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E- or *Z*-Selective Knoevenagel Condensation of Acetoacetic Derivatives: Effect of Acylated Substituent, that is, TEMPO and Amines, as an Auxiliary, and New Accesses to Trisubstituted *E*- and *Z*-2-Alkenals and Furans

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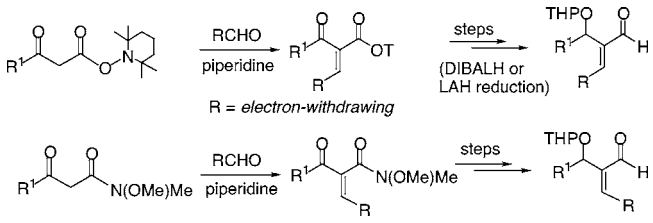

Knoevenagel condensation of *O*-acetoacetylTEMPOs (2,2,6,6-tetramethylpiperidine-1-oxyl) with aldehydes substituted with an electron-withdrawing group such as aromatic and heteroaromatic ones leads preferentially to E-adducts, while acylacetoamides including Weinreb amides produce Z-adducts, exclusively. These E- and Z-adducts are selectively converted to the corresponding (2*E*)- and (2*Z*)-2-hyroxyalkyl-2-alkenals, respectively, by stepwise reductions of the acyl group with DIBALH and then the carboxylic functions after protection of the hydroxy group. Transformation of the Knoevenagel products by taking advantage of the E-geometry to trisubstituted furans is also developed.

Introduction

Knoevenagel condensation is highly useful for the synthesis of functionalized enones and enoates, since addition reaction of the methylene components, activated with two electron-withdrawing groups, to aldehydes can be performed with secondary amines.[1] Although adducts with two different electron-withdrawing groups are regarded to be highly versatile and interconvertible trisubstituted olefins, stereocontrol of the reaction has mainly relied on the steric effects of one of the withdrawing groups over the other one, and hence the scope is limited to a combination of a bulky/less bulky pattern like CO_2R versus CN,[2] SO_2Me versus CO_2R,[3] and $PO(OR)_2$ versus CO_2R.[4] Furthermore, a stereoselective approach has been scarcely achieved with respect to condensation of acetoacetic derivatives with aldehydes,[1a,2c] despite such being more important in bioactive natural product syntheses.[5] Thus far, to the best of our knowledge, there is only one example where benzoyl acetate was employed as the active methylene for the condensation with benzaldehyde, leading to the trans relationship between the phenyl group from benzaldehyde and the PhCO group in the resulting adduct.[6]

In our continuing studies on exploring 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) substitution as a reaction-controlling element,[7] we examined Knoevenagel condensation of *O*-acetoacetylTEMPO **1** with aldehydes **2** and discussed the effect

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† Okayama University.
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(1) Reviews: (a) Jones, G. *Org. React.* **1967**, *15*, 204. (b) Tietze, L. F.; Beifuss, U. *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 2, pp 341−394.

(2) (a) Schwarz, M. *J. Chem. Soc., Chem. Commun.* **1969**, 212−213. (b) Zabicky, J. *J. Chem. Soc.* **1961**, 683−687. (c) Tietze, L. F.; Beifuss, U. *Liebigs Ann. Chem.* **1988**, 321−329. Recently, Ti-enolate of acetoacetate was shown to be useful for E-selectivity in some extent: (c) Hayanshi, M.; Nakamura, N.; Yamashita, K. *Tetrahedron* **2004**, *60*, 6777−6783.

(3) Happer, D. A. R.; Steenson, B. E. *Synthesis* **1980**, 806−807.

(4) Lehnert, W. *Tetrahedron* **1974**, *30*, 301−305.

(5) Z-isomers from acetoacetate derivatives were used in natural product syntheses: (a) Hong, R.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3478−3481. (b) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043−2046. (c) Munakata, R.; Katakai, H.; Ueki, T.; Kurosawa, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722−14723.

(6) Tanikaga, R.; Konya, N.; Hamamura, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3211−3216.

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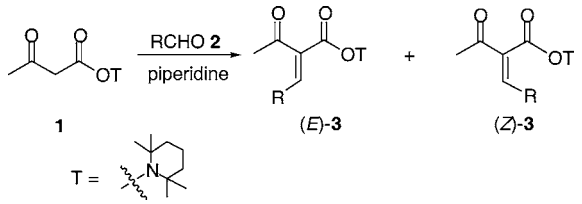
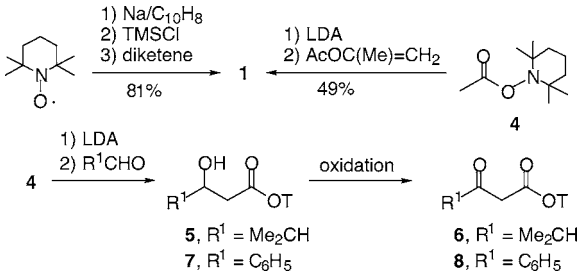
SCHEME 1. Knoevenagel Condensations of *O*-Acetoacetyl TEMPO



SCHEME 2. Preparation of *O*-AcetoacetylTEMPO and Its Homologues



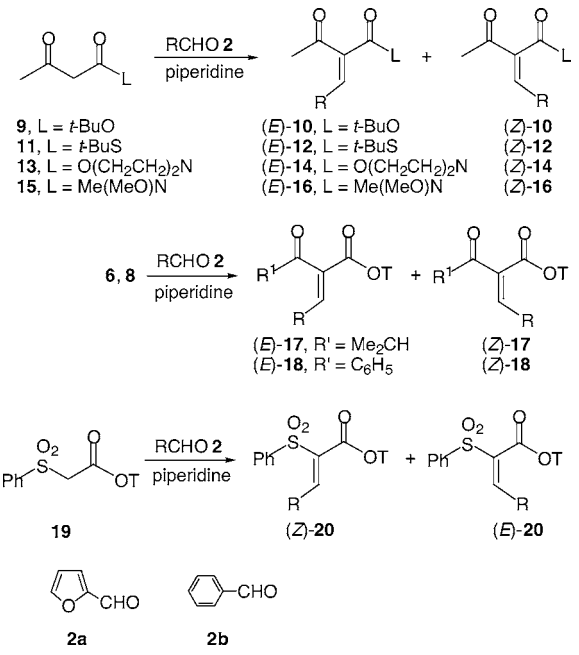
of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as an auxiliary on the geometry of the resulting adducts **3** (Scheme 1). In the meantime, other acyl substituents such as Me(MeO)N were also employed for comparison. Subsequently, a new access to 2-(1-hydroxyalkyl)-2-enals **31** of defined geometry, useful analogues of the Morita−Baylis−Hillman reaction products,[8] was developed by stepwise reductions of the acyl groups and then the carboxylic functions of **3** and its congener. A novel method for the synthesis of trisubstituted furans by taking advantage of E-geometry of the Knoevenagel adducts is also explored.

Results and Discussion

The starting *O*-acetoacetyl-(2,2,6,6-tetramethylpiperidine)-1-oxyl (*O*-acetoacetylTEMPO, **1**) was prepared either by addition of the *O*-trimethylsilylTEMPO, generated by silylation of the TEMPO anion,[7a] to diketene[9] in 81% yield from TEMPO• or by Claisen condensation of *O*-acetylTEMPO (**4**) with isopropenyl acetate with LDA as a base in 49% yield (Scheme 2).[10] Other *O*-alkanoylacetylTEMPOs, that is, **6** and **8**, were prepared by aldol reaction of **4** with the respective aldehydes followed by oxidation of the resulting aldol adducts **5** and **7** with the Swern reagent or the TEMPO•/$RuCl_2(PPh_3)_3/O_2$ system.[11]

As shown in Table 1, we first examined the effect of the acylated substituents, L, that is, *t*-BuO, *t*-BuS, R_2N, and Me(MeO)N, and TEMPO, on the E/Z selectivity of Knoevenagel condensation with 2-furaldehyde (**2a**). Thus, the piperidine-catalyzed condensation of *tert*-butyl acetoacetate **9** with **2a** produced the corresponding adducts **10a** as a 1:1.5 E/Z mixture

TABLE 1. Effect of Acylated Substituents L and TEMPO on the E/Z-Selectivity of Knoevenagel Condensations[a]



entry	dicarbonyl	RCHO	product	yield (%)[b]	E/Z ratio[c]
1	**9**	**2a**	**10a**	69	1:1.5
2	**11**	**2a**	**12a**	94	1:2.2
3	**13**	**2a**	**14a**	76	1:>50[d]
4	**15**	**2a**	**16a**	69	1:>50[d]
5	**1**	**2a**	**3a**	76	38:1[e]
6	**6**	**2a**	**17a**	82	20:1
7[f]	**8**	**2b**	**18b**	75	3:1
8	**19**	**2a**	**20a**	95	>50:1[d]

[a] Carried out by using acetoacetic derivatives (1.0∼2.5 mmol) and **2** (1.5∼2.0 equiv) in EtOH or CH_2Cl_2 at room temperature with piperidine. AcOH was added when the reaction was sluggish. [b] Yields are based on isolated products. [c] Determined on the basis of ^1H NMR. [d] One isomer was exclusively formed. [e] 6:1 when carried out in the presence of AcOH. [f] Conducted in MeCN at reflux for 12 h.

(entry 1).[12] Similar Z-preference was found with thioester **11**, where the adduct **12a** was obtained with a 1:2.2 E/Z mixture (entry 2). Furthermore, to our surprise, the condensation of *N*-acetoacetylmorpholine **13** and the Weinreb amide **15**[13] with **2a** afforded the corresponding (*Z*)-**14a** and (*Z*)-**16a**, respectively, with exclusive selectivity (entries 3 and 4). On the other hand, gratifyingly, the condensation of *O*-acetoacetylTEMPO **1** with **2a** resulted in a reversal of the E/Z ratio to 38:1, giving the adducts (*E*)-**3a** in 76% yield (entry 5).

Since the preferential formation of the E-isomer with *O*-acetoacetylTEMPO **1** was witnessed, we next examined other *O*-alkanoylacetylTEMPOs, **6** and **8**, to probe the effect of bulkiness of the alkanoyl R^1 on the E/Z selectivity. The condensation of 2-methylpropanoyl derivative **6** with **2a** produced adducts **17a** with an E/Z ratio of 20:1 (entry 6). Thus, no significant steric effect causing decrease of E-selectivity was observed with the spatially spread isopropyl group on the condensation. Furthermore, a similar E-preference was found

(7) (a) Inokuchi, T.; Kawafuchi, H. *Tetrahedron* **2004**, *60*, 11969−11975. (b) Inokuchi, T.; Kawafuchi, H.; Nokami, J. *Chem. Commun.* **2005**, 537−539.

(8) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062.

(9) Lawesson, S.-O.; Sandberg, R. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. 5, pp 155−157.

(10) Davis, B. R.; Garratt, P. J. *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 2, pp 795−863.

(11) Inokuchi, T.; Nakagawa, K.; Torii, S. *Tetrahedron Lett.* **1995**, *36*, 3223−3226.

(12) (a) Inokuchi, T. *J. Org. Chem.* **2005**, *70*, 1497−1500. (b) Inokuchi, T.; Okano, M.; Miyamoto, T. *J. Org. Chem.* **2001**, *66*, 8059−8063. (c) Inokuchi, T.; Okano, M.; Miyamoto, T.; Madon, H. B.; Takagi, M. *Synlett* **2000**, 1549−1552.

(13) Inglesi, M.; Nicola, M.; Magnetti, S. *Farmaco* **1990**, *45*, 1327−40.

TABLE 2. Coupling Constants of ^3J(COOT, H) or ^3J(COL, H) of Selected Knoevenagel Condensation Products

compounds	*E*-isomer	Z-isomer
3a	7.8	[a]
3b	7.9	12.5
3c	7.5	[a]
3e	[a]	11.4
3f	[a]	12.4
17a	7.7	[a]
18b	8.1	[a]
10a	7.8	11.7
12a	[a]	11.0
14a	[a]	11.5
16a	[a]	10.4
20a	11.2[b]	[a]

[a] Not characterized because of scant availability of compounds. [b] trans-Relationship between COOT and vinylic proton.

even in the condensation of benzoyl derivative **8** with benzaldehyde (**2b**), giving the adducts **18b** in an E/Z ratio of 3:1 (entry 7), which is markedly contrasted with the exclusive formation of the Z-isomer (E/Z = 1:99), reported by Kaji et al., in the condensation of ethyl benzoyl acetate with **2b**.[6] The condensation of phenylsulfonylacetylTEMPO **19** with **2a** proceeded smoothly but afforded the usual E-isomer **17a** (trans relationship between $PhSO_2$ and 2-furyl groups), exclusively (entry 8).[3]

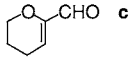
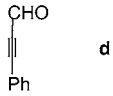
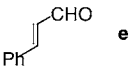
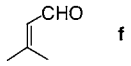
The E- and Z-geometries of adducts were unambiguously deduced on the basis of line separations of the carbonyl carbons of the COOT or COL in the ^{13}C NMR because of coupling with the vinylic ^1H nucleus.[14] As shown in Table 2, the Z-isomers (trans relationship between COOT or COL and vinylic H) show a larger line separation with 11.2∼12.5 Hz for the COOT or COL carbonyl carbons, while the E isomers (cis relationship) show reduced values of 7.5∼8.1 Hz in the line separation.[15]

We examined the effect of the kind of aldehydes on the E/Z selectivity by employing oxa-2-cyclohexene-2-carbaldehyde (**2c**),[16] phenylpropargyl aldehyde (**2d**), *trans*-cinnamaldehyde (**2e**), and 3-mehyl-2-butenal (**2f**) (Table 3). Thus, the substituent R of enals and ynal was chosen as being of an electronically different nature: inductively electron-withdrawing,[17] more or less electron-withdrawing, and electron-donating.

As shown in entry 1, the condensation of **1** with **2c** afforded the E-isomer **3c**, predominantly. This E-preference executed with **2c** reappeared in the condensation with the derivatives of 2-methylpropanoyl, **6**, and benzoyl, **8**, giving the corresponding adducts **17c** and **18c** in 87% and 56% yields, respectively, with an E/Z ratio of 25∼20:1(entries 2 and 3). On the other hand, the runs of **1** with the ynal **2d** and enal **2e** resulted in formation of adducts **3d** and **3e** with a reversed E/Z ratio of ca. 1:3−1:2 (entries 4 and 5). Furthermore, the condensation of **1** with **2f** produced the Z-adduct **3f**, exclusively (entry 6).

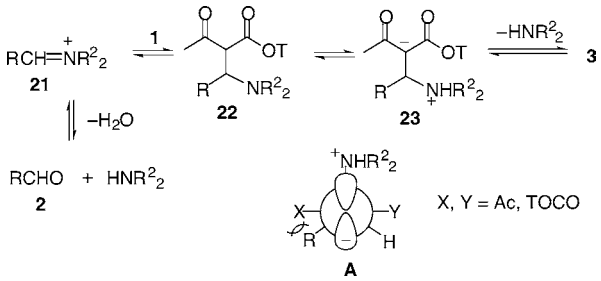
As shown in Scheme 3, the amine-catalyzed Knoevenagel reaction includes many reversible steps, in which the amine

TABLE 3. Effect of Substituent R of Aldehydes 2 on the E/Z-Selectivity of Knoevenagel Condensations of 1, 6, and 8[a]

entry	RCHO, **2**		*O*-acylTEMPOs	product	yield[b]	*E*/*Z* ratio[c]
1		**c**	**1**	**3c**	97	26:1
2			**6**	**17c**	87	25:1
3			**8**	**18c**	56	20:1[e]
4		**d**	**1**	**3d**	42	1:3
5		**e**	**1**	**3e**	46	1:2[d]
6		**f**	**1**	**3f**	46	1:>30[e]

[a] Carried out by using the substrates (0.5∼1.0 mmol) and **2** (1.5∼2.0 equiv) in EtOH at 0∼10 °C with piperidine until the substrates were consumed. AcOH was added when the reaction was sluggish. [b] Yields are based on isolated products. [c] Determined on the basis of ^1H NMR. [d] *E*-**3e** isomerized to *Z*-**3e** on standing or in $CDCl_3$. [e] One isomer was exclusively produced.

SCHEME 3. Mechanism of Knoevenagel Reaction



compound **22**, produced by addition of **1** to the iminium salt **21**, plays an important role in the stereochemical outcome of the reaction.[6] The intermolecular or intramolecular acid−base reaction of **22** may form the betaine **23**, which would undergo elimination of the secondary amine via the conformation **A**, leading finally to thermodynamically favorable (E)- or (Z)-isomer of adducts **3**. Since the E/Z ratio of the Knoevenagel reaction of **1** was affected by the kind of substitution R of aldehydes **2** (Table 3), we discussed these stereochemical results from the electronic and steric points of view as follows.

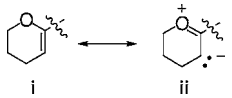
Accordingly, we postulated that these results might be ascribable to the harmony of electron-withdrawing or -donating nature of the substituents R of aldehydes and their steric bulkiness. It is conceived that Z-geometry is more favorable than its E-geometry, when R is an electron-donating nature like the 2-methyl-2-propenyl group (Table 3, entry 6), irrespective of steric hindrance between R and *O*-acylTEMPO group (structure (*Z*)-**3**, eq 1).[19] It is due to stereoelectronic reason of

(14) Kingsbury, C. A.; Draney, D.; Sopchik, A. Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863−3868.

(15) E- and Z-geometry of **3** was further confirmed by NOE experiments (Supporting Information).

(16) Paquette, L. A.; Schulze, M. M.; Bolin, D. G. *J. Org. Chem.* **1994**, *59*, 2043−2051.

(17) According to resonance structure **ii**, the oxa-2-cyclohexenyl substituent of **2c** is considered to be of electron-withdrawing nature.



(18) (a) Kirby, A. J. *Stereoelectronic Effect*; Oxford University Press: Oxford, U.K., 1996; Chapter 4. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1993; Part A, Chapter 3.

(19) Because of such conjugative interaction in Z-isomers as **B**, the ^{13}C NMR absorption due to an acyl CO usually appears at higher field than that of E-isomers, for example, (*Z*)-**3b**, 202.4 ppm versus (*E*)-**3b**, 195.4 ppm.

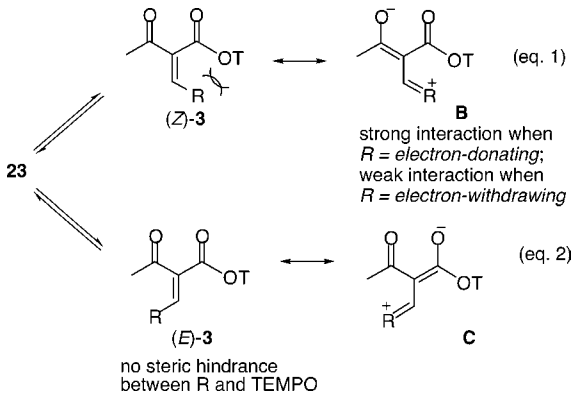


FIGURE 1. Interpretation for preference of E- and Z-adducts dependent on the kind of aldehyde substituents R.

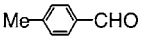
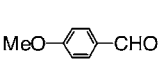
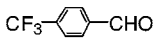
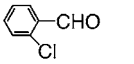
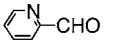
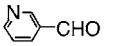
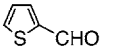
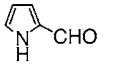
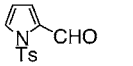
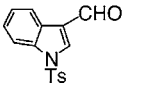
R and the acyl group, that is hyper- or π-conjugative donor−acceptor interaction, as indicated in the resonance structure **B** (Figure 1, eq 1). On the other hand, when R is the electron-withdrawing one, that is, oxa-2-cyclohexenyl (Table 3, entries 1−3), the interaction between R and the acyl group will be weakened and the reaction may be crucially influenced by steric hindrance between the auxiliary TEMPO and R. Therefore, the condensation of **1** with such aldehydes leads to preferential formation of E-isomers (eq 2), where stabilization by a hyper- or π-conjugative interaction between R and the COOT group is also accounted for in some extent.[20]

Alternatively, the marked Z-preference by the reaction of the morpholine amide **13** and Weinreb amide **15**, compared with the alkyl ester **9** and *O*-acylTEMPOs **1**, can be explained by the decreased electron-withdrawing ability of the amide groups, in which the stabilization by hyper- or π-conjugative interaction between R and the CONR′R″ groups on the structure of adducts **14** and **16** is canceled out.[20]

The conformation of Knoevenagel adduct (*E*)-**3a** was determined by X-ray crystallographic analysis (Supporting Information). The COOT group and the 2-furyl group in trans relationship with each other spread over the same plane of the conjugated π-system. The carboxyl oxygen and the piperidine nitrogen are located within the same plane, which looks like assisting hyperconjugative interaction between the 2-furyl and the COOT groups. The conformation of the acetyl group takes orientation orthogonal to the conjugated π-system. Furthermore, the calculation of the conformation of *O*-acylTEMPO by PM3 showed that cis conformation between C═O and O−N bonds on the C−O bond was a favorable one.[21]

To assess the generality of the present method to construct the E-adducts by Knoevenagel condensation of *O*-acetoacetyl-TEMPO **1**, various aromatic and heteroaromatic aldehydes **2** were examined by using piperidine as a base. As shown in Table 4, entries 1−4, 6−8, 10, and 11, a similar trend of E-preference as in the case of 2-furaldehyde (**2a**) was observed. On the other hand, low E-preference was encountered in the case of 2-chlorobenzaldehyde (**2j**) and pyrrole-2-carboxaldehyde (**2n**), in which E- and Z-adducts were produced in almost equal amount (entries 5 and 9). However, E-preference of pyrrole **2n**, *E*/*Z* = 1.1:1, was greatly improved to the E/Z ratio of 14:1 by use of

TABLE 4. Knoevenagel Condensations of *O*-AcetoacetylTEMPO 1 with Various Aromatic Aldehydes 2 to 3

entry	2		cond.[a]	**3**, yield (%)[b]	*E*/*Z* ratio[c]
1		**b**	B	99	3.5/1
2		**g**	A	89	1.5/1
3		**h**	B	88	8.8/1
4		**i**	A	84	1.7/1
5		**j**	A	95	1.1/1
6		**k**	A	98	6.5/1
7		**l**	B	89	2.5/1[d]
8		**m**	A	80	2.3/1
9		**n**	B	89	1.1/1
10		**o**	C	85	14/1
11		**p**	B	61(80)	2.3/1

[a] Carried out by using **1** (0.5∼2.0 mmol) and **2** (1.3∼1.5 equiv) in EtOH (three drops) (A), in CH_2Cl_2 (few drops)-AcOH (two drops) (B), or in DMF (0.5 mL)-AcOH (two drops) (C) at room temperature with piperidine base (two drops). [b] Yields are based on isolated products and the value in the parentheses is the conversion (%) of **1**. [c] Determined on the basis of ^{1}H NMR. [d] Z-Adduct isomerized to E-isomer during recrystallization.

N-tosyl analogue **2o** (entry 10). Furthermore, some of inferior E-preferences in Table 4 can be recovered by adopting a contiguous chromatographic separation and Z/E isomerization of the separated Z-adducts, as described below.

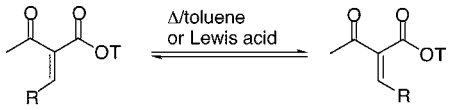
Alkyl alkylideneacetoacetates are prone to Z/E isomerization by heating or upon treatment with a Lewis acid such as Yb(OTf)$_3$.[1b,10] Accordingly, we submitted individually the *O*-acylTEMPO derivatives (*E*)- and (*Z*)-**3b** to heating at 100 °C for 12 h in toluene, giving a 6.7:1 mixture of E- and Z-isomers **3b**, respectively (Table 5, entries 1 and 2). The same treatment of (*E*)-**3a** as above for 7 h led to a 6:1 mixture of (*E*)- and (*Z*)-**3a** (entry 3), while that of (*Z*)-**3a** for 14 h resulted in a 1:2 mixture of E/Z-isomers (entry 4). It is likely that isomerization of the (Z)-isomer of **3a** to its (E)-isomer is sluggish compared with that of (*Z*)-**3b**. On the other hand, the treatment of the separated (Z)-isomer **3j**, one of low E-preference products, with Yb(OTf)$_3$ in toluene at room temperature for 34 h afforded a 1:1.8 mixture of (*E*)- and (*Z*)-**3k** (entry 5). Thus, this procedure can induce Z/E isomerization of a low E-preference product, which enabled us to regain the (E)-isomers from the (Z)-isomers and to improve totally the ratio of (E)-isomers. Similarly, the treatment of the separated indole derivative (*Z*)-**3n** with Me_3Al in CH_2Cl_2 led to a 1:1.7 mixture of (*E*)-and (*Z*)-**3n** (entry 6).

In contrast to the E-preference condensations of acetoacetylTEMPO **1**, as shown in Table 6, Knoevenagel condensations of *N*-methoxy-*N*-methylacetoacetamide (Weinreb amide

(20) *O*-acylTEMPO seems to be more electron-withdrawing than Weinreb amide, CON(OMe)Me, on the basis of IR absorption, $\upsilon_{C=O}$ of RCOOT = ∼1760 cm^{-1} (RCOOT); that of CON(OMe) = ∼1665 cm^{-1}.

(21) The calculation was probed by using PM3 semiempirical energy minimizations (MOPAC2002 in CAChe Worksystem Pro 5.04).

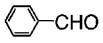
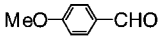
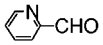
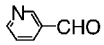
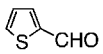
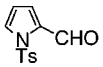
TABLE 5. Z/E-Isomerization by Heating or Treatment with Lewis Acid



(*E*)-**3** (*Z*)-**3**

entry	compds	R	conditions/time	E/Z ratio
1	(*E*)-**3b**	C_6H_5	100 °C/12 h	6.7/1
2	(*Z*)-**3b**	C_6H_5	100 °C/12 h	6.7/1
3	(*E*)-**3a**	2-furyl	100 °C/7 h	6.0/1
4	(*Z*)-**3a**	2-furyl	100 °C/14 h	1/2
5	(*Z*)-**3k**	2-ClC_6H_4	Yb(OTf)$_3$/RT/34 h	1/1.8
6	(*Z*)-**3n**	*N*-Ts-3-indolyl	Me_3Al/0 °C/2 h	1/1.7

TABLE 6. Knoevenagel Condensations of *N*-Methoxy-*N*-methylacetoacetamide (Weinreb Amide 15) with Various Aromatic Aldehydes to (*Z*)-16[a]

entry	**2**		**16**, yield (%)[b]
1		**b**	77
2		**h**	92
3		**k**	84
4		**l**	71
5		**m**	75
6[c]		**o**	79

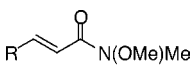
[a] Carried out by using **15** (1.0∼2.0 mmol) and **2** (1.3∼1.5 equiv) in CH_2Cl_2 (few drops)-AcOH (two drops) at 28∼30 °C for 2 days. [b] Yields are based on isolated products. [c] DMF (0.2 mL) was added.

15) with various aromatic aldehydes **2** lead to (Z)-adducts **16**, exclusively. In this case, when prolonged, a very small amount of deacetylated byproduct was found, presumably because of retro-Claisen condensation of **22** with amine base followed by elimination of amine.[22]

Having succeeded in stereoselective Knoevenagel condensation of acetoacetic derivatives, we next examined reduction of the adducts with hydride-transferring reagents to obtain the corresponding 2-(1-hydroxyalkyl)-(2*E*)- or -(2*Z*)-carboxylate derivatives, which are γ-substituted but hardly accessible homologues by the Morita−Baylis−Hillman procedure.[8] As shown in Table 7, the LAH-reduction of (*E*)-**3a** at −78 °C gave **25a** as a main product (75% yield) as a result of 1,4-addition of hydride as well as a small amount of the carbinol (*E*)-**24a** (24% yield) because of the 1,2-addition (entry 1). On the other hand, the reduction of (*E*)-**3a** with DIBALH (2 equiv) at −78 °C for 15 min afforded the desired (*E*)-**24a** (83% yield) as a major product and a small amount of **25a** (7% yield, entry 2) as a byproduct. Similarly, (*E*)-**17a** and (*E*)-**3c** were reduced with DIBALH to give the corresponding 1,2-reduction products (*E*)-**26a** and (*E*)-**24c** in 72 and 78% yields, respectively (entries 3 and 4). Furthermore, the reduction of Weinreb amide (*Z*)-**16a** with DIBALH (1.5 equiv) at −78 °C gave the corresponding (*Z*)-**28a** in 85% yield (entry 5).

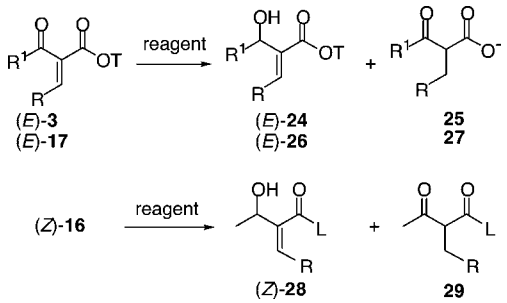
According to propensity of the *O*-acylTEMPOs and Weinreb amides to leave selectively the aldehydes upon reduction,[7,23] we examined transformation of the above 2-hydroxyalkyl derivatives (*E*)-**24a** and (*Z*)-**28a** to the corresponding *E*- and *Z*-enals **31a** (Scheme 4). Thus, reduction of the THP ether (*E*)-**30a**, accessible by protection of (*E*)-**24a** with dihydropyran (78% yield), with DIBALH (3 equiv) at −78 °C for 1 h afforded the desired

(22) Formation of a small amount of conjugated amides **iii** as a byproduct was accompanied. In contrast to efficient condensations with aromatic aldehydes, the reaction of *trans*-cinnamaldehyde (**2e**) with **15** under the same conditions resulted in a low yield of the desired Z-adduct.



iii

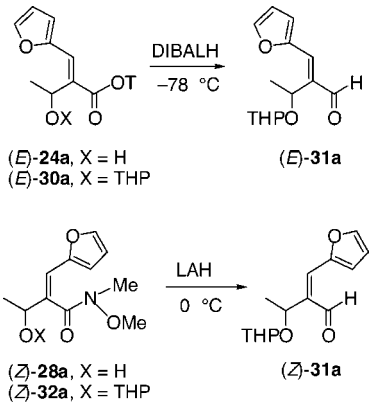
TABLE 7. Reduction of Knoevenagel Adducts with Hydride-Transferring Reagents



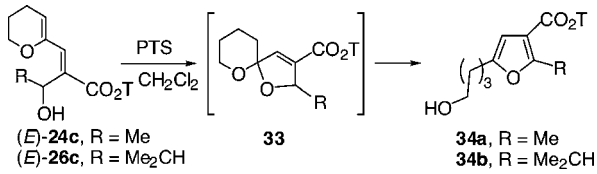
			product, yield, %[a]		
entry	substrate	reagent (equiv)	1,2-red	1,4-red	SM
1	**(*E*)-3a**	**LAH (2.5)**	**(*E*)-24a**, 24	**25a**, 75	
2	**(*E*)-3a**	**DIBALH (2.0)**	**(*E*)-24a**, 83	**25a**, 7	9
3	**(*E*)-17a**	**DIBALH (2.0)**	**(*E*)-26a**, 72	**27a**, 13	14
4	**(*E*)-3c**	**DIBALH (2.0)**	**(*E*)-24c**, 78	**25c**, 7	5
5	**(*Z*)-16a**	**DIBALH (1.5)**	**(*Z*)-28a**, 85	**29a**	

[a] Isolated yields are based on starting substrates.

SCHEME 4. Preparation of *E*- and *Z*-2-Alkenals by Reduction



SCHEME 5. Conversion of Knoevenagel Adducts to Furans



(23) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

aldehyde (*E*)-**31a** in 86% yield along with the corresponding carbinol (7%) because of overreduction. The obtained *E*-enal **31a** was contaminated with ca. 5% of *Z*-enal because of olefin isomerization possibly during the reduction with DIBALH. Olefin isomerization also proceeded, though slowly, on standing in $CDCl_3$. On the other hand, the reduction of the THP-protected Weinreb amide (*Z*)-**32a**, obtained in 84% yield by protection of the hydroxy group of (*Z*)-**28a**, with DIBALH at 0 °C resulted in an intractable mixture comprised of aldehydes (ca. 1:1 mixture of (*E*)/(*Z*)-**31a**), the corresponding carbinol because of overreduction, and the unidentified. However, the reduction of (*Z*)-**32a** with lithium aluminum hydride (LAH) at 0 °C afforded cleanly the desired *Z*-enal **31a** in 72% yield. This conversion was accompanied by formation of a ca. 4:1 Z/E mixture of 3-(2-furyl)-2-hydroxy-2-propenal (8%) because of hydrolysis of THP ether presumably during acidic workup with aqueous tartaric acid.

We attempted transformation of (*E*)-**24c** to spiro[4.5] acetal **33** by acid-catalyzed cyclization of the hydroxy group to enol olefin by virtue of cis configuration of the olefinic linker. However, it turned out that the treatment of (*E*)-**18c** with PTS in CH_2Cl_2 led to trisubstituted furan **34a** in 93% yield as a result of cyclization to **27** followed by aromatization.[24,25] Similarly, (*E*)-**26c**, obtained by the DIBALH reduction of the corresponding precursor (*E*)-**17c** as above (85% yield), was transformed to **34b** in 94% yield.

Conclusion

In summary, the first E-selective Knoevenagel condensation of acetoacetic derivatives has been developed by using TEMPO for the acylated substituent. Alternatively, Z-selective Knoevenagel condensation was achieved by use of amide analogues including the Weinreb amide. The E-selectivity, successful for the kind of aldehydes bearing electron-withdrawing substituents, can virtually be explained in terms of steric hindrance caused by an acylated substituent TEMPO toward a substituent R at the vinylidene carbon of the adducts. Furthermore, effect of the kind of aldehydes as well as the acylated substituent of nucleophiles on the E-selectivity was discussed from the steric and electronic viewpoints. The E- and Z-adducts are shown to be a useful precursor of *E*- and *Z*-2-hydroxyalkyl-2-propenals owing to propensity of *O*-acylTEMPO and the Weinreb amide to leave the formyl group by reduction with either DIBALH or LAH. Utility of E-geomety of the products was also shown by another application to the facile synthesis of trisubstituted furans.[26]

Experimental Section

Preparation of 1 by Reaction of the TEMPO Anion and Diketene. In a 50-mL one-necked flask were placed $C_{10}H_8$ (160 mg, 1.25 mmol), TEMPO• (2.0 g, 12.8 mmol), and THF (20 mL). To this solution was added Na metal (354 mg, 15.4 mmol) at −60 °C, and the mixture was stirred at room temperature until Na dissolved and the blue-black color of $Na^+[C_{10}H_8]^{-\bullet}$ persisted. To the mixture was added Me_3SiCl (2.0 mL, 15.8 mmol) at room temperature. The resulting mixture was transferred dropwise to a solution of diketene (4.9 mL, 64.0 mmol) in THF (15 mL), cooled at 0 °C. After being stirred at room temperature for 24 h, the reaction was quenched with aqueous NH_4Cl and was worked up in the usual manner, and the products were purified by column chromatography (SiO_2, hexane-AcOEt, increasing the gradient from 40:1 to 5:1 V/V) to give 2.51 g (81%) of **1** (R_f = 0.34, hexane-AcOEt 5:1): bp 98−99 °C/0.06 Torr; IR (neat) 1766, 1724, 1662, 1635, 1365, 1313, 1211, 1170, 1132, 1047, 935, 904, 873, 806 cm^{-1}; ^1H NMR (300 MHz) δ 1.08, 1.13 (major form) and 1.05, 1.15 (minor form) (s, 12H), 1.33−1.70 (m, 6H), 1.98 (minor form) and 2.31 (major form) (s, 3H), 3.50 (s, 2H), 5.02 and 12.19 (brs); ^{13}C NMR (75.5 MHz) δ 16.6, 20.2 (2C), 30.2, 31.7 (2C), 38.9 (2C), 48.4, 60.0 (2C), 87.2, 166.7, 200.2. HRMS (ESI) calcd for $C_{13}H_{24}NO_3$ (MH^+) 242.3385, found 242.1750 (MH^+).

Preparation of 8. A mixture of the carbinol **7** (R^1 = Ph, 307 mg, 1.0 mmol), TEMPO• (312 mg, 2 mmol), and $RuCl_2(PPh_3)_3$ (96 mg, 0.1 mmol) in toluene (10 mL) was stirred at 60−62 °C for 3 days under O_2.[11] The mixture was passed through a short column packed with SiO_2, and the eluate was concentrated and purified by column chromatography (SiO_2, hexane-AcOEt, increasing the gradient from 10:1 to 5:1 V/V) to give 170 mg (56%) of **8** (R_f = 0.46, hexane-AcOEt 3:1) as solids (ca. 13:1 keto/enol mixture): mp 103−104 °C; IR (KBr) 1770, 1760, 1679, 1595, 1581, 1450, 1405, 1382, 1332, 1257, 1213, 1116, 1045, 941, 806, 748, 690, 632, 594 cm^{-1}; ^1H NMR (300 MHz) δ 1.01, 1.05 (major form) and 1.11, 1.20 (minor form) (s, 12H), 1.33−1.73 (m, 6H), 4.01 (s, 2H), 7.46−7.52 (m, 2H), 7.57−7.63 (m, 1H), 7.97−8.00 (m, 2H); ^{13}C NMR (75.5 MHz) δ 16.40 + 16.47, 19.90 + 20.05, 31.31 + 31.43, 38.6 (2C), 44.3, 59.8 (2C), 84.6, 125.6, 128.06, 128.10, 128.3, 130.9, 133.3, 135.7, 166.5, 191.7.

General Procedure for Knoevenagel Condensaton of *O*-AcetoacetylTEMPO (1), Giving 3, and Its Homologues Using Piperidine. To a cooled (0−4 °C) mixture of *O*-acetoacetylTEMPO (**1**, 243 mg, 1.0 mmol), 2-furaldehyde (**2a**, 192 mg, 2.0 mmol), and EtOH (4 drops, 20 mg) was added piperidine (two drops, 10 mg). The mixture was allowed to warm gradually to room temperature and was stirred for 2 days. The reaction was quenched with cold aqueous NH_4Cl, and the products were extracted with AcOEt. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude products were purified by column chromatography (SiO_2, hexane-AcOEt, increasing the gradient from 10:1 to 3:1 V/V) to give 243 mg (76%) of (*E*)-**3a** (R_f = 0.34, hexane-AcOEt 5:1) and trace of (*Z*)-**3a** (R_f = 0.13). (*E*)-**3a**: mp 131−132 °C; IR (KBr) 3141, 3100, 2976, 1739, 1625, 1551, 1473, 1381, 1365, 1233, 1159, 1071, 1043, 1014, 957, 905, 873, 778, 753 cm^{-1}; ^1H NMR (300 MHz) δ 1.11, 1.14 (s, 12H), 1.38−1.79 (m, 6H), 2.54 (s, 3H), 6.49 (d,d, J = 3.3, 1.6 Hz, 1H), 6.74 (d, J = 3.3 Hz, 1H), 7.40 (s, 1H, CH), 7.53 (m, 1H); ^{13}C NMR (75.5 MHz) δ 16.7, 20.6 (2C), 31.0, 31.7, 38.8 (2C), 60.3 (2C), 112.5, 117.6, 126.0, 128.6, 146.0, 149.1, 164.7 (^3J(COO, H) = 7.8 Hz), 201.2. HRMS (ESI) calcd for $C_{18}H_{25}NO_4$ (MH^+) 320.1862, found 320.1838 (MH^+).

Knoevenagel Condensation of *N*-methoxy-*N*-methylacetoacetamide (15) with 2, Giving 16, with Piperidine and AcOH. To a mixture of *N*-methoxy-*N*-methylacetoacetamide (**15**, 360 mg, 2.48 mmol) and **2a** (309 mg, 3.2 mmol) in CH_2Cl_2 (0.2 mL) were added consecutively AcOH (two drops) and piperidine (three drops) at 0−4 °C. The mixture was stirred at 28−30 °C for 2 days and was quenched with aqueous NH_4Cl. Products were extracted with AcOEt and were worked up in the usual manner. The crude products were purified by column chromatography (SiO_2, hexane-AcOEt, increasing the gradient from 10:1 to 1:3 V/ V) to give 382 mg (69%) of (*Z*)-**16a** (R_f = 0.21, hexane-AcOEt 1:1): mp 101−103 °C (partially decompose); IR (KBr) 3155, 3119, 3049, 2975, 1665, 1625, 1547, 1482, 1429, 1393, 1371, 1335, 1283, 1256, 1209, 1185, 1154, 1081, 1022, 993, 951, 932, 915, 883, 827, 761, 703 cm^{-1}; ^1H NMR (300 MHz) (a ca. 5.5:1 rotatory mixture on amide C−N bond) δ 2.34 (major) and 2.38 (minor) (s, 3H), 3.12 (minor) and 3.36 (major) (s, 3H), 3.47 (major) and 3.91 (minor) (s, 3H), 6.59 (major) and 6.52 (minor) (m, 1H), 6.78 (major) and 6.85 (minor) (d, J = 3.6

(24) Aparicio, F. J. L.; Herrera, F. J. L.; Ballesteros, J. S. *Carbohydr. Res*. **1979**, *69*, 55−70.

(25) (a) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett*. **2004**, *6*, 3679−3681. (b) Brown, R. C. D. *Angew. Chem., Int. Ed*. **2005**, *44*, 850−852 and references therein.

(26) Syntheses of natural products bearing a trisubstituted furan-3-carboxyl structure: (a) Toro, A.; Deslongchamps, P. *J. Org. Chem*. **2003**, *68*, 6847−6852. (b) Marshall, J. A.; Devender, E. A. V. *J. Org. Chem*. **2001**, *66*, 8037−8041. (c) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283−5292.

Hz, 1H), 7.31 (s, 1H), 7.53 (major) and 7.57 (minor) (d, J = 1.6 Hz); ^{13}C NMR (75.5 MHz) (major isomer) δ 26.4, 32.5, 61.4, 112.7, 117.7, 125.3, 131.7, 146.1, 149.3, 168.7 (^3J(COO, H) = 10.4 Hz), 194.2. HRMS (ESI) calcd for $C_{11}H_{14}NO_4$ (MH^+) 224.0923, found 224.0928 (MH^+).

General Procedure for Reduction of Knoevenagel Adducts 3 to *O*-2-(1-Hydroxyalkyl)-2-alkenoylTEMPOs (*E*)-24. To a cooled (−78 °C) solution of (*E*)-**3a** (R = 2-furyl, 80 mg, 0.25 mmol) in toluene (5 mL) was added dropwise DIBALH (1.0 N in toluene, 0.5 mL, 2.0 equiv) over 1 min. The mixture was stirred at the same temperature for 15 min, and excess DIBALH was decomposed with AcOEt and the reaction was quenched with aqueous $NaHCO_3$. The mixture was diluted with AcOEt and a small amount of benzene, and the supernatant pipetted off was dried ($MgSO_4$), and concentrated. The crude products were analyzed by GC (150 °C) and were purified by column chromatography (SiO_2, hexane-AcOEt, by increasing the gradient from 10:1 to 2:1) to give 6 mg (7%) of the 1,4-reduction product **25a** (R_f = 0.46, hexane-AcOEt 3:1), 7 mg (9%) of the starting (*E*)-**3a** (R_f = 0.27), and 67 mg (83%) of the 1,2-reduction product (*E*)-**24a** (R_f = 0.21). (*E*)-**24a**: mp 112−113 °C; IR (KBr) 3469, 3102, 1716, 1631, 1552, 1251, 1201, 1122, 1093, 767 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.086, 1.09, 1.21, 1.22 (s, 12H), 1.40−1.46 (m, 1H), 1.50−1.78 (m, 5H), 1.53 (d, J = 6.6 Hz, 3H), 3.94 (br d, J = 10.4 Hz, 1H), 5.39 (m, 1H), 6.50 (d,d, J = 3.6, 1.7 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 7.24 (s, 1H), 7.56 (d, J = 1.7 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 16.9, 20.93 and 20.96, 23.1, 31.87 and 31.91, 39.1 (2C), 60.33 and 60.41, 65.9, 112.2, 116.7, 123.4, 130.3, 145.0, 150.3, 167.7 (^3J(COO, H) = 7.78 Hz). HRMS (ESI) calcd for $C_{18}H_{28}NO_4$ (MH^+) 322.2018, found 322.2023 (MH^+). **25a**: IR (neat) 1770, 1722, 1508, 1380, 1365, 1245, 1182, 1132, 1010, 954, 734 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.95, 1.01, 1.11, 1.12 (s, 12H), 1.35−1.46 (m, 1H), 1.47−1.73 (m, 5H), 2.30 (s, 3H), 3.26 (d, J = 7.7 Hz, 2H), 4.00 (t, J = 7.7 Hz, 1H), 6.07 (m, 1H), 6.25 (m, 1H), 7.29 (m, 1H); ^{13}C NMR (75.5 MHz) δ 16.8, 20.5 (2C), 26.9, 30.0, 31.7 (2C), 39.08 and 39.18, 57.0, 60.39 and 60.48, 106.9, 110.4, 141.5, 151.6, 168.0, 202.1.

Similarly, (*E*)-**26c** was obtained in 85% yield from (*E*)-**17c**. (*E*)-**26c**: mp 125−126 °C; IR (KBr) 3398, 1745, 1693, 1635, 1596, 1463, 1384, 1365, 1245, 1236, 1201, 1120, 1045, 1022, 960, 941, 767 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.80 and 1.04 (d, J = 6.9 Hz, 6H), 1.04 (s, 6H), 1.16 and 1.18 (s, 6H), 1.35−1.75 (m, 6H), 1.80−1.95 (m, 3H), 2.20 (m, 2H), 3.82 (t, J = 11.3 Hz, 1H), 4.07 (m, 2H), 4.83 (m, 1H), 5.24 (m, 1H), 6.79 (s, 1H); ^{13}C NMR (75.5 MHz) δ 16.9, 19.55 and 19.63, 20.86 and 20.88, 21.49 and 21.53, 31.80 and 31.83, 39.1 (2C), 60.15 and 60.34, 65.9, 74.5, 113.2, 130.3, 134.1, 150.9, 168.4.

Similarly, (*Z*)-**28a** was obtained in 85% yield from (*Z*)-**16a** as a ca. 1.7:1 mixture of rotatory isomers of amide bond. (*Z*)-**28a**: IR (neat) 3411, 1629, 1556, 1486, 1388, 1151, 1110, 1018, 979, 885, 746, 595 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.40 (d, J = 6.3 Hz, 3H), 2.52 (br), 3.11 and 3.30 (brs, 3H), 3.47 and 3.84 (brs, 3H), 4.57 (m, 1H), 6.35 (br m, 2H), 6.43 (brs, 1H), 7.36 (brs, 1H); ^{13}C NMR (75.5 MHz) δ 21.8 and 22.2, 32.0 and 32.2, 60.96 and 61.2, 68.8, 110.3, 111.3 and 111.5, 114.6, 137.3, 142.6 and 143.0, 150.0 and 150.4, 166.1 and 170.4.

General Procedure for THP-Protection of (*E*)-24a and (*Z*)-28a Followed by DIBALH or LAH Reduction to (*E*)- and (*Z*)-31a. To a mixture of (*E*)-**24a** (37 mg, 0.12 mmol) and DHP (170 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was added PPTS (catalytic). The mixture was stirred at room temperature for 43 h and was worked up in the usual manner including washing with aqueous $NaHCO_3$ followed by purification on column chromatography (SiO_2, hexane-AcOEt by increasing the gradient from 10:1 to 3:1 V/V) to give 48 mg (78%) of (*E*)-**30a**. To a solution of the THP-protected (*E*)-**30a** (0.11 mmol) in toluene (5 mL) was added dropwise DIBALH (0.33 mL, 3 equiv) at −78 °C. After being stirred at the same temperature for 1 h, the mixture was worked up as above and the crude products were purified by column chromatography (SiO_2, hexane-AcOEt by increasing the gradient from 10:1 to 1:1 V/V) to give 25 mg (86%) of (*E*)-**31a** (R_f = 0. 52, hexane-AcOEt 2:1) and 2 mg (7%) of the corresponding carbinol (R_f = 0.32) because of overreduction. (*E*)-**31a**: IR (neat) 1679, 1625, 1469, 1371, 1199, 1076, 1022, 983, 939, 815 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.45 and 1.51 (d, J = 6.9 Hz, 3H), 1.50−1.90 (m 6H), 3.30−3.65 (m 2H), 4.41 and 4.79 (m, 1H), 5.27 and 5.40 (q, J = 6.9 Hz, 1H), 6.55 (m, 1H), 7.01 and 7.11 (s, 1H), 7.12 and 7.15 (d, J = 3.57 Hz, 1H), 7.61 (m, 1H), 9.579 and 9.583 (s, 1H); ^{13}C NMR (75.5 MHz) δ 18.6 and 19.2, 19.3 and 19.5, 25.2 and 25.3, 30.57 and 30.69, 62.1 and 62.5, 65.5 and 68.4, 96.4 and 98.1, 112.73 and 112.89, 118.43 and 118.91, 131.69 and 133.69, 137.18 and 145.73, 150.15 and 150.47, 192.83 and 192.99. HRMS (ESI) calcd for $C_{14}H_{18}O_4$ (MH^+) 250.1205, found 250.1184 (MH^+).

Similarly, (*Z*)-**31a** was obtained from (*Z*)-**28a** as follows. The protection of (*Z*)-**28a** with THP as above afforded (*Z*)-**32a** (84% yield), and reduction of the resulting THP ether (*Z*)-**32a** with LAH (7 equiv) at 0 °C for 10 min followed by usual workup including treatment with aqueous tartaric acid and purification on SiO_2 (hexane-AcOEt by increasing the gradient from 10:1 to 1:1 V/V) gave (*Z*)-**31a** (R_f = 0.57, hexane-AcOEt 2:1) in 72% yield and a ca. 4:1 Z/E mixture of 3-(2-furyl)-2-hydroxyethyl-2-propenal (R_f = 0.19) in 8% yield. (*Z*)-**31a**: IR (neat) 1660, 1625, 1473, 1365, 1301, 1201, 1120, 1076, 1022, 985, 929, 815 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.29 and 1.36 (d, J = 6.9 Hz, 3H), 1.50−1.90 (m 6H), 3.40−3.53 and 3.72−3.95 (m 2H), 4.49 and 4.75 (m, 1H), 4.87 and 4.95 (q, J = 6.9 Hz, 1H), 6.51 (m, 1H), 6.69 (m, 1H), 7.19 and 7.35 (s, 1H), 7.57 and 7.59 (d, J = 1.9 Hz, 1H), 10.61 and 10.64 (s, 1H); ^{13}C NMR (75.5 MHz) δ 19.8 and 19.9, 21.2 and 22.8, 25.3 and 25.4, 30.94 and 30.97, 62.1 and 62.8 and 62.9, 67.8 and 68.2, 97.1 and 97.2, 112.2 and 112.3, 117.1 and 117.3, 128.2 and 128.5, 138.9, 145.9 and 146.2, 151.4, 192.6 and 192.9. HRMS (ESI) calcd for $C_{14}H_{18}O_4$ (MH^+) 250.1205, found 250.1194 (MH^+).

Preparation of Furan (34). To a solution of the carbinol (*E*)-**26a** (15 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was added *p*-TsOH (catalytic). The mixture was stirred at room temperature for 5 h and was worked up in the usual manner, and the crude product was purified by column chromatography (SiO_2, hexane-AcOEt, increasing the gradient from 7:1 to 1:1 V/V) to give 14 mg (93%) of **34b** (R_f = 0. 51, hexane-AcOEt 1:1) as colorless oil: IR (neat) 3455, 3120, 1735 1727, 1618, 1583, 1456, 1365, 1265, 1232, 1182, 1132, 1052, 1041, 989, 952, 914, 873, 767, 690 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.09 and 1.21 (s, 12H), 1.40−1.80 (m, 11H), 2.57 (s, 3H), 2.61 (t, J = 7.1 Hz, 2H), 3.68 (t, J = 6.3 Hz, 2H), 6.27 (s, 1H); ^{13}C NMR (75.5 MHz) δ 14.0, 17.0, 21.0 (2C), 24.1, 27.4, 31.9, 32.1 (2C), 39.0 (2C), 60.0 (2C), 62.5, 105.7, 112.4, 153.9, 157.4, 164.2. HRMS (ESI) calcd for $C_{19}H_{32}NO_4$ (MH^+) 338.2331, found 338.2347 (MH^+).

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Supporting Information Available: Spectral data including IR, ^{1}H NMR, and ^{13}C NMR spectra of **1**, **6**, **8**, (*E*)- and (*Z*)-**3a**-**p**, (*E*)- and (*Z*)-**12a**, (*Z*)-**14**a, (*Z*)-**16a**,**b**,**h**,**k**,**l**,**m**,**o**, (*E*)-**17a**,**c**, (*E*)-**18b**,**c**, (*E*)-**20a**, (*E*)-**24a**,**c**, **25a**,**c**, (*E*)-**26a**,**c**, (*E*)-**27a**, (*E*)-**28a**, (*E*)-**30a**, (*E*)- and (*Z*)-**31a**, (*Z*)-**32a**, and **34a**,**b**, and the crystallographic data of (*E*)-**3a** are provided. This material is available free of charge via the Internet at http://pubs.ac.org.

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