 h at 50 °C and cooled to room temperature. The mixture was combined with 1N-NaOH (20 mL) and extracted with Et_2O (50 mL). The aqueous layer was treated with 5N-HCl (40 mL) and extracted with AcOEt (200 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. To an Et_2O solution (5 mL) of the carboxylic acid thus obtained was added dropwise diazomethane (CH_2N_2) in Et_2O until the color of this reagent began to remain. Evaporation and column chromatography on silica gel afforded the corresponding methyl ester of the Michael adduct.

The *tert*-butyl ester Michael adduct was converted to the methyl ester as follows. To a solution of the crude Michael adduct in THF (3 mL) was added 5N-HCl (3 mL) at room temperature. The solution was stirred for 18 h at 50 °C and cooled to room temperature. The mixture was combined with 1N-NaOH (25 mL) and extracted with Et_2O (50 mL). The aqueous layer was washed with 5N-HCl (50 mL) and extracted with AcOEt (200 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give the carboxlic acid that was treated with CH_2N_2 as described above.



	13	14	15	16	17	18	19	20	21	22	23
R^1	^{t}Bu	^{t}Bu	^{t}Bu	^{t}Bu	Ph	Ph	Anis	Mes	Mes	Mes	Mes
R^2	Neop	Born	Et	Me	Born	Me	Me	Neop	Born	Et	Me

The Michael adducts, **14**,[3b] **15**,[3b] **16**,[3b] **18**,[3b] and **22**,[10] were known. Characterization data for the new compounds are as follows.

13: ^{1}H NMR δ 0.84-1.10 (m, 6H), 0.93 (s, 9H), 1.10 (s, 9H), 2.43-2.45 (m, 4H), 3.69-3.79 (m, 2H); ^{13}C NMR δ 13.34, 16.84, 26.27, 26.45, 31.08, 31.26, 40.80, 44.12, 44.19, 73.65, 175.80, 214.56; MS (m/z) 272 (M^{+}+2); HRMS calcd for $C_{16}H_{30}O_3$ (M^{+}) 270.2195, found 270.2189; Anal. Calcd for : $C_{16}H_{30}O_3$: C, 71.09; H, 11.18. Found: C, 70.72; H, 11.51.

17: ^{1}H NMR δ 0.81-0.95 (m, 9H), 0.96-1.00 (m, 3H), 1.11-1.36 (m, 5H), 1.66-1.80 (m, 3H), 1.88-2.06 (m, 1H), 2.31-2.44 (m, 1H), 2.47-2.63 (m, 2H), 2.77-2.88 (m, 1H), 3.02-3.21 (m, 1H), 4.86-4.93 (m, 1H), 7.42-7.57 (m, 3H), 7.94-7.97 (m, 2H); MS (m/z) 356 (M^{+}); HRMS calcd for $C_{23}H_{32}O_3$ (M^{+}) 356.2351, found 356.2322.

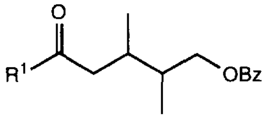
19: ^{1}H NMR δ 0.94 (d, 3Hx0.41, J=5.98Hz), 0.96 (d, 3Hx0.59, J=6.29Hz), 1.15 (d, 3Hx0.41, J=6.83Hz), 1.18 (d, 3Hx0.59, J=6.71Hz), 2.47-2.60 (m, 2H), 2.67-2.77 (m, 1H), 2.95-3.13 (m, 1H), 3.67 (s, 3Hx0.41), 3.68 (s, 3Hx0.59), 3.86 (s, 3H), 6.93 (d, 2H, J=8.92Hz), 7.92-7.96 (m, 2H); ^{13}C NMR δ 13.37 (*syn*), 13.81 (*anti*), 16.81 (*syn*), 17.25 (*anti*), 32.23 (*syn*), 32.39 (*anti*), 42.10 (*anti*), 42.80 (*syn*), 43.98 (*syn*), 44.13 (*anti*), 51.44 (*anti*), 51.54 (*syn*), 55.45 (*syn* and *anti*), 113.66 (*anti*), 113.68 (*syn*), 130.14 (*anti*), 130.27 (*syn*), 130.36 (*anti*), 130.41 (*syn*), 163.39 (*anti*), 163.41 (*syn*), 176.00 (*anti*), 176.38 (*syn*), 197.93 (*syn*), 198.12 (*anti*); MS (m/z) 265 (M^{+}+1); HRMS calcd for $C_{15}H_{20}O_4$ (M^{+}) 264.1299, found 264.1362.

20: ^{1}H NMR δ 0.94 (s, 9H), 1.04 (d, 3H, J=5.98Hz), 1.15 (d, 3H, J=6.78Hz), 2.18 (s, 6H), 2.27 (s, 3H), 2.48-2.66 (m, 3H), 2.71-2.81 (m, 1H), 3.71-3.80 (m, 2H), 6.82 (s, 2H); ^{13}C NMR δ 13.30, 16.96, 19.00, 20.96, 26.44, 30.64, 31.26, 44.10, 49.15, 73.67, 128.47, 132.33, 138.20, 139.52, 175.60, 209.16; MS (m/z) 333 (M^{+}+1); Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.63; H, 9.97. Found: C, 75.92; H, 9.95.

21: ^{1}H NMR δ 0.82-0.95 (m, 9H), 1.02-1.36 (m, 8H), 1.65-1.81 (m, 3H), 1.89-2.05 (m, 1H), 2.18 (s, 6H), 2.27 (s, 3H), 2.30-2.41 (m, 1H), 2.47-2.81 (m, 4H), 4.83-4.91 (m, 1H), 6.82 (s, 2H); MS (m/z) 398 (M^{+}); HRMS calcd for $C_{26}H_{38}O_3$ (M^{+}) 398.2821, found 398.2833.

23: ^{1}H NMR δ 1.02 (d, 3Hx0.81, J=6.17Hz), 1.03 (d, 3Hx0.19, J=6.22Hz), 1.12 (d, 3Hx0.81, J=6.78Hz), 1.14 (d, 3Hx0.19, J=6.65Hz), 2.17 (s, 6H), 2.26 (s, 3H), 2.49-2.70 (m, 3H), 2.72-2.79 (m, 1H), 3.64 (s, 3Hx0.19), 3.66 (s, 3Hx0.81), 6.81 (s, 2H); ^{13}C NMR δ 13.06 (*syn*), 13.07 (*anti*), 16.83 (*syn*), 17.15 (*anti*), 18.86 (*syn*), 19.06 (*anti*), 20.87 (*syn*), 29.58 (*anti*), 30.56 (*syn*), 30.87 (*anti*), 43.50 (*anti*), 43.66 (*syn*), 48.70 (*anti*), 49.05 (*syn*), 51.24 (*anti*), 51.35 (*syn*), 128.41 (*syn*), 128.67 (*anti*), 132.25 (*syn* and *anti*), 138.13 (*anti*), 138.15 (*syn*), 139.47 (*syn* and *anti*), 175.69 (*anti*), 175.98 (*syn*), 209.05 (*syn*), 209.23 (*anti*); MS (m/z) 277 (M^{+}+1); HRMS calcd for $C_{17}H_{24}O_3$ (M^{+}) 276.1726, found 276.1748; Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.96; H, 9.08.

The neopentyl and bornyl Michael adducts were converted to keto benzoates **24-27**. To a suspension of $LiAlH_4$ (184 mg, 4.85 mmol) in THF (5 mL) was added a THF solution (5 mL) of the Michael adduct (0.97 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and cooled with ice bath followed by quenching with 1N-NaOH (2 mL). The mixture was diluted with Et_2O (50 mL), and dried over $MgSO_4$. Filtration and evaporation afforded a crude diol. The resulting diol was dissolved in pyridine (5 mL) and 4-dimethylaminopyridine (10 mg, 0.08 mmol). Benzoyl chloride (177 mg, 0.146 mL, 1.26 mmol) was added to this solution at 0 °C. The solution was stirred at room temperature for 8 h, and quenched with H_2O (2 mL). The quenched mixture was diluted with AcOEt (60 mL), and washed with H_2O (20 mL), 3N-HCl (30 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and concentrated to provide the crude products. Column chromatography on silica gel afforded hydroxy benzoate (100 %). To a mixture of PCC (418 mg, 1.94 mmol) and MS 4A (200 mg) in CH_2Cl_2 (5 mL) was added a THF solution (3 mL) of the hydroxy benzoate (0.97 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h and filtered through celite. The filtrate was evaporated and subjected to column chromatography on silica gel to give the desired keto benzoate (96 %). HPLC analysis of this compound determined the *syn/anti* ratio.



24: R^1 = ^{t}Bu; **25**: R^1 = Ph; **26**: R^1 = Anis; **27**: R^1 = Mes

Characterization data for these keto benzoates are as follows.

24: ^{1}H NMR δ 0.86 (d, 3Hx0.56, J = 6.60Hz), 0.91 (d, 3Hx0.44, J = 6.78Hz), 0.95 (d, 3Hx0.56, J = 7.02Hz), 1.02 (d, 3Hx0.44, J = 7.02Hz), 1.12 (s, 9Hx0.44), 1.13 (s, 9Hx0.56), 1.90-2.03 (m, 1H), 2.25-2.41 (m, 1H), 2.42-2.50 (m, 2H), 4.13-4.30 (m, 2H), 7.41-7.58 (m, 3H), 8.02-8.07 (m,2H); *syn* isomer ^{13}C NMR δ 12.50, 15.23, 26.12, 29.62, 36.34, 41.30, 44.25, 68.03, 128.34, 129.55, 130.38, 132.84, 166.64, 214.83; *anti* isomer ^{13}C NMR δ 14.52, 16.70, 26.22, 30.61, 36.96, 40.44, 44.14, 67.41, 128.25, 129.43, 130.30, 132.78, 166.50, 214.82; MS (m/z) 234 (M^+-Bu^t+1); HRMS calcd for $C_{11}H_{21}O_2$ (M^+-COPh) 185.1542, found 185.1540; Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.14; H, 9.25.

25: ^{1}H NMR δ 0.98 (d, 3Hx0.31, J=6.78Hz), 1.02 (d, 3H, J=6.84Hz), 1.08 (d, 3Hx0.69, J=7.03Hz), 2.04-2.12 (m, 1H), 2.40-2.53 (m, 1H), 2.79-3.15 (m, 2H), 4.19-4.38 (m, 2H), 7.39-7.59 (m, 6H), 7.91-8.05 (m, 4H); ^{13}C NMR δ 12.41 (*anti*), 14.23 (*syn*), 15.30 (*anti*), 16.98 (*syn*), 30.72 (*anti*), 31.46 (*syn*), 36.54 (*anti*), 37.19 (*syn*), 42.36 (*syn*), 43.58 (*anti*), 67.40 (*syn*), 67.87 (*anti*), 128.03 (*syn*), 128.05 (*anti*), 128.33 (*anti*), 128.35 (*syn*), 128.55 (*syn* and *anti*), 129.53 (*syn* and *anti*), 130.28 (*syn*), 130.29 (*anti*), 132.85 (*anti*), 132.90 (*syn*), 132.91 (*syn* and *anti*), 137.18 (*anti*), 137.23 (*syn*), 166.57 (*syn* and *anti*), 199.76 (*anti*), 199.86 (*syn*); MS (m/z) 205 (M^+-COPh); HRMS calcd for $C_{13}H_{17}O_2$ (M^+-COPh) 205.1229, found 205.1225; Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.68; H, 7.07.

26: ^{1}H NMR δ 0.96 (d, 3Hx0.26, J=6.77Hz), 1.00 (d, 3Hx0.74, J=6.78Hz), 1.01 (d, 3Hx0.26, J=7.01Hz), 1.06 (d, 3Hx0.74, J=7.02Hz), 2.00-2.13 (m, 1H), 2.36-2.52 (m, 1H), 2.72-2.86 (m, 2H), 2.95-3.09 (m, 2H), 3.83 (s, 3Hx0.74), 3.85 (s, 3Hx0.26), 4.19-4.37 (m, 2H), 6.84-6.91 (m, 2H), 7.40-7.58 (m, 3H), 7.88-8.05 (m, 2H); ^{13}C NMR δ 12.42 (*anti*), 14.00 (*syn*), 15.15 (*anti*), 16.87 (*syn*), 30.78 (*anti*), 31.49 (*syn*), 36.38 (*anti*), 37.05 (*syn*), 41.75 (*syn*), 43.10 (*anti*), 55.20 (*syn* and *anti*), 67.26 (*syn*), 67.74 (*anti*), 113.51 (*syn* and *anti*), 128.16, 128.19, 129.38, 130.15, 132.67 (*syn*), 132.71 (*anti*), 163.19 (*syn* and *anti*), 166.34 (*syn* and *anti*), 198.09 (*anti*), 198.20 (*syn*); MS (m/z) 218 (M^+-OCOPh-1); HRMS calcd for $C_{14}H_{19}O_3$ (M^+-COPh) 235.1334, found 235.1336; Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.80; H, 7.39.

27: ^{1}H NMR δ 0.97 (d, 3Hx0.90, J=7.02Hz), 1.02 (d, 3Hx0.90, J=6.78Hz), 1.03 (d, 3Hx0.10, J=7.01Hz), 1.11 (d, 3Hx0.10, J=6.78Hz), 1.99-2.36 (m, 1H), 2.18 (s, 6Hx0.1), 2.20 (s, 6Hx0.9), 2.27 (s, 3H), 2.46-2.58 (m, 1H), 2.60-2.88 (m, 2H), 4.17-4.31 (m, 2H), 6.83 (s, 2H), 7.41-7.60 (m, 3H), 8.01-8.07 (m, 2H); ^{13}C NMR δ 12.17 (*syn*), 13.92 (*anti*), 15.07 (*syn*), 17.17 (*anti*), 18.92 (*syn* and *anti*), 20.83 (*syn* and *anti*), 28.94 (*syn*), 29.82 (*anti*), 36.33 (*syn*), 36.88 (*anti*), 48.24 (*anti*), 49.59 (*syn*), 67.17 (*anti*), 67.71 (*syn*), 128.18 (*syn* and *anti*), 128.39 (*syn* and *anti*), 129.38 (*syn* and *anti*), 130.06 (*anti*), 130.14 (*syn*), 132.16 (*anti*), 132.21 (*syn*), 132.70 (*syn* and *anti*), 138.04 (*syn* and *anti*), 139.50 (*syn* and *anti*), 166.35 (*syn* and *anti*), 209.19 (*syn*), 209.34 (*anti*); MS (m/z) 353 (M^++1); HRMS calcd for $C_{23}H_{28}O_3$ (M^+) 352.2039, found 252.2061; Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.63; H, 8.19.

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